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Annex 1 Some Major Companies in the Pharmaceutical Industry
Chapter 1: Understanding the Pharmaceutical Industry

1.1 Development of the Industry

An awareness of how pharmaceuticals and the pharmaceutical industry have evolved makes it easier to understand the modern industry: its manufacturing methods, the strict regulatory environment, the health issues affecting workers, and the social and ethical issues faced today. Professional hygienists need such knowledge in order to be credible with their technical and managerial colleagues in industry. It is not necessary for students to remember all the details of the historical events mentioned below, or to know about all the individual pharmaceuticals discussed, but knowledge of the specific pharmaceuticals that your company works with will prove very useful. Key learning points for hygienists are summarised at the end of each section.

1.1.1 Origins

The pharmaceutical industry is concerned with the manufacture of drugs. A drug can be defined as “any chemical substance, synthetic or natural, of known or unknown composition, which is used as a medication to prevent or cure a disease.” There are many types of drugs. They can be categorised into around 15 classes by site of primary action (gastro-intestinal system, cardiovascular system, respiratory system, etc.) then subdivided into around 100 further subgroups by drug type - antacids, laxatives, anticoagulants, analgesics, cytotoxics to name but a few.

Up until the industrial revolution the pharmaceutical industry only existed in the form of apothecaries and pharmacies that offered traditional remedies. It was not until the 1800s that an industry involving large scale manufacture started to emerge.

**1827** – Heinrich Emanuel Merck worked in the family pharmacy in Darmstadt, Germany and started to isolate all the known alkaloids and sold them to other chemists and physicians.

**1842** – Thomas Beecham started selling “Beecham’s Pills”, a laxative tablet, building up a network of sales throughout the north of England and by 1859 opening the world’s first pharmaceutical factory.

**1849** – In the USA Pfizer is founded, initially making Sanonin, an antiparasitic. During the American Civil War they expanded to meet the demand for painkillers, preservatives and disinfectants.

**1858** - Edward Robinson Squibb, set up a laboratory supplying the union armies in the civil war. Despite being badly burned by an ether explosion and the laboratory being burned a further two times, by 1883 the company was manufacturing 324 products and selling them around the world.

**1876** - Colonel Eli Lilly a pharmacist and veteran of the American Civil War began his medical wholesale company. Lilly pioneered new methods in the industry, being one of the first to focus on R&D as well as manufacturing.

**1888** - As a result of the demand for more exact dosing and sophistication of drug formulation, the physician and pharmacist Dr. Wallace C. Abbott, using the active part of a medicinal plant, known
as the "alkaloid," formed tiny pills called "dosimetric granules," which provided more accurate and effective dosing for his patients than other treatments available at the time. From these modest origins inside a physician's residence, was born Abbott which is now AbbVie Inc.

During the latter half of the 19th Century Switzerland also developed a pharmaceutical manufacturing industry. Companies set up to manufacture dyestuffs realized that their products had antiseptic qualities and started to market them as pharmaceuticals. A lack of patent laws in the country allowed companies to manufacture and sell products invented by other companies. Novartis, Roche and the Basel hub of the pharmaceutical industry all have their roots in this boom.

Key learning points:
- The first pharmaceutical companies grew out of traditional pharmacies.
- Early pharmaceuticals were based on natural remedies.
- There was no clear dividing line between prescription medicines and other products.
- Modern pharmaceutical manufacturing has its origins in the fine chemicals industry of the 19th century.
- Even today, the geographic distribution of the major companies reflects this history.

1.1.2 The Story of Aspirin

Aspirin was perhaps the first synthetic pharmaceutical and remains the one of the most widely taken drugs in the world. The story of its development and subsequent use illustrates several principles that have come to typify the pharmaceutical industry.

Ancient Sumerian and Egyptian texts recommended willow bark for various complaints. Greek, Roman and Islamic medical authors noted its power to reduce pain and relieve fevers. However, its tendency to cause inflammation and occasionally bleeding of the stomach lining considerably diminished its utility.

In 1828 the German chemist Joseph Buchner isolated the active ingredient, a yellowish, bitter tasting substance that he called salicin (*salix* being the Latin for willow). Two years later Johann Pagenstecher, a Swiss apothecary, extracted the same material from the meadowsweet plant, whose botanical name *spirea* later suggested the brand name aspirin.

In 1838 Raffaele Pirea succeeded in converting salicin to salicylic acid. This compound proved to be a more useful remedy, but unfortunately it irritated the stomachs of some patients. In 1853, the French chemist Charles Gerhardt prepared its acetyl ester, which had similar analgesic, anti-inflammatory and fever-reducing properties to salicylic acid but was less harmful to the stomach. The ester was not hydrolysed until it reached the alkaline environment of the small intestine.

Bayer, a dyestuffs company established in 1863, developed a new industrial synthesis for acetyl salicylic acid and commercialised it as aspirin in 1899. Early synthetic drugs were tested haphazardly and often failed to fulfil all the marketing claims made but Bayer took a more systematic approach.
Both commercial and medical factors contributed to the drug’s success. Aggressive advertising hammered aspirin’s reassuringly non-technical name into the public consciousness, while astute lawyers defended its trademark status in every important marketplace. Taking a tablet to relieve distress quickly became an integral part of western culture.

The national rivalries and conflicts that characterised this period also had their impact on the developing industry. Bayer had the aspirin trademark and its US assets seized during World War I, whilst “American” Merck (now Merck & Co. in the US or Merck Sharp & Dohme [MSD] elsewhere) was compulsorily split off from its Germany parent company (Merck KGaA) at the same time. Bayer also had its Russian subsidiary seized during the Russian revolution. This disruption to Germany’s position as the leader in pharmaceuticals in the early 20th century by the war meant that others, particularly in the US, could take relative advantage. The beginnings of the globalisation of the industry were seen both before and after the war – in the UK, import duties incentivised many foreign companies such as Wyeth, Sandoz, CIBA, Eli Lilly and MSD to set up subsidiaries in Britain in the post-war years.

In the 1950s and 60s the dominant position of aspirin was challenged by paracetamol (acetaminophen) and ibuprofen. The use of aspirin by children was discouraged in the 1980s because of a suspected link with Reye’s syndrome, a very rare but extremely unpleasant childhood illness. Yet as its mechanism of action has been researched, new uses of aspirin have emerged. It has been shown to reduce the formation of blood clots, by blocking the production of thromboxane, a lipid which encourages the clotting of blood through its action on platelets. This can reduce the likelihood of cardiac failure or strokes. Recent research also indicates that aspirin may be effective against some varieties of cancer.

**Key learning points:**
- Synthetic molecules often have fewer side effects than the natural products.
- Systematic testing of efficacy is essential with a new pharmaceutical.
- Marketing is key to the commercial success of new drugs and the industry has often been accused of being too aggressive.
- Defense of intellectual property rights through patents is a major concern for companies that discover and develop new drugs.
- Concern about unforeseen side effects sometimes arise when the drug reaches a mass market.
- New indications for the drug to treat other health conditions sometimes emerge later.

### 1.1.3 The Development of Antibiotics

The use of toxic metal compounds to treat syphilis infection, caused by the bacterium *Treponema pallidum* had been known since the days of Paracelsus in the 16th century though many people would have died from the toxic side effects. Paul Ehrlich announced the first true antisyphtilic, an
arsenic compound later patented as Salvarsan in 1910 after testing many hundreds of compounds. It became the mainstay of treatment until the discovery of penicillin and led to the use of the term “magic bullet” for pharmaceuticals that selectively targeted a disease-causing organism.

In the early 20th century common bacterial infections were often fatal. The discovery of antibiotics, which kill bacteria, transformed survival rates and life expectancy.

Penicillin antibiotics stem from a chance discovery by Alexander Fleming in 1928. He observed that certain *Penicillium* moulds killed bacteria and isolated from them an extract which proved to have impressive potency. The active ingredient was named penicillin. Chain and Florey in Oxford, UK developed the first production method involving fermentation to culture the mould and extraction. Large scale production of penicillin began in 1940. Natural penicillins degrade easily in acid, so have to be injected into the blood stream and cannot be taken by mouth.

Elucidation of the *beta-lactam* chemical structure of penicillin led in the 1960s to the incorporation of a number of different side chains (shown as R in the diagram), giving a range of semi-synthetic antibiotics. The first major development was ampicillin, which offered a broader spectrum of activity than the original penicillin. Later, amoxycillin proved highly effective against Gram-positive bacteria.

Figure 1: Alexander Fleming (source: Calibuon via English Wikibooks)

![Figure 1: Alexander Fleming](source: Calibuon via English Wikibooks)

Figure 2: Core beta-lactam structure of penicillin

![Figure 2: Core beta-lactam structure of penicillin](source: Calibuon via English Wikibooks)
such as *staphylococci* and *streptococci* though infections caused by Gram-negative bacteria such as *salmonella* and *pseudomonas* do not respond. Penicillins can also provoke severe allergic reactions in some patients so they are not suitable for everyone.

Amoxycillin remains a broad-spectrum antibiotic of choice but penicillins are now subject to increasing antibiotic resistance. Bacteria have adapted to produce enzymes called beta-lactamases which breakdown the beta-lactam structure of the antibiotics, rendering some essentially useless. Further development yielded β-lactamase-resistant penicillins, including flucloxacillin, and methicillin. These were significant for their activity against β-lactamase-producing bacterial species, but were ineffective against the methicillin-resistant *Staphylococcus aureus* (MRSA) strains that subsequently emerged.

Industry efforts to find substances that would destroy the beta-lactamases were unsuccessful until in 1975, clavulanic acid was isolated from a soil microorganism and found to be an effective inhibitor of beta-lactamases. When used in combination with amoxicillin, as co-amoxiclav (trade name Augmentin), this proved to be highly effective and it remains one of the world’s bestselling pharmaceuticals.

Much of the problem of penicillin resistant bacteria results from the overuse of antibiotics. Penicillins have often been prescribed for common colds and flu, which are viral infections and do not respond to antibiotics. They have even been added to cattle and poultry feed to promote growth and improve yields. Another factor has been that patients often fail to finish the full course of treatment, allowing bacteria the opportunity to survive and adapt to the antibiotic.

This overuse and misuse has resulted in pathogenic bacteria having abundant opportunity to come in contact with the drug and mutate into resistant forms. In most cases, the drug resistance genes of bacteria are carried on plasmids (small DNA molecules that are physically separate from, and can replicate independently of, chromosomal DNA within a cell). Plasmids can be passed from cell to cell, allowing for a drug resistance to be passed to a large group of bacteria and to different types of bacteria. Some plasmids have as many as 8 drug resistances on them. For decades, the pharmaceutical industry has been searching for alternative antibiotics.

In 1948, Giuseppe Brozu from Sardinia published a report of another group of antibiotics cultured from a strain of mould that grows on sewage, the cephalosporins. Years of research finally showed that these compounds also had a beta-lactam structure (see Figure 3). Again, the commercial exploitation of this class of drugs depended on the development of a semi-synthetic route involving removal of the side-chain to give 7-amino-cephalosporanic acid and then substitution of an artificial side-chain. The cephalosporins proved to have activity against both Gram-positive and Gram-
negative bacteria, and their effectiveness has been enhanced in successive generations of drugs. And again, they have proved susceptible to the development of antibiotic resistance, though it has been less of a problem because the cephalosporins have not been as widely used as the penicillins.

Another major antibiotic, streptomycin, was discovered in 1943 and found to be effective against tuberculosis (TB), one of the world’s major killer diseases. About one-third of the world’s population carries the bacillus but people typically do not develop the disease unless their immune system becomes impaired. In countries where poverty and overcrowding are the norm, it causes around 1.5 million deaths each year. At one time it appeared possible to eradicate the disease, but by the mid-1980s it became clear that resistant forms of TB had developed and infection rates were no longer falling. This was found to be because people with the disease failed to complete their lengthy course of treatment once the symptoms subsided, and the bacteria remaining in their bodies, which had had prolonged exposure to the streptomycin were able to adapt. Infection rates began to rise, compounded by the spread of AIDS which compromises the immune system, and the availability of global air travel. In 1993 the World Health Organisation declared a global emergency for TB. More modern drugs have continued to show some effectiveness but “totally drug-resistant TB” was first observed in 2003 and was becoming widespread by 2012.

Further important antibiotics in the same class as streptomycin include neomycin (1949), erythromycin (1952), vancomycin (1956) and gentamycin (1963). Vancomycin has been called the “antibiotic of last resort” because until recently no bacteria had developed resistance to it. Vancomycin resistant *Staphylococcus aureus* (VRSA) has now been identified. Use of vancomycin is heavily restricted to prevent resistance spreading further.

Antibiotic resistance now poses a major threat to human health, with the clear possibility of a return to the situation of the early 1900s where simple infections can be fatal. Research has offered a number of leads to the development of new classes of antibiotic that act in different ways and might overcome the problem of resistance for a while. However, antibiotics have become so cheap that developing new ones offers little prospect of recouping the development costs and many commercial companies have cut their research programmes.

**Key learning points:**

- Pharmaceuticals have transformed human life over the last century, dramatically reducing mortality rates and extending lifespans.
- Social factors have a massive impact on the spread of disease and on the pressures for drug discovery.
- Discovery was often a chance process of screening of natural products for activity.
- Manufacture often involves a process of fermentation and extraction.
- Chemical modification of side chains can produce a range of drugs with slightly different properties.
The stability of the drug in the body is an important consideration governing how it is administered and how effective it is.

- All drugs have side effects which constrain their use.
- Efficacy of drugs is often improved by the modifications to structure and formulation made from one generation to the next.
- Antibiotic resistance is becoming a major threat to society and development of new antibiotics is one of the biggest challenges for the pharmaceutical industry.

### 1.1.4 Rational Drug Design

As recently as the 1970’s, a peptic ulcer could be a life-threatening condition. Sufferers often endured periods of intense pain over many years, especially at mealtimes and at night, with social and economic consequences for themselves and their families. Left untreated, an ulcer could result in severe bleeding and death.

A major cause of ulcers is the release of excess stomach acid which leads to breaches in the lining of the intestinal tract. Continuing acid secretion prevents healing. The main treatment used to be the administration of alkalis which provided only temporary relief. Patients were told to rest and follow a bland diet. Surgery to remove part of the stomach was a last resort.

The discovery of cimetidine (brand name Tagamet) and ranitidine (Zantac) transformed the lives of millions of people. They profoundly decrease acid secretion so promoting healing and avoiding the need for surgery.

The research programmes leading to these drugs also transformed the way that pharmaceuticals are developed. Traditionally the development of a new drug would often depend on the fortuitous discovery of a plant or microbial extract that showed some of the required biological activity. Using that extract as a lead, many similar compounds would be developed and tested for pharmacological effectiveness. In many cases the researchers did not know how the drug worked, so finding an optimal compound was difficult.

In the discovery of cimetidine and ranitidine, the researchers first looked at the physiological cause of acid secretion. They confirmed that a molecule found in the body called histamine triggers the release of acid when it binds to a specific receptor (now called the H2-receptor) in the stomach lining. Their aim was to find a molecule that successfully competed with histamine in combining with the receptor, but then blocked, rather than stimulated, acid release. Such a molecule was called a histamine H2-receptor antagonist and represented a new class of drugs.

These were the first examples of “rational” (or “logical”) drug design, where an understanding of the biochemistry of an illness allowed development of a drug that targeted a specific point in the disease process. It became the standard approach to drug discovery and led to many innovations.
During the 1990’s, however, rational design seemed to have stalled as the obvious targets had already been addressed. Company “pipelines” of new products began to dry up. At that time, innovations in analytical techniques and computer technology made possible High-Throughput Screening. Using robotics, data processing and control software, liquid handling devices, and sensitive detectors, High-Throughput Screening allows a researcher to conduct millions of chemical, genetic or pharmacological tests very quickly. Through this process one can rapidly identify active compounds, antibodies or genes which modulate a particular biomolecular pathway. The results of these experiments provide many starting points for drug design and for understanding the interaction or role of a particular biochemical process in biology.

Major pharmaceutical companies developed libraries of millions of compounds for screening and there was also renewed interest in screening of natural products from plants, soil bacteria and marine life. However, the expected flood of new active ingredients did not materialize quickly. It became clear that the most important illnesses needing cures were caused by complex factors and simple small molecule interventions were unlikely to be effective. Also, society was becoming less tolerant to the side-effects of medication and many promising drugs were never brought to market because of concerns identified during clinical trials.

New hope has come with the sequencing of the human genome and improved knowledge of the biochemical pathways of disease. These create the potential for create more selective therapies using genetics. We will discuss this further in a later section.

**Key learning points:**

- Rational (logical) drug design transformed the pharmaceutical industry, leading to more effective treatments for many illnesses.
- High Throughput Screening makes it possible to search vast libraries of compounds for ones having the desired pharmaceutical activity.

### 1.1.5 The Growth of Regulation

The latter half of the 20th century saw an increase in the regulation of pharmaceuticals. In 1948 the National Health Service (NHS) was created in the UK, as part of a welfare state. It created a much more structured system both for the sale and pricing of medicines. In 1957, the NHS brought in what was essentially a price fixing scheme to allow reasonable return on investment for drug manufacturers, solidifying the incentive to invest in new medicines. Increased regulation of medicines in other European countries as well as the US also occurred at this time.

In 1961 the Thalidomide scandal forced an increase in the level of regulation of drugs. Thalidomide was used by thousands of pregnant women to ease the symptoms of morning sickness, yet it had not been thoroughly tested for potential harm to the foetus (US spelling = fetus). This resulted in:
• An amendment to US Food and Drug Administration (FDA) rules which demanded proof of efficacy and accurate disclosure of side-effects for new medications.

• The Declaration of Helsinki, which is a statement of ethical principles developed by the World Medical Association to: "provide guidance to physicians and other participants in medical research involving human subjects".

Nowadays, testing of pharmaceuticals for **efficacy, quality and safety** is an essential part of bringing a new product to market. Regulations vary around the world, but normally a New Drug Application (NDA) must be approved before a new pharmaceutical can be marketed or sold. The NDA aims to establish that:

• The drug is safe and effective when used as directed and the benefits of the drug outweigh the risks.

• The manufacturer provides appropriate information with the drug.

• The methods used in manufacturing the drug and the controls used to maintain the drug’s quality are adequate to preserve the drug’s identity, strength, quality and purity.

Pharmaceuticals that are approved by the regulatory authorities receive a marketing authorisation (sometimes referred to as a product licence). Such drugs can only be supplied on medical prescription, though different jurisdictions have different definitions of what constitutes a prescription drug.

The authorisation defines the procedures that must be adopted for manufacturing, packaging, labelling and storage. For example, the package insert for a prescription drug must contain information about the intended effect of the drug and how it works in the body. It also contains information about side effects, how a patient should take the drug, and cautions for its use, including warnings about allergies.

![Figure 4: Prescription tablets clearly marked to identify the name and dose of the drug (Source: Wikimedia Commons)](image)

It is the rules governing manufacturing that are likely to have most impact on the occupational hygienist, as any changes to the manufacturing process will need to comply with the conditions imposed. It is possible to get the authorisation conditions changed, but it can be a long and
expensive process. Also, companies are often unwilling to take the risk of re-opening discussions on the product authorisation. Hygienists will need to be familiar with the constraints and the attitude of management towards making changes. It is also helpful to understand the regulatory requirements, as some changes / modifications may not impact filings or require a lesser degree of scrutiny.

Prescription drugs are sometimes known as “Rx”, which is an abbreviation for the Latin "recipe", an imperative form of "recipere", meaning "take". The term is used to distinguish it from over-the-counter (OTC) drugs which can be obtained without a prescription.

As a general rule, over-the-counter drugs are used to treat conditions that do not require the direct supervision of a doctor and must be proven to be reasonably safe and well tolerated. OTC drugs are usually also required to have little or no abuse potential. One of the oldest OTC drugs is aspirin.

Over time, often 3–6 years, drugs that prove themselves safe and appropriate as prescription medicines may be switched from prescription to OTC. Cimetidine is an example of a medicine that has been switched in most jurisdictions. OTC “switches” represent a major commercial opportunity for manufacturers.

Often a lower strength of a drug will be approved for OTC use, while higher strengths require a prescription to be obtained; a notable case is ibuprofen, which has been widely available as an OTC pain killer since the mid-1980s but is still available by prescription in doses up to four times the OTC dose for use in cases of severe pain not adequately controlled by the lower, OTC strength.

It is somewhat unusual for an OTC drug to be withdrawn from the market as a result of safety concerns, rather than market forces, though it does happen occasionally.

Herbal preparations, amino acids, vitamins, minerals, and other food supplements, sometimes referred to as “nutraceuticals”, are regulated in many jurisdictions, but usually less strictly than prescription pharmaceuticals. Because specific health claims cannot be made, the consumer must make informed decisions when purchasing such products.

Cosmetics are also subject to regulation and can sometimes overlap with pharmaceutical regulation. Some products meet the definitions of both cosmetics and drugs. This may happen when a product has two intended uses. For example, a shampoo is a cosmetic because its intended use is to cleanse the hair. An antidandruff treatment is a drug because its intended use is to treat dandruff. Consequently, an antidandruff shampoo is both a cosmetic and a drug. Among other cosmetic/drug combinations are toothpastes that contain fluoride, deodorants that are also antiperspirants, and moisturizers and makeup marketed with sun-protection claims. Such products must comply with the requirements for both cosmetics and drugs.
Key learning points:

- The introduction of new pharmaceuticals is heavily regulated by governments around the world.
- Healthcare systems play a major role in prescribing, purchasing and setting the price of pharmaceuticals.
- New Drug Applications must demonstrate efficacy, quality and safety before marketing authorisation is granted.
- Marketing authorisations impose requirements on the manufacture, packaging and storage of products.
- Different rules apply to prescription pharmaceuticals, Over-The-Counter products, food supplements and cosmetics. There can be commercial incentives to switch products between categories.

1.1.6 Regulatory regimes

As the largest markets for pharmaceuticals are in the US and the EU, the most influential regulatory agencies are the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA). They are responsible for the scientific evaluation of applications for marketing authorisations. They also prepare guidelines and detailed requirements for the demonstration of quality, safety and efficacy.

Occupational hygienists will need to be acquainted in particular with the regulatory requirements for:

- **Good Laboratory Practice (GLP)**, which defines the rules and criteria for the way that non-clinical health and environmental safety studies are planned, performed, monitored, recorded, reported and archived.

- **Good manufacturing practice (GMP)**, which requires that manufacturers adequately control manufacturing operations to ensure that products are consistently produced to the quality standards appropriate to their intended use. Adherence to GMP assures the identity, strength, quality, and purity of drug products.

As the rules of these quality systems are updated periodically, it is important to refer to the current versions, denoted by cGLP and cGMP. They provide for systems that ensure proper design, monitoring, and control of processes and facilities. cGMP includes establishing strong quality management systems, obtaining appropriate quality raw materials, establishing robust operating procedures, detecting and investigating product quality deviations, and maintaining reliable testing laboratories. It helps to prevent instances of contamination, mix-ups, deviations, failures, and errors.
The cGMP requirements are designed to be flexible in order to allow each manufacturer to decide individually how to best implement the necessary controls. The flexibility in these regulations allows companies to use modern technologies and innovative approaches to achieve higher quality through continual improvement. Systems and equipment that may have been "top-of-the-line" to prevent contamination, mix-ups, and errors 10 or 20 years ago may be less than adequate by today’s standards.

It is important to note that cGMPs are minimum requirements. Many pharmaceutical manufacturers are already implementing comprehensive, modern quality systems and risk management approaches that exceed these minimum standards.

Occupational hygienists will need to comply with these quality assurance requirements. Some examples of where that may prove important are:

- Rules on entry into manufacturing or laboratory areas, including use of protective clothing and changing procedures.
- Choice of sampling equipment and techniques that are compatible with the quality assurance requirements, particularly in aseptic areas.
- Recommendations for exposure control measures, including airflows and filtrations systems. One common instance of this is in “clean rooms” which are kept under positive pressure to protect the product against contamination. In contrast, hygienists would normally keep processes under negative pressure to protect the operators.

**Key learning points:**

- Occupational hygienists must comply with the requirements of cGLP and cGMP.
- Changes to processes and working practices that affect cGMP can prove surprisingly expensive.
1.2 Areas of the Business

1.2.1 Drug Discovery

Drug discovery typically happens in one of three environments:

- Industrial research conducted by the “Big Pharma” companies. Historically, such research has mostly focused on small molecule drugs made by chemical synthesis, although large molecules are the emphasis in today’s biopharmaceuticals. High-throughput screening remains an important way of generating leads. Such large organisations usually have in-house capabilities to develop the product formulation, conduct clinical trials, bring the drug to market and manufacture it. Increasingly, they may contract out some stages, such as manufacturing, for commercial, technological, or legislative reasons.

- Academia, funded by government or other grants. Academic researchers typically focus on radically new therapeutic approaches which offer possibilities of radical breakthroughs but with a low probability of success.

- Small biotech companies, often venture capital backed. Typically, these have focussed on large biological molecules such as proteins derived from fermentation.

Academic departments and small biotechs usually need funding and facilities once they pass the discovery stage and will often look for partnerships with large companies. Large companies often seek to acquire small biotechs with promising portfolios. Also, they are increasingly researching large molecules themselves.

Systematic drug discovery generally begins with target identification – choosing either a biological state or a biochemical “pathway” involved in the development of a disease condition. Drug candidates are then tested for their interaction with the biological target.

Up to 5,000 to 10,000 molecules for each potential drug candidate are subjected to a rigorous screening process. Computer modelling is increasingly used to help identify suitable candidate molecules and reduce the amount of physical testing required.

Once scientists confirm interaction with the drug target, they typically validate that target by checking for activity versus the disease condition for which the drug is being developed. After careful review, one or more lead compounds are chosen, taking into account their selectivity (to reduce the potential of side effects), efficacy, potency, metabolic stability, and oral bioavailability.

Despite advances in technology and understanding of biological systems, drug discovery is still a lengthy, "expensive, difficult, and inefficient process" with a low rate of new therapeutic discovery.
Chapter 1: Understanding the Pharmaceutical Industry

Key learning points:

- Different types of organisations – eg. large pharmaceutical companies, universities, small biotech companies – will have different research interests and capabilities.
- Partnerships and acquisitions are commonplace in the industry.
- Systematic drug discovery typically involves identifying a disease pathway and screening potential drugs that will interfere with the disease process.
- A lead drug candidate is chosen for further assessment and development.
- Drug discovery remains a lengthy, difficult and expensive process.

1.2.2 Drug Development

New compounds which emerge from the process of drug discovery are known as New Chemical Entities (NCEs, also called New Molecular Entities or NMEs). These will have promising activity against a particular biological target thought to be important in disease; however, little will be known about the safety, toxicity, pharmacokinetics and metabolism of this NCE in humans. It is the function of drug development to assess all of these parameters prior to human clinical trials. Together these processes of preclinical development are known as Chemistry, Manufacturing and Control (CMC).

Preclinical testing

The lead compound must be characterised by means of computer modelling, in vitro and in vivo tests. These include:

- Physicochemical tests to determine the molecule’s size, shape, stability and solubility.
- Animal testing to demonstrate bioactivity, and bioavailability and to reveal any toxicity.

These early stage pharmacology studies characterise the underlying mechanism of action of the compound. This data allows researchers to estimate a safe starting dose of the drug for clinical trials in humans. Most pre-clinical studies must adhere to Good Laboratory Practices (GLP) to be acceptable for submission to regulatory agencies.

Studies of a drug's toxicity include which organs are targeted by that drug, as well as if there are any long-term carcinogenic effects or toxic effects on mammalian reproduction. Such effects might require the development of the candidate drug to be terminated. They also provide essential information about possible hazards for exposed employees.

Pre-clinical testing in animals itself creates a significant health risk to staff working with animals in the form of Laboratory Animal Allergy.
Chemical Development
The process by which the chemical is made will be optimised so that from being made at the bench on a milligram scale by a medicinal or analytical chemist, it can be manufactured on the kilogram and, if necessary, on the ton scale. This scale-up will involve experimental work on a pilot plant.

Scaling-up the process can affect the characteristics of the chemical product, for example by changing particle size which affects solubility, or by causing the production of isomeric forms of the molecule which may have different biological activity.

This stage also determines the efficiency of the manufacturing process, affecting the quantities of raw materials that will need to be processed and the amount of waste that will be generated.

Traditionally, most pharmaceuticals are made by batch processes, though increasingly continuous processes are being introduced. Continuous processing offers advantages for occupational hygiene because there is reduced need for manual handling of materials. Process safety is another key consideration in scale-up, with potential for runaway reactions if the thermal characteristics of the reaction are not properly assessed.

Formulation
Once primary manufacture of the Active Pharmaceutical Ingredient (API) is completed, secondary manufacture begins with formulation of the final dosage form meant for actual patient treatment. Drug developers must devise a formulation that ensures the proper drug delivery parameters. Options include capsules, tablets, aerosols, skin patches, intramuscular injectable, subcutaneous injectable, or intravenous formulations.

Each technology has advantages and drawbacks. Some can be designed to give slow (controlled) release of the active ingredient, maintaining a more consistent level of the drug in the body over time and extending the action of the drug so that fewer doses are needed. Others bypass the digestive system, avoiding break down (metabolism) of the drug. Some technologies, such as injectables, require sterile products which must be produced under conditions that prevent any microbial contamination.

The Active Pharmaceutical Ingredient (API) is typically delivered at a relatively low dose, so an inert bulk material (known as an “excipient”) has to be added to make tablets or capsules large enough to handle. Water-soluble sugars such as lactose are often used. In addition, other materials are needed to give improve manufacturability and the physical properties of the finished product. For example, a binder might be needed to make sure the mixture forms free flowing granules, and adding microcrystalline cellulose can help reduce the brittleness of tablets. Size, colour and taste can have a massive impact on getting people to take their medication properly. Flavourings may be added or tablets may be coated with a polymer film so that they do not dissolve in the mouth.
Scientists determine the drug’s stability in the formulation itself, and all the parameters involved with storage and shipment, such as heat, light, and time. The formulation must remain potent, and sterile if necessary; and it must also remain safe (non-toxic).

Drug formulation and delivery may be refined continuously until, and even after, the drug’s final approval.

**Clinical Trials**
A major outcome of drug development is to make a recommendation of the dose and schedule to be used the first time an NCE is used in a human clinical trial ("first-time-in-humans" [FTIH] or “First Human Dose” [FHD]).

Clinical trials are commonly classified into several phases. Each phase has a different purpose and helps scientists answer a different question. The full clinical trials process will normally take many years to complete.

- **Phase 1: Screening for safety**
  Phase 1 trials (some organisations split them into ‘Phase 0’ and ‘Phase 1’ trials) are the first-in-human trials. Researchers test an experimental drug or treatment in a small group of healthy volunteers (typically 20-80 people) to evaluate its safety, determine the therapeutic dosage range and identify any major side effects. The trials will clarify that the drug can reach the targeted body area and remain there long enough to deliver its benefits. They will gain preliminary evidence that it could offer therapeutic value or prevent the disease or condition. Phase 1 may take several months.

- **Phase 2: Establishing efficacy**
  In Phase 2 trials, the experimental treatment is given to a group of patients (perhaps 100-300) who actually have the disease to see if it is effective. At this stage, the performance of the medicine may be compared against a group of patients receiving a placebo. A placebo is a treatment that looks the same as the potential new medicine but has no active ingredients. It is important that neither the patients nor the researchers have any idea which volunteers receive which treatment. This is known as double blind placebo-controlled trial and ensures there can be no bias in the reporting of the results. Phase 2 may take up to 2 years.

- **Phase 3: Main trial – efficacy, safety and dosage**
  In Phase 3 trials, the treatment is given to large groups of patients (typically 1,000-3,000) to confirm its effectiveness, determine side effects, compare it to commonly used treatments, and collect information that will allow it to be used safely (eg. dosage levels). Phase 3 trials might take up to 4 years and are very expensive to run.

  If the drug successfully passes through Phases 1, 2, and 3, it can be submitted for approval by the national regulatory authority for use in the general population. Approval may be subject to caveats, including requirements for further evaluation.
• **Phase 4: Post-approval studies.**
  Studies after the medicine is launched on the market allow information to be collected from a much larger number of patients and so to improve knowledge about the treatment’s risks, benefits, and optimal use.

  
  
  Key learning points:
  
  - Pre-clinical testing of NCEs provides the first indications of likely occupational hazards from the drug.
  - Chemical Development leads to the choice of synthetic route for manufacture of the Active Pharmaceutical Ingredient (API) and strongly influences the occupational hygiene issues that will occur.
  - Formulation determines the physical characteristics of the API and the excipients that will be used, both of which will have an important impact on occupational exposures.
  - Clinical trials proceed via phased testing which may take years before the drug is authorised for marketing.

1.2.3 **Manufacturing**

The industry typically divides the manufacturing process into two stages:

**Primary manufacture**

The Active Pharmaceutical Ingredient (API) is synthesised from raw materials as a bulk powder or liquid, usually via a series of intermediates. The manufacturing processes are usually based upon chemical synthesis, but sometimes the starting point for the synthesis will be a complex molecule produced by fermentation, for example in the production of antibiotics. Other common manufacturing techniques include extraction and purification of naturally occurring compounds. The increased use of biotechnology will result in the development of more novel means of production, for example, the isolation of protein based drugs in the milk of genetically modified sheep.

Manufacture of pharmaceutical intermediates is a fine chemicals operation usually carried out in batch processes. The manufacture of these intermediate forms, is generally considered to be part of the fine chemicals industry. Only final creation of the active drug substance itself is considered to be part of the pharmaceutical industry proper.

Plant capacities vary considerably. Capacities can be 50-100 tonnes per annum for high volume plant producing oral antibiotics, whilst only a few kilograms per annum may be required for very potent drugs, or drugs with limited applications.
New primary plants may be designed to handle a range of highly potent and specific actives. These general-purpose plants are specifically designed for ease of cleandown and modification to allow a variety of products to be readily manufactured. The key to these plants is flexibility.

As in the rest of the fine chemicals industry, a wide range of materials may be used in primary processes including organic solvents, chemical intermediates, liquid chemical reagents, inorganic solids, inorganic and organic acids, bases and organo-metallic compounds.

**Secondary production**

It is during secondary manufacture that a recognisable pharmaceutical product is made. During secondary manufacture the Active Pharmaceutical Ingredient (API) produced at the primary manufacturing site is formulated with excipients (non-active ingredients, such as preservatives, flavouring etc) and processed in a wide variety of ways into the final dosage form: tablets, capsules, injectable products, aerosol inhalers, syrups etc for onward packaging and ultimately supply to the patient.
Secondary manufacture reflects the traditional view of the pharmaceutical industry, with high standards of cleanliness and product/operator segregation.

Common dosage forms produced in secondary operations include:
- Oral Solid Dose products (tablets, capsules etc)
- Sterile products (vials, syringes, ampoules, eye drops etc)
- Inhaled products (aerosol inhalers, clean liquid devices for seasonal rhinitis etc)
- Topical products (patches, creams & ointments).

This secondary conversion into final dosage form may not necessarily all occur at one time or indeed at one site or in one country. Processes requiring specialist equipment or expertise (such as spray granulation) may be undertaken at one site with the partly processed material being off-loaded into bulk containers. These bulk products, tablets for example, may then be transferred to another site for final processing or packaging.

At large secondary sites, a broad range of products may be manufactured and packaged into hundreds of different presentations which may then be shipped to more than a hundred countries worldwide. This complexity of operation requires sophisticated planning and logistics capabilities to operate efficiently.

**Key learning points**
- Manufacturing is typically divided into primary and secondary stages.
- Primary manufacture of the API involves a range of chemical processes, typically in batch production, with concomitant occupational exposures to intermediates and solvents as well as the API.
- Secondary production involves formulation to create the finished product, which can take a wide range of forms.
1.3 Commercial pressures on the industry

1.3.1 The Blockbuster Model
In 1977, Tagamet, an ulcer medication, became the first ever “blockbuster” drug, earning its manufacturers more than USD($)1 billion a year and its creators the Nobel Prize. This marked a new departure as companies competed to be the developer of the next big blockbuster, and many achieved great success. Eli Lilly released the first selective serotonin reuptake inhibitor (SSRI), Prozac, in 1987, once again revolutionising health practice. The first statin blockbuster, to protect against heart disease, was also approved in 1987, manufactured by Merck (MSD).

One problem with the blockbuster model of pharmaceutical industry is that when the patent on the drug runs out, income reduces very quickly. This is sometimes called the “patent cliff”. For example, Pfizer annual sales for the blockbuster cholesterol-cutting drug Lipitor peaked at USD($)12.9 billion but after the loss of U.S. exclusivity in 2011 when competing generic versions became available, total sales fell 80% in little more than a year. The blockbuster model therefore requires a constant stream (or “pipeline”) of new blockbuster drugs to maintain company revenue.

Candidates for a new drug to treat a disease might theoretically include from 5,000 to 10,000 chemical compounds. On average about 250 of these will show sufficient promise for further evaluation using laboratory tests, mice and other test animals. Typically, about ten of these will qualify for tests on humans. A study covering the 1980s and 1990s found that only 21.5 percent of drugs that start Phase I human trials are eventually approved for marketing, and the success rate is decreasing as drug manufacturers take on more challenging areas like Alzheimer’s, arthritis and cancer. The high failure rates associated with pharmaceutical development are referred to as the "attrition rate". Careful decision making during drug development is essential to avoid costly failures.

The full cost of bringing a new drug (i.e. a drug that is a new chemical entity) to market - from discovery through clinical trials to approval - is complex and controversial. One element of the complexity is that the much-publicised final numbers often do not include just the simple out-of-pocket expenses, but also "capital costs", which are included to take into account of the long time period (often at least ten years) during which the out-of-pocket costs are expended; it is often not stated whether a given figure includes the capitalized cost or comprises only out-of-pocket expenses. Another element of complexity is that all estimates are based on confidential information owned by drug companies, released by them voluntarily. There is currently no way to validate these numbers. The numbers are controversial, as drug companies use them to justify the prices of their drugs and various advocates for lower drug prices have challenged them.

A study published in 2010 which compares many of the studies, provides both capitalised and out-of-pocket costs for each, and lays out the assumptions each makes. The authors offer their own estimate of the capitalized cost as being USD($)1.8billion with out-of-pocket costs of around USD($)870M. An independent UK study in 2012 produced similar figures. More extensive regulation
and complex science also mean that time from drug discovery to market has increased from around 8 years to an average of 13.5 years.

**Key learning points**

- Development of a new drug is lengthy and extremely expensive, creating very high risk for the pharmaceutical companies conducting the research.
- Intellectual property rights to new drugs are protected by the patent system and a financial “cliff edge” looms when the patent expires.
- Research-based pharmaceutical companies need a constant stream of new blockbuster drugs to maintain their revenues.

### 1.3.2 The Generics industry

Traditionally pharmaceutical companies have been divided into two main types: research-based companies and generic companies.

The research-based companies invest heavily in the discovery and development of new medicines through to launch in the marketplace where the tremendous investment made during the development programme must be recouped, primarily during the patent period.

The second major type of company is the generics manufacturer. Generic companies manufacture and market pharmaceuticals developed by the research-based companies once patent protection expires. Without the extensive infrastructure and investment required for drug discovery and development, generics companies have the potential to significantly undercut the prices of the research based companies. This is attractive to governments and health insurers who are trying to keep down the costs of healthcare. It can also make medicines affordable in developing countries.

The introduction of competition by generics prevents any single company from dictating the overall market price of the drug. Competition is also seen between generic and name-brand drugs with similar therapeutic uses when physicians or healthcare plans adopt policies of preferentially prescribing generic drugs.

The generics industry remained relatively small scale until in the 1970s new regulations revoked permanent patents and established fixed periods on patent protection for branded products. As a result companies flourished by producing generic products and they started earning huge profits. From 1978, India took over as the primary centre of pharmaceutical production of bulk drugs and products without patent protection. In the US, the Hatch-Waxman Act of 1984 was introduced to encourage and regularise production of generic copies.

Over subsequent decades, the market for generics has grown dramatically. According to the Association for Accessible Medicines in the United States (formerly the Generic Pharmaceutical
Association), 89% of all US prescriptions are now filled with generic medicines and the use of generic drugs generated USD($)1.2 trillion in U.S. healthcare savings over the 10-year period 2003-2012.

Most countries require generic drug manufacturers to prove that their formulation exhibits “bioequivalence” to the original product. This does not necessarily mean that they contain exactly the same active ingredients as, for example, there may be differences in salt composition. Demonstrating bioequivalence becomes more difficult with the newer drugs that are based on large molecule “biologics” such as peptides and recombinant proteins. New provisions are being introduced to allow “biosimilar” products to be licensed as generics based on a thorough demonstration of "comparability" of the "similar" product to an existing approved product.

Key learning points

- Generic companies manufacture and market off-patent pharmaceuticals, giving them much lower costs and risks than research-based companies.
- Generics now dominate the markets for prescription pharmaceuticals because they save money for healthcare systems.
- Generic drug manufacturers are typically required to prove that their formulation exhibits “bioequivalence” to the original product.

1.3.3 Intellectual Property

Patents protect research-based drug companies from direct competition for a limited period by providing proprietary rights for innovative pharmaceutical compounds. Given a technical environment where products are difficult to develop but easy to copy, the pharmaceutical industry is particularly dependent upon the patent system. Patent lifetime differs from country to country. In the US, drug patents give 20 years of protection, but they are applied from before clinical trials begin, so the "effective" life of a drug patent tends to be between seven and 12 years from market launch.

Patents allow pharmaceutical companies to recover the costs of their research and development efforts, thereby stimulating them to engage in such efforts in the first place. One study concluded that 65% of new drugs would not have been commercially introduced in the absence of patent protection.

Patents, however, have created both commercial risks and public relations problems for the research-based companies. The industry has become more focussed on marketing to maintain market share against generic competition, on lobbying politicians to protect commercial interests, and enforcing legal claims on intellectual property rights. These activities have generated greater suspicion of the industry amongst the public at large.
The use of patents for pharmaceuticals has long been controversial, but it was the arrival of Acquired Immune Deficiency Syndrome (AIDS) that led to global challenges to the patent system. The first fatal cases of AIDS were reported in California in 1980. By 1991, the World Health Organisation estimated that 10 million people were infected worldwide. WHO now estimates that, since its discovery, AIDS has caused 35 million deaths (as of 2017) with more than 70 million people infected including children.

The origins and transmission routes of the disease were initially a mystery. Although the first cases arose in the homosexual community, cases were soon identified in heterosexuals, as well as in drug users and haemophiliacs. Public alarm was exacerbated by media stories about promiscuity and drug abuse and speculation about possible infection routes.

Intensive research eventually identified a viral pathogen which is now known as Human Immunodeficiency Virus (HIV). The virus can remain latent for a number of years in the lymph nodes while actively multiplying before it rapidly destroys the T-lymphocytes which mediate the body’s normal immune response. Death occurs from opportunistic infections, tumours or dementia that would normally be defeated by the immune system.

The virus is now believed to have evolved from a related virus in African monkeys, which crossed into humans around 1940. It has already mutated into a number of different forms, indeed HIV is one of the most variable viruses known.

Identifying suitable treatments posed many challenges for the industry, although the first helpful medication, azidothymidine (AZT), was applied as early as 1985. Drug resistant forms of HIV have already emerged. Current best practice is to apply a combination of drugs, which in many cases induces remission and reduces AIDS from a fatal condition to a manageable one. By 2010, however, the cost of such treatment was around USD($) 20,000 per annum, clearly beyond the means of the poorer countries where HIV/AIDS is most prevalent.

Patent protection meant that the drugs could not be manufactured locally without the agreement of the patent owners, the rules being set under the World Trade Organization (WTO) Agreement on Trade-Related Aspects of Intellectual Property Rights (the “TRIPS Agreement”). Some countries introduced “compulsory licences” that allowed competitors to use the patented invention without the patent owner’s permission. This brought the pharmaceutical industry into legal conflict with the governments of countries like South Africa and Brazil. In the case of HIV/AIDS, it has eventually resulted in supply of pharmaceuticals at differential prices and through local companies under licence.

Differential pricing created a further problem for the pharmaceutical industry because of “parallel importation”, where drugs acquired in a lower-priced country are imported into a higher-priced country without the authorisation of the patent holder, thereby undercutting the normal price in that country.
Patent disputes continue. Companies have sometimes sought to extend patent protection by introducing improved variants of existing treatments.

India has revoked patents and denied applications for a number of such products, including cancer treatments, and has allowed local manufacturers to make the same products. Some international companies are suing Indian generic manufacturers for copying their products. In 2017 the TRIPS agreement was modified to secure for developing countries a legal pathway to access affordable generic drugs under WTO rules.

Key learning points

- Patents protect new products from direct competition for a limited period of time, often 7-12 years beyond launch.
- Patents provide an incentive for research and development by allowing pharmaceutical companies to recover their investment.
- Constant legal challenges by generics industry create “cliff edge” risks to sales for R&D companies.
- Patent protection supports high prices and has become a major public relations issue for research-based pharmaceutical companies.
- Developing countries have fought against patents and high prices for essential drugs.
- The World Trade Organization “TRIPS” agreement governs the access to patent protected and affordable generic drugs in developing countries.
- Differential pricing has produced new issues such as parallel imports and continues to be controversial.

1.3.4 Litigation and Liabilities

The cost and practicability of clinical trials means that new medicines are typically tested on only a few hundred patients. Once they receive marketing authorisation, they may be taken by thousands or millions of patients. Hence side effects that were not noticed during testing may become apparent after the launch. They may lead to health damage or even death of patients, with consequent litigation and massive liabilities as well as loss of sales for the companies. As examples:

- GSK’s Avandia (rosiglitazone) for Type 2 diabetes. First released in 1999, annual sales peaked at approximately USD($)2.5bn in 2006, but declined to around USD($)9m in 2012 after the drug was found to increase risk of heart attacks. It was estimated to have caused 83,000 heart attacks in the United States alone. Adverse effects caused by rosiglitazone became the subject of over 13,000 lawsuits against GSK and the company was fined USD($)3bn by US authorities in 2012.
- Merck’s Vioxx (rofecoxib), a nonsteroidal anti-inflammatory drug (NSAID) used as a painkiller for arthritis that was voluntarily withdrawn over safety concerns. Shortly before the FDA
approved Vioxx in 1999, Merck launched a study it hoped would prove that Vioxx was superior to older painkillers, because it caused fewer gastrointestinal problems. Instead, the study would eventually show Vioxx could cause heart attacks and strokes. Research published in the medical journal Lancet estimates that 88,000 Americans had heart attacks from taking Vioxx, and 38,000 of them died. In November 2007 Merck announced it would pay USD($)4.85 billion to end thousands of lawsuits. The amount, to be paid into a so-called settlement fund, was believed to be the largest drug settlement to that date. Merck emphasized that it did not admit fault.

Concern over such side effects has accelerated industry efforts to seek more targeted therapies. For example, targeted cancer therapies are designed to block the growth of cancer cells by interfering with specific molecules needed for carcinogenesis and tumour growth, rather than by simply interfering with rapidly dividing cells as in traditional chemotherapy. They may be more effective than current treatments and less harmful to normal cells, reducing the likelihood of side effects.

Companies have also been accused of hiding adverse research findings. Pharmaceutical manufacturers, like other businesses, keep many details of their research and development (R&D) secret to gain and preserve a competitive advantage. Traditionally, data they collect while conducting clinical trials have been considered confidential along with other business information. However, instances of incomplete disclosure of safety data and delayed discovery of risks of widely used drugs have raised questions about the limits of this secrecy and whether the regulatory bodies make sufficient provision for public access to drug-safety data.

Drug companies point to the economic value that preclinical and clinical trial data may have for generic manufacturers and other competitors, including those seeking approval of rival products in international markets. Balanced against the need to protect companies’ investments in drug development, however, is the risk that withholding this information can frustrate accurate evaluation of drug safety.

When GlaxoSmithKline studied the use of its antidepressant paroxetine (Paxil) in treating major mood disorders in paediatric patients, it found indications that the drug might have increased the risk of suicidal thoughts in this population. In 2004 the New York attorney general charged that GlaxoSmithKline had fraudulently concealed adverse findings from two studies of the proposed use. A lawsuit for this and other charges was settled for USD($)3 billion in 2012. GSK now makes the detailed raw data underlying its clinical trials systematically available to researchers, which has been heralded as the start of a new era of public disclosure.
**Key learning points**

- Clinical trials may not be large enough to detect side effects which become apparent once a drug is launched into a mass market.
- Such side effects may prove harmful to patients and can lead to litigation against the manufacturers.
- Fines and penalties can cost a company millions or billions of dollars.
- Concern over such side effects has pushed the industry towards seeking more targeted therapies.
- Companies have also been accused of hiding adverse research findings. The issue has badly affected trust in the sector.
- The industry is now moving towards full disclosure of clinical trial data.

### 1.3.5 Commercial Responses

Companies have responded to these various commercial challenges in a range of different ways. There has been more pressure to reduce costs, more outsourcing of business processes, more acquisitions of smaller companies that perhaps retain more innovative entrepreneurialism, and more merging and restructuring of large companies. New technologies are adding to the pressure and opportunities for new commercial alignments. The industry is in a state of flux and undergoing rapid change.

Mergers solve some problems, but not others. For example, they can make better use of commercial infrastructure but they don’t improve research and development productivity. It is new scientific and technological approaches, and an ability or willingness to redesign the development process that have been shown proven to improve productivity.

The failure of big mergers and acquisitions to deliver on the innovation front, is helping to drive a shift away from in-house research towards an "innovation ecosystem," in which pharma companies mix corporate research with universities, research charities and small or medium-sized biotechs.

The continuing pressure on pharmaceutical pricing has also resulted in a geographical shift of the industry. Initially this was most evident in manufacturing, where production was relocated to emerging economies with lower wage costs. More recently, with improved standards of education in countries like India and China, there has been a migration of research and development. Lower tax rates and development incentives have also played a part in driving relocation.

This migration has brought with it numerous supply chain issues that can affect occupational health and safety, protection of the environment and product quality. Local regulations and practices vary from country to country and it is difficult for global employers to achieve consistent standards.
Many large companies have therefore developed their own standards for safety and environmental issues including occupational hygiene. Hygienists with responsibilities for multiple sites or countries will often find themselves having to make difficult judgments about the acceptability of working practices and may encounter conflicts with the natural inclinations of local management.

Mergers, acquisitions, divestitures and organisational changes can massively disrupt established protocols and management systems. Hygienists may find themselves having to adapt to new internal standards, ways of working and resource levels.

**Key learning points**

- Commercial pressures often have indirect impacts on health and safety in the workplace, whether through cost pressures, regulatory changes or geographical relocation.
- Hygienists may need to adapt to changes in organisational structure and resources, or changed management systems and processes.
1.4 Present and Future Trends

The trends in the development of pharmaceuticals are driven by market factors and the sociopolitical pressures as much as by medical need. National policies in many countries are being implemented to rein in spending on expensive therapies, increase the use of generics, address pricing through price cuts or indirectly via discounts or rebates, and develop a market for biosimilars as a lower-cost alternative to original biologics.

The fast-growing emerging markets are driven predominantly by national economic gains and rising personal incomes. This rise in incomes, particularly for the lowest earners, coupled with government commitments to support expanded access to basic healthcare services, will make medicines more broadly available and affordable to millions of people. Despite this progress, however, significant gaps remain in the drug arsenal for the underprivileged, especially in developing nations.

However, new therapies for a range of diseases affecting both developed and developing world populations are currently, or will soon become, available transforming patient care. Bioinformatics (computing), biotechnology and genetics have allowed great leaps forward in both development and production of new drugs. There are now possibilities to create more effective drugs with fewer side effects by targeting the pharmaceutical action much more closely.

The number of biotechnologically produced pharmaceuticals is increasing rapidly. Some of these molecules such enzymes and hormones or hormone-like compounds as well as small molecules coming from biotech processes have their very specific toxicological and pharmacological characteristics and need to be assessed individually.

Starting with the production of biosynthetic insulin in the 1970s, genetic modification has allowed production of human proteins by bacteria. And biological drugs such as the monoclonal antibodies, introduced around the turn of the millennium, hint at a whole new panorama of far more specific drugs that could impact on human health as much as the medicines of last century.

In this section, we will look at the some of the emerging technologies that hygienists might encounter, which are changing both the nature of pharmaceutical manufacturing and the hazards found in the workplace.

1.4.1 Genetics and Personalised Medicine

Each of us is born with inherited traits passed down from our parents. This information is called our genome. It is encoded in a long chain molecule called DNA (deoxyribonucleic acid). DNA occurs naturally in a double stranded helical form, with each strand complementary to the other. Each strand can act as a template for creating a new partner strand, which is how life is replicated.

DNA molecules are composed of chemical groups called nucleotides. There are only 4 types of nucleotides - Adenine, Cytosine, Thymine and Guanine - represented by four chemical letters: A, C, T and G. It is the sequence of nucleotides (eg. ATTCCGGA) that determines our biology. The human genome has around three billion nucleotides. Segments of the DNA molecules, comprising a shorter
sequence of nucleotides that confer particular biological properties, are known as genes. The gene is the molecular unit of heredity of a living organism.

Inside cells, the DNA code is translated to create (or “express”) long chains of amino acids called proteins. Proteins perform a vast array of functions within living organisms, including replicating DNA, responding to stimuli, and transporting molecules from one location to another. Enzymes are proteins that catalyse metabolic reactions. The order of amino acids in a protein corresponds to the order of nucleotides in the gene.

Life processes are controlled by small molecules that interact with the proteins and the DNA. Most pharmaceuticals use small molecules to treat disease. New understanding of the genome now creates the possibility of personalised precision drugs that target specifically the particular genetic features of a disease. These drugs may be more effective and better tolerated and may eventually displace the one-size–fits-all drugs. Cancer treatment is one of the first areas to benefit as antibody-drug conjugates are already in development and production for a number of pharmaceuticals. This technology also holds promise for reduced toxicity to the worker as the linkage between the antibody and API reduces its potential for harming healthy cells while targeting only diseased cells.

The study of how an individual's genetic inheritance affects the body's response to drugs is called pharmacogenomics. It holds the promise that drugs might one day be tailor-made for individuals and adapted to each person's own genetic makeup. Environment, diet, age, lifestyle, and state of health all can influence a person's response to medicines but understanding an individual's genetic makeup is thought to be the key to creating personalized drugs with greater efficacy and safety.
Key learning points

- Analysis of the human genome is now enabling us to identify genetic issues that might predispose people to illnesses.
- Genetic factors also influence whether a particular medication is likely to be effective for an individual patient.
- Genetic testing opens the possibility of personalised medicine with greater efficacy and fewer side effects.

1.4.2 Gene Therapy

We each have millions of variations in nucleotide sequence and most of these seem benign, but a single letter difference in DNA between individuals – known as a single nucleotide polymorphism (SNP) - can sometimes be a marker for disease.

By comparing cancer patients with healthy controls, scientists have identified genetic differences that occurred repeatedly in the cancer group. For example, SNPs have been found associated with breast cancer, prostate cancer and ovarian cancer. These provide targets for medical intervention.

**Genome editing** (or gene-editing) is a group of technologies which allow potentially harmful SNPs to be deleted, modified or replaced with “healthy” genes. The most common method of gene editing today is commonly known as CRISPR, standing for 'clustered regularly inter-spaced short palindromic repeats'. It is sometimes referred to, more completely, as CRISPR/Cas9. Cas9 is an enzyme known as ‘CRISPR-associated protein 9’ which snips the genome at the exact place to insert the new or modified gene.

Altering genes to correct genetic defects and thus prevent or cure genetic diseases is known as gene therapy. Potentially, it allows doctors to treat a disorder by inserting a gene into a patient’s cells instead of using drugs or surgery.

The first gene therapy products were approved in 2017 for acute lymphoblastic leukaemia and diffuse large B cell lymphoma. Although gene therapy is a promising treatment option for a number of diseases (including inherited disorders, some types of cancer, certain viral infections, haemophilia and a multiplicity of rare diseases), the technology is new and still under study to make sure that it will be safe and effective. It also raises ethical concerns which are being hotly debated.

Key learning points

- Gene-editing is now possible and opens the possibility of gene therapies to prevent or cure diseases that were previously untreatable.
- Technical and ethical issues are still under study.
1.4.3 Epigenetics

Another area holding medicinal promise is epigenetics. Epigenetic changes modify the action of certain genes, without changing the sequence of nucleotides in the DNA. In essence, they switch genes on and off.

Epigenetic changes can result from many factors, including development in utero and in childhood, environmental chemicals, drugs and pharmaceuticals, aging, and diet. Two common mechanisms are:

- DNA methylation, which occurs when methyl groups, found in some dietary sources, become attached to DNA and activate or repress genes.
- Histones modification, when DNA winds itself around histone proteins changing the availability of genes in the DNA to be activated.

![Epigenetic Factors](source: National Institutes of Health, via Wikipedia)

It is likely that epigenetic changes can be triggered by adverse environmental factors such as bad diets or smoking. They are thought to play a role in cancer, autoimmune disease, Alzheimer’s disease and diabetes among other illnesses.

Epigenetic cancer drugs have now been approved to inhibit both methylation and histone pathways. They tend to have side effects such as immunosuppression, lack of appetite and vomiting but many more epigenetic drugs are now under development. These second-generation drugs are more selective and should have reduced side effects.
Key learning points

- Epigenetic changes can activate or regulate genes.
- New epigenetic drugs are being developed and some are already approved.

1.4.4 Monoclonal Antibodies

Antibodies are proteins produced naturally by the B lymphocytes of the immune system in response to foreign proteins, called antigens. Antibodies function as markers, binding to the antigen so that the antigen molecules can be recognized and destroyed by phagocytes.

**Monoclonal antibodies** (mAb or moAb) are antibodies that are all identical because they are made from immune cells that are all clones of a unique parent cell. In contrast, antibodies obtained from the blood of an immunized animal are polyclonal because they are made from many different immune cells.

Given almost any substance, it is possible to produce monoclonal antibodies that specifically bind to that substance. When used as medications, the generic drug name ends in –mab.

Monoclonal antibodies have already been used for autoimmune diseases. Examples are adalimumab (Humira®), which has become the world’s top-selling drug, and infliximab (Remicade®), both of which are effective in rheumatoid arthritis, Crohn’s disease and ulcerative colitis.

One possible treatment for cancer involves monoclonal antibodies that bind only to cancer cell-specific antigens and induce an immunological response against the target cancer cell.

Such monoclonal antibodies can also be modified for delivery of a toxin, radioisotope, or other active agent, creating antibody-drug conjugates which have been called “**armed antibodies**”. There are lots of possibilities for different combinations of small molecules with antibodies to address a range of diseases.

Most monoclonal antibodies have very high molecular weights (around 150 kDa). Their bioavailability by ingestion and by skin contact is near zero, and it is also very low by inhalation. For this latter route, industry bases its scenarios on worst case assumptions of 1 to 5% systemic absorption. The true figure is probably lower. Therefore, monoclonal antibodies, even if they have a target in the healthy worker, cause systemic workplace exposures that are many orders of magnitude below the internal exposure of patients.

In animal tests, reproductive effects have been found when given parenterally in therapeutic doses or higher. As no formal bioavailability studies exist, it has been suggested that the compounds and their formulations should be handled as if labelled toxic to reproduction, and that pregnant and breast-feeding women should be excluded from their occupational handling. Such proposals are based on a confusion of hazard with risk.
There is also concern about the possibility of sensitization from monoclonal antibodies but none has yet been reported.

Depending on the manufacturing process, antibody-drug conjugates contain higher or lower amounts of unbound small (generally highly active) molecules. These amounts are an important determinants of occupational risk, along with the actual toxicological and pharmacological characteristics of the small molecule itself.

**Key learning points**

- Monoclonal antibodies are produced by cloning from a single immune cell.
- They are often effective against auto-immune conditions and several of the world’s top selling drugs are monoclonal antibodies.
- Therapeutic monoclonal antibodies are usually identified by the suffix -mab in their name.
- Monoclonal antibodies usually have very low bioavailability which reduces the risk to workers.
- Some monoclonal antibodies are “armed” with a drug or toxin to be delivered to the target cells. Residual free drug content may pose a risk to workers.
1.5 Related Industries

1.5.1 Biotechnology and Biopharmaceuticals

Biotechnology is the use of living systems and organisms to develop or make useful products. The modern biotech industry uses a wide range of processes, combining knowledge from biology with chemical engineering.

The industry now produces biopharmaceuticals, which are large, biologically active molecules. The term includes proteins (including antibodies, enzymes, some vaccines) and nucleic acids (DNA, RNA or antisense oligonucleotides) used for therapeutic or in vivo diagnostic purposes, and produced by means other than direct extraction from a native (non-engineered) biological source. While this definition is broad, it does exclude some APIs derived from fermentation processes, e.g. penicillin and cephalosporin antibiotics.

These molecules are developed to target specific areas within the body, something which is hard to achieve using the simpler smaller molecules historically produced by the pharmaceutical industry.

Due to the nature of the molecules produced, biopharmaceuticals cannot normally be taken orally since they would be broken down in the stomach and intestines. As a result, biopharmaceuticals tend to be given by injection.

Some of the biopharmaceutical products now available are:

- Blood-clotting factors (e.g., Factor VIII and Factor IX)
- Thrombolytic agents (Tissue Plasminogen Activator)
- Hormones (Insulin, Glucagon, Human Growth Hormone, gonadotropins)
- Haematopoietic growth factors (e.g. erythropoietin)
- Interferons (Interferons-α, -β, -γ)
- Interleukin-based products (Interleukin-2)
- Protein-based vaccines (Hepatitis B surface antigen)
- Monoclonal antibodies
- Non-hormonal, non-antibody peptides and proteins
- Additional products (tumour necrosis factor, therapeutic enzymes)

One commercial advantage arising from biopharmaceuticals being complex biological molecules is that they cannot be easily copied, and hence they are less prone to the “patent cliff”. Unique cell lines are utilised to make the regulated products so competitors have to demonstrate that their process produces “biosimilar” materials that have equivalent properties.

Biotransformation is the chemical conversion of a substance mediated by living organisms or enzyme preparations derived therefrom. Once isolated, the use of living organisms means that the
process can be done relatively easily/cheaply. Compared with other chemical processes, biotransformations can be very specific in terms of chirality, position and functional group. Biotransformation is a minor part of industrial biotechnology but benefits from the significant ongoing investment in technical innovation applied to products of very high value (eg. therapeutic proteins, cosmetics). It can often mean that solvent based chemical processes are replaced with aqueous biological ones, with increased mass efficiency and simple, less toxic starting materials and reagents.

Biopharmaceuticals are typically associated with the use of genetically altered microorganisms, animals and plants. Some examples include:

- The use of genetically altered Ecoli to make a synthetic human insulin.
- The use of yeast in the manufacture of antibiotics.
- Developing molecular diagnostic devices that can be used to define the target patient population for a given biopharmaceutical.
- Cheaper manufacture of human growth hormone, clotting factors for haemophiliacs, fertility drugs, enzymes, erythropoietin and other drugs.

It is now possible to create through synthetic biology, new molecules and potentially even new life forms. Biosafety and biosecurity concerns are the understandable response to this new science and technology that have the potential to profoundly change the nature of life forms as we know it.

Key learning points

- Biotechnology uses living systems or organisms to make biopharmaceuticals.
- Biopharmaceuticals are large molecules which can address very specific targets in the body opening up new therapeutic options.
- Examples include antibodies, enzymes and some vaccines.
- They can often be produced in aqueous solutions rather than in organic solvents which reduces risks to workers and environmental issues.
- The use of genetically altered organisms creates some novel safety and ethical concerns.
- Biopharmaceuticals are often administered by injection rather than orally.
1.5.2 Vaccines

Development of Vaccines

A vaccine is a biological preparation that improves immunity to a particular disease. It typically contains an agent that resembles the disease-causing microorganism, and is often made from weakened or killed forms of the microbe, its toxins or one of its surface proteins. The agent stimulates the body's immune system to recognize the agent as foreign, destroy it, and "remember" it, so that the immune system can more easily recognize and destroy any of these microorganisms that it later encounters.

Vaccines may be used as a prophylactic to prevent or ameliorate the effects of a future infection, or therapeutic (e.g. vaccines against cancer are also being investigated).

Most commonly, vaccines are used against viruses. Unlike bacteria, viruses can only replicate inside the cells of a host. They consist of two or three parts:

i) the genetic material made from either DNA or RNA, long molecules that carry genetic information;

ii) a protein coat that protects these genes;

iii) in some cases, an envelope of lipids that surrounds the protein coat when they are outside a cell.

In size, they are typically about 100 times smaller than bacteria and often too small to be visible under a light microscope, with some as small as 25nm.

The first vaccine against a virus was invented in 1796 by Edward Jenner, a doctor in rural England. Jenner discovered that immunity to smallpox could be produced by inoculating a person with material from a cowpox lesion. Cowpox is a virus in the same family as smallpox which causes only mild effects in humans. Jenner called the material used for inoculation a “vaccine”, from the root word vacca, which is Latin for cow. Smallpox was responsible for an estimated 300–500 million deaths during the 20th century. After vaccination campaigns throughout the 19th and 20th centuries, the WHO certified the eradication of smallpox in 1979.

Vaccines followed against whooping cough, mumps, meningitis, diphtheria and polio amongst other potentially lethal diseases. Immunisation campaigns in developed countries have greatly reduced the death toll from these viruses. Viruses remain responsible for a great deal of morbidity, with the common cold accounting for 35% of acute medical illness and influenza a further 40%). Viruses are also responsible for many sexually transmitted infections and childhood diseases like chicken pox.

In developing countries, however, there is much greater mortality. There are millions of deaths each year from measles, influenza, rotavirus (which causes gastroenteritis), yellow fever, dengue fever and other viral infections. The Human Immunodeficiency Virus (HIV) which causes Acquired Immunodeficiency Syndrome (AIDS) is less infectious but no vaccine has yet been developed.
Vaccines in general have a low incidence of side effects or adverse reactions and so mass immunisation programmes have proved viable. However, reactions do sometimes occur, including reactions to the microorganism when attenuated live virus is used, and allergic reactions to other constituents of the vaccine preparation (e.g. albumen).

Thiomersal is an organomercury compound used as a preservative in vaccines since the 1930s to prevent bacterial and fungal contamination. It caused a major controversy when it was alleged to be linked with the development of autism in vaccinated children and led to a massive fall in vaccination rates. Subsequent research has disproved the hypothesis but public concerns linger. Since the 1990s, the industry has substantially reduced the use of thiomersal.

The recent introduction of gene technology into vaccines can produce cleaner synthetic vaccines with fewer side effects. In simple form, DNA fragments are inserted into plasmids (see above under antibiotic resistance) which are replicated in cells of *E. coli* or yeast bacteria and act as stimulants for the immune system against a particular virus. This ‘recombinant DNA’ technology is used in Hepatitis B vaccine, and in the vaccines (Cervarix and Gardasil) against Human Papilloma Virus (HPV) which causes cervical cancer.

Gene technology has also created opportunities for new types of therapeutic vaccines that can treat active cancer, by creating proteins that will stimulate the immune system to fight the cancer cells.

**The Vaccine Industry**

The industry is subject to market and financial forces that include lower profit margins than pharmaceuticals, costly research, development and production as well as liability concerns. The up front development costs of vaccines are substantial (USD($) 0.5 – 1 billion). In addition, the timescale involved can be up to 15 years.

A relatively small number of companies account for most of the worldwide vaccine market. These include GlaxoSmithKline, Merck, Novartis, Sanofi Pasteur, and Pfizer.

In recent years there has been an increased interest in the vaccine market. This has largely been fuelled by technological advances which allow for the manufacture of vaccines aimed at influenza, AIDS and cancers. The industry accounts for only about 2% of total pharmaceutical sales but is one of the fastest growing sectors.

Small biotechnology companies often play a significant role in the vaccine industry by improving upon vaccine technologies and development at early stages of research. Nearly without exception, however, the high cost and challenges of large-scale vaccine development and testing requires partnerships between these small firms and the major manufacturers.

Commercial companies do not build large amounts of spare capacity into their manufacturing capabilities. This means that high demand for vaccines such as during epidemics there is an
inevitable under supply. Shortages of vaccines can force public health policy makers and physicians to alter immunization schedules. This in turn puts the population at risk from infections.

Differences in production standards and regulatory requirements in different countries also mean that it can be difficult or even impossible to import vaccines. This may even apply to slightly different formulations of vaccines produced by a manufacturer of a licensed vaccine in a particular country.

Historically the development of vaccines has been undertaken by pharmaceutical companies who have been driven by a commercial supply and demand model. Many infectious diseases occur in populations which are unable to pay for medication and in countries where the governments are less able to influence the research and development agenda. Increasingly, not-for-profit institutions such as the Bill and Melinda Gates Foundation have been playing a role in funding vaccine research and development.

**Occupational Hygiene Issues in Vaccine Manufacture**

A number of occupational hygiene issues arise in vaccine manufacture:

- Biosafety is mostly Level 1 in production because live virus is not used. However, higher levels may be needed in research laboratories.

- Sterilization of vaccines may use chemicals such as ethylene oxide, hydrogen peroxide and ozone, though ethylene oxide is becoming less common. Typically, sterilizers are fitted with safety interlocks that prevent opening until the gas has dispersed. There are also sterilization techniques using ionising (gamma or electron beam) radiation. Steam sterilization using autoclaves may be an alternative option but can damage sensitive materials. Steam sterilization of waste may be required to avoid possibilities of gene transfer in soil and development of antibiotic resistance.

- Fumigation of aseptic areas (used for sterile products) may use formaldehyde or hydrogen peroxide vapour. Procedural controls are needed to exclude people during the operations. Releases to the external environment may also need control.

- Ergonomic issues can arise from manual production lines, just as in pharmaceutical production, from repetitive activities such as putting caps on vials or stacking boxes.
Key learning points

- A vaccine is a biological preparation that improves immunity to a particular disease.
- Traditional vaccines are produced from live or inactivated viruses. Modern genetic techniques allow synthetic vaccines to be produced from genetic material.
- Occupational hygiene issues mostly relate to incidental operations such as sterilisation, fumigation and ergonomics rather than to the active material.

1.5.3 Medical devices

A medical device is an instrument or article that is used to diagnose, prevent, or treat disease, and which does not achieve its purposes through chemical action on the body (which would make it a drug). A number of major pharmaceutical companies also produce medical devices (e.g. Johnson and Johnson, Baxter International, Abbott, Hospira, Bayer AG).

![Examples of inhaler devices for administration of asthma medications](image)

Figure 8: Examples of inhaler devices for administration of asthma medications

As with pharmaceuticals, medical devices are heavily regulated, usually by the same regulatory authorities as pharmaceuticals. This introduces constraints on any changes to the manufacturing processes involving such devices.

Hygienists in the pharmaceutical industry are most likely to encounter medical devices when they are used to deliver medications, for example inhalers used for asthma treatments or injectors for diabetes treatments.

1.5.4 Other Related Industries

**Consumer Healthcare.** The term includes nutritional products, vitamins and supplements, skin and hair care, oral care and over the counter medicines for gastrointestinal conditions, coughs and colds, pain (analgesics), allergies, smoking cessation etc.

The regulatory frameworks and manufacturing standards may differ between product categories. Pharmaceuticals companies with consumer healthcare divisions include Johnson and Johnson, Novartis, Merck, Abbott, Sanofi and Pfizer.
**Veterinary medicines.** Many human pharmaceuticals are used in animal health as well, though typically animal treatments are restricted to more basic conditions such as pain relief or treatment of infections. Animal health is generally regulated through veterinary authorities rather than through the human medicines agencies, and regulatory requirements do differ from those for human pharmaceuticals.

Companies that make animal health products include pharmaceutical manufacturer Boehringer Ingelheim as well as specialist animal health companies such as Zoetis and Elanco which have been divested from large pharma companies.

As well as the periodic acquisitions and divestitures of animal health businesses by the major pharmaceutical companies, there are other interactions between the industries. For example, animal use contributes significantly to the build-up of pharmaceutical residues in the environment, with potential implications for human health. It has been strongly implicated in the development of antibiotic resistance. In another instance, the veterinary use of a human painkiller (diclofenac) in livestock in India led to the near extinction of the population of vultures which fed on the carcasses. This has had far-reaching effects on humans, and has incurred calls for greater regulation of both human and veterinary pharmaceuticals.

**Key learning points**

- Related industries such as vaccines, medical devices, consumer healthcare and animal health each have their own regulations but issues sometimes overlap between the industries and they can influence each other.
## Annex 1: Some Major Companies in the Pharmaceutical Industry

(2018 revenue greater than USD($)10 billion)

<table>
<thead>
<tr>
<th>Rank</th>
<th>Company</th>
<th>2018 USD ($) billions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Johnson &amp; Johnson</td>
<td>81.60</td>
</tr>
<tr>
<td>2</td>
<td>Roche</td>
<td>56.86</td>
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<tr>
<td>3</td>
<td>Pfizer</td>
<td>53.60</td>
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<td>4</td>
<td>Novartis</td>
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<tr>
<td>5</td>
<td>Bayer</td>
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<td>6</td>
<td>GlaxoSmithKline</td>
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<td>7</td>
<td>Merck &amp; Co.</td>
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</tr>
<tr>
<td>8</td>
<td>Sanofi</td>
<td>39.07</td>
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<tr>
<td>9</td>
<td>AbbVie</td>
<td>32.75</td>
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<tr>
<td>10</td>
<td>Abbott Laboratories</td>
<td>30.60</td>
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<tr>
<td>11</td>
<td>Eli Lilly &amp; Co</td>
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</tr>
<tr>
<td>12</td>
<td>Amgen</td>
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</tr>
<tr>
<td>13</td>
<td>Bristol-Myers Squibb</td>
<td>22.56</td>
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<tr>
<td>14</td>
<td>Gilead Sciences</td>
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<td>15</td>
<td>AstraZeneca</td>
<td>22.09</td>
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<tr>
<td>16</td>
<td>Teva Pharmaceutical Industries</td>
<td>18.90</td>
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<tr>
<td>17</td>
<td>Boehringer Ingelheim</td>
<td>NA</td>
</tr>
<tr>
<td>18</td>
<td>Merck Group</td>
<td>8.83 (Q2)</td>
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<td>19</td>
<td>Novo Nordisk</td>
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<td>20</td>
<td>Allergan plc</td>
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<td>20</td>
<td>Takeda Pharmaceutical</td>
<td>12.68 (Q3)</td>
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<tr>
<td>21</td>
<td>Celgene</td>
<td>15.28</td>
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<tr>
<td>22</td>
<td>Biogen</td>
<td>13.45</td>
</tr>
</tbody>
</table>


Note that the industry changes frequently due to mergers, acquisitions and joint ventures as well as through organic growth and patent expiries.

Further reading

References


Chapter 1: Understanding the Pharmaceutical Industry


Chapter 2: Pharmaceutical Products and their Hazards

2 PHARMACEUTICAL PRODUCTS AND THEIR HAZARDS

2.1 APIs and their Significance for Exposure

2.2 Excipients

2.3 Hazards of APIs
   2.3.1 Central Nervous System
   2.3.2 Renal and Cardiovascular System
   2.3.3 Gastrointestinal System
   2.3.4 Anti-Infectives and Target Organs
   2.3.5 Immune System
   2.3.6 Chemotherapy Agents
   2.3.7 Endocrine System

2.4 Hazards of Associated Materials
   2.4.1 Animal Allergens
   2.4.2 Latex Allergies

2.5 Precautionary Approach and Assumptions
2.1 APIs and their Significance for Exposure

Whilst many airborne contaminants may be given consideration in the pharmaceutical research and manufacturing environment, the focus in this chapter will be on the hazards of the active pharmaceutical ingredients (API) themselves and the finished products.

In the workplace, unlike in the general population, there exists a nominally healthy workforce. Employees who do not have the illness a particular drug is designed to treat have the potential to be exposed. Their exposure may be to an uncontrolled ‘dose’ and duration giving rise to the potential for adverse health effects and, due to the varied routes of exposure, health effects rarely seen in treatment can be observed. Exposure by skin contact may result in dermal sensitisation and inhalation may result in respiratory sensitisation, effects rarely seen in treatment.

In controlling exposure to therapeutic substances the pharmaceutical industry must control not only the toxic effects of substances, but also the pharmacological effects. These pharmacological effects, which may be either side effects or therapeutic effects, often occur at lower doses than toxic effects.

It is the therapeutic action of APIs that often creates the primary occupational hazard. By design, desirable APIs have powerful positive effects on patient health with minimal adverse effects. However, effects that may be acceptable or even beneficial to a patient receiving treatment under medical supervision may be intolerable in workers subject to occupational exposure.

While epidemiological studies are few for morbidity and mortality in pharmaceutical workers, it is well documented that certain classes of pharmaceuticals can produce adverse health effects with both acute and chronic exposures (Heron and Pickering). In a healthy worker, any effects of drugs, whether positive or negative, should be considered serious and should be prevented. For example:

- Side effects that are acceptable in treating serious illness such as cancer, such as suppressing the effectiveness of the immune system, are undesirable in healthy workers
- Workers may have individual susceptibilities to a drug, e.g. there may be adverse effects on a worker who is pregnant, or a drug intended to reduce blood pressure may have an adverse effect on a worker whose blood pressure is already low
- Workers who become sensitized to a drug may be unable to receive that drug subsequently to combat disease (e.g. penicillins)
- Workers may be taking a medication which can lead to additive or synergist effects

API’s are designed to be biologically active and to produce their intended effects at as low a dose as possible. The potency of New Chemical Entities (NCEs) has tended to increase over the last 40 years. A “highly potent” drug (e.g. fentanyl, alprazolam, chlorpromazine) evokes a larger response at low
concentrations, while a drug of lower potency (ibuprofen, acetylsalicylic acid) evokes a small response at low concentrations.

Many drugs now have safe airborne exposure levels in the order of micrograms rather than milligrams per cubic metre of air, one company indicated that 80% of their small molecules NCEs have occupational exposure limits of 10 micrograms per cubic metre or less. Such drugs are often referred to as “High Hazard”, “High Containment”, “Potent” or “Highly Potent” compounds. Some drugs, including cytotoxics and some hormones, may have exposure limits in the nanogram per cubic metre range. Terminology varies, resulting in confusion between terms such as “potent” and “highly potent”. Typically a “potent” drug is defined as one where:

- The daily therapeutic dose is 10 mg/day or less; or
- A dose of 1 mg/kg/day in laboratory animals produces
  - serious organ toxicity; and/or
  - developmental toxicity or reproductive toxicity; and/or
  - irreversible effects
- The Occupational Exposure Limit (OEL) is less than 10 μg/m³ after applying appropriate uncertainty factors

Where control of airborne exposure has to be maintained to such low levels, skin absorption becomes an increasing concern as a route of potential exposure. For APIs that can be absorbed through the skin, e.g. opioid analgesics, accumulated deposits on room and equipment surfaces and protective clothing can contribute significantly to exposure. It should be noted that at these low levels, it is possible that the API is present at a detectable level potentially above the occupational exposure limit, but cannot be seen by the visible eye.

2.2 Excipients

Pharmaceutical excipients are substances other than the API which are included in the secondary manufacturing process and are contained in the finished pharmaceutical product dosage form. Tablet or capsule ingredients, for example, consist of Active Pharmaceutical Ingredient(s) (API) and excipients. In order to deliver an accurate amount of a drug for its intended clinical use in a convenient unit dosage form, excipients perform very important functions, specifically as:

- Fillers/Diluents
- Binders
- Disintegrants/Super Disintegrants
Excipients, from an occupational hygiene perspective are commonly the least toxicological concern, whilst the API is the primary concern. However, the degree of dilution by excipients must be taken into account when interpreting gravimetric analysis results and in deciding on the control measures needed when handling materials. It may be beneficial to perform a hazard assessment of excipients to ensure they do not introduce any additional hazards.

Exposure assessment studies in manufacturing should be conducted with the highest drug loading to ensure worst-case exposure potential is taken into consideration with data interpretation and recommendations. This is especially important when assessing containment capabilities of facilities that will process highly potent compounds.

Formulation issues will be considered in more detail in Chapter 3.

### 2.3 Hazards of APIs

It should be noted that for all specific drugs and drug classes described below, potential health effects and health conditions aggravated are only provided here in abbreviated form:

- Within most product classes, there are subclasses categorized by API, chemical type or by mechanism that may have specific toxicological properties differing greatly from the information presented here. It is not possible to represent adequately all the effects for any group of pharmaceutical product.
- For some of the newer drugs, the toxicological information is too limited to predict every potential health outcome as there has been less time to conduct toxicology studies and observe therapeutic side effects.

The information presented here is therefore limited to known effects for some of the most popular products chosen to represent the product class.

#### 2.3.1 Central Nervous System
Certain neurotransmitters are associated with depression — particularly serotonin, norepinephrine and dopamine. Most antidepressants relieve depression by affecting these neurotransmitters. Each type (class) of antidepressant affects these neurotransmitters with slightly different mechanisms.

Many types or classes of antidepressant medications are available to treat depression, including:

- **Selective serotonin reuptake inhibitors (SSRIs).** SSRIs include fluoxetine (Prozac), paroxetine (Paxil, Pexeva), sertraline (Zoloft), citalopram (Celexa) and escitalopram (Lexapro).

- **Serotonin and norepinephrine reuptake inhibitors (SNRIs).** Examples of SNRI medications include duloxetine (Cymbalta), venlafaxine (Effexor XR), desvenlafaxine (Pristiq, Khedezla) and levomilnacipran (Fetzima).

- **Atypical antidepressants.** These medications don’t fit neatly into any of the other antidepressant categories. They include trazodone, mirtazapine (Remeron), vortioxetine (Trintellix), vilazodone (Viibryd) and bupropion (Wellbutrin, Aplenzin, Forfivo XL).

- **Tricyclic antidepressants.** Tricyclic antidepressants — such as imipramine (Tofranil), nortriptyline (Pamelor), amitriptyline, doxepin and desipramine (Norpramin) — tend to cause more side effects than newer antidepressants.

- **Monoamine oxidase inhibitors (MAOIs).** MAOIs — such as tranylcypromine (Parnate), phenelzine (Nardil) and isocarboxazid (Marplan). These medications can't be combined with SSRIs.

Intended clinical effects of many antidepressant treatments include regulation of patient mood by the reduction of extreme mood changes. This translates to a sedation of the central nervous system that can be seen even at moderate exposures along with tachycardia (high heart rate), tremors, irritability, and nausea. At higher levels of toxicity, reported effects were serotonin syndrome, hyperreflexia, and possible coma. Hypotension or hypertension has been observed as an acute health effect depending on the exposed antidepressant.

The most common health conditions potentially aggravated are existing psychological disorders, glaucoma, history of seizures, use of non-steroidal anti-inflammatory drugs (NSAIDs), and cardiovascular disease. Antidepressants only directly affect the central nervous system but this can have indirect effects on many other organs, in particular the cardiovascular system, the liver, and the skeletal system.

### 2.3.2 Renal and Cardiovascular System

As a result of the rise in type 2 diabetes especially in developed economies, there is a growing need for and supply of antidiabetic agents that allow patients to manage symptoms of diabetes through regulation of insulin, glucose, or glucagon (and their associated metabolic pathways). Possible acute
health effects from exposures to antidiabetic agents are hypoglycemia, pancreatitis, renal failure, rhabdomyolysis, and hypersensitivity reactions. Antidiabetic agents can aggravate conditions of the liver, kidney, dehydration, individuals who have recently had surgery. These agents target mostly the liver and pancreas. Common antidiabetic agents include the following:

- alpha-glucosidase inhibitors (acarbose, miglitol)
- amylin analogs (pramlintide)
- dipeptidyl peptidase 4 inhibitors (alogliptan, linagliptan, saxagliptin, sitagliptin)
- incretin mimetics (albiglutide, dulaglutide, exenatide, liraglutide, lixisenatide)
- insulin
- meglitinides (nateglinide, repaglinide)
- non-sulfonylureas (metformin)
- SGLT-2 inhibitors (canagliflozin, dapagliflozin, empagliflozin)
- sulfonylureas (chlorpropamide, glimepiride, glipizide, glyburide, tolazamide, tolvaptamide)
- thiazolidinediones (rosiglitazone, pioglitazone)

**Angiotensin II antagonists** are uses for the treatment of hypertension (high blood pressure) when patients cannot use angiotensin-converting-enzyme (ACE) inhibitors. Common acute health effects associated with angiotensin II antagonist exposures are associated with hypotension (the clinical effect) such as dizziness and headache. Some of these agents are also known to cause coughing, and in severe cases renal failure.

*Example:* Diovan® is an angiotensin II antagonist treatment produced by Novartis Pharmaceuticals Corporation. This product contains two API’s: one for treating hypertension and one that is a diuretic. The API for treating blood pressure (valsartan) is the angiotensin II antagonist. This API treats high blood pressure by promoting vasodilation and regulating hormones that control salt concentrations. Diovan is also indicated for prevention of heart failure and myocardial infarctions.

As with many other drug classes, angiotensin II antagonists can aggravate conditions involving the kidneys and liver. Additionally, there is a high risk of fetal toxicity to women who are pregnant. Some of these agents are known to cause inflammation to the skin and respiratory system as well.

**Statins** are a class of drugs for lowering the level of cholesterol in the blood by reducing the production of cholesterol by the liver, often used to offset the other source of cholesterol in the blood, which is dietary cholesterol. Statins block the enzyme in the liver that is responsible for making cholesterol called
hydroxy-methylglutaryl-coenzyme A reductase (HMG-CoA reductase). Therefore, statins are referred to as HMG-CoA reductase inhibitors.

Typical examples of statins are atorvastatin (Lipitor®) and rosuvastatin (Crestor®).

Statins most common adverse reactions include upper respiratory infection, headache, abdominal pain, constipation and nausea. Most notably, statins to a varying extent cause myopathy (muscle deterioration) manifested as muscle pain, tenderness or weakness. The target organs for statins are the liver, kidneys and muscles and present a multitude of drug interactions with various antibiotics and any other class of drug that interrupts the Cytochrome P450 liver enzyme.

Other pharmaceuticals are utilized for the control of blood cholesterol besides statins and include niacin (Niaspan®) and fibrates (Gemfibrozil®). They are often utilized when one component of cholesterol, such as triglycerides, is a factor and when the statins are contraindicated for the patient.

2.3.3 Gastrointestinal System

Antiulcerants are typically indicated for treatment of gastro-oesophageal acid reflux disease (GERD), ulcer disease, gastric ulcers, and erosive oesophagitis.

Example: Esomeprazole (Nexium®) is an antiulcerant agent produced by AstraZeneca. As with most of the current generation of antiulcerants, Nexium® operates by inhibiting proton pumps that secrete gastric acid in the digestive system.

Common health effects from acute exposures include some of the most non-specific symptoms such as abdominal pain, diarrhea, dizziness, nausea, and headaches. Repeated exposures may aggravate osteoporosis-related conditions, as well as compromised renal and hepatic systems. Antiulcerants clinically affect the digestive system but depending on exposure route, exposure levels and the specific agent may affect a variety of other organs.

2.3.4 Anti-Infectives and Target Organs

Anti-infective agents cover a large scope of therapies that treat bacterial, fungal and viral conditions. As a result of the variety, there are a number of acute and chronic health effects that potentially occur upon occupational exposure.

As an example, HIV Antiviral products, like products for other viruses, focus on inhibiting the growth of the virus. HIV antiviral products are usually protease inhibitors or reverse transcriptase inhibitors, as above. Expected health outcomes for acute exposures to some protease inhibitor-class products included vomiting, abdominal pain, and headaches throughout a wide range of doses. For reverse transcriptase inhibitors, the most common reported effects from acute exposures were psychomotor
agitation and psychiatric disturbances such as mania and agitation of mood. Whilst overdoses are possible, no acutely toxic effects are documented for some HIV antiviral products. Expected exposure outcomes from these products are limited to known side-effects associated with the therapeutic doses of the product such as: headache, dizziness, rash, nausea, vomiting, and hyperlipidemia.

Antiviral product mechanisms are directed towards the virus itself. At this time, there is no evidence of specific target organs for these effects other than the aforementioned effects that impact the nervous system. There is a significant list of contraindications and drug interactions that may cause additional health effects. Some examples of adverse drug interactions are treatments for mental illness, hepatitis B or C, kidney problems, liver problems, or fat and cholesterol problems. Exposures to HIV antiviral products are also known to aggravate pre-existing impairment of the kidneys and the liver.

*Example:* Atripla®, produced by Bristol-Myers Squibb and Gilead, is a combination of three HIV products combined into one pill. It contains two products that inhibit nucleoside reverse transcriptase and one that inhibits non-nucleoside reverse transcriptase. Inhibitions of these enzymes inhibit HIV-1 growth in the blood. This product is indicated for treatment of HIV-1.

**Respiratory agents** can range from potent corticosteroids (which are immunosuppressants) to over-the-counter allergy medications and can therefore be placed in either the anti-infective or endocrine system categories. Common acute health effects can be headache, somnolence, fatigue, tachycardias, and dysrhythmias. Employees with impaired liver or renal function, as well as existing immune system suppression may have these conditions aggravated by exposure to respiratory agents. Respiratory agents all target the respiratory system, but in cases of acute exposures, the kidneys and liver may be affected as well. Chronic exposures have been shown in few cases to affect the cardiovascular system.

*Example:* Advair®: It is a fluticasone/salmeterol combination produced by GlaxoSmithKline and administered in multi-dose inhalers or dry powder inhalers. Advair® is indicated for asthma, allergic rhinitis, and atopic dermatitis. Advair® and other respiratory agents are mainly used to reduce or eliminate respiratory inflammation.

The API of Advair®, fluticasone, is a glucocorticoid – a type of corticosteroid for which the adverse effects are described further below in the endocrine system category.

**Antibiotics** are chemical substances capable of destroying micro-organisms such as bacteria and viruses that cause infection in animals and humans. The principal ones are: erythromycin, the penicillins, the tetracyclines, streptomycin, and clindamycin.
The effects of occupational exposure to antibiotics can include:

- **Allergic reactions**: itching and redness of the eyes, runny nose, skin rashes, asthma, and occasionally shock due to an allergic reaction (anaphylaxis)
- **Vitamin deficiency**: Workers with repeated exposure to antibiotics experience a change in the number and type of bacteria which are normally present in the intestines which break down and absorb vitamins in the intestines
- **Fungal infections**: Daily exposure to antibiotic dust can lead to fungal infections of the skin and nails. Additionally, women workers may develop vaginal yeast infections following exposure to antibiotics
- **Toxic effects**: Exposure to certain antibiotics may lead to development of some of the toxic side effects that occur when that drug is given as medicine
- **Other Effects**: Older female workers have been incorrectly told that flushing may be due to hormonal changes rather than the antibiotic drugs they are inadvertently taking in. Headaches and stuffy nose are other common complaints. Allergic heart disorders, bronchial asthma, poisoning, and allergic disorders of the liver have also been reported. Some experts are concerned that prolonged contact with antibiotics may cause cancer, although there have been no studies confirming this suspicion

Described below are common adverse reactions to some specific antibiotics.

**Penicillins.** Because of the highly allergenic nature of the penicillins and their extensive use, many people have become allergic to them. The most serious reaction is shock. This type of acute reaction usually occurs minutes after exposure. Symptoms are tightness in the chest, asthmatic breathing, dizziness, swelling of the lips, tongue, or face, edema of the lungs, heart failure and in some cases, death. Other reactions are hives, "black hairy tongue," fungus infection, and rectal itch.

**Tetracyclines.** Modification of the bacteria of the intestines and other organs has been reported following occupational exposure to tetracycline (as well as to streptomycin and penicillin). In workers exposed to tetracycline and to streptomycin, modification of the bacteria led to a drop in the body's vitamin content, especially of the B vitamins. Another problem associated with occupational exposure to tetracycline is drug resistance. Workers may develop infections that are resistant to treatment with tetracycline.
2.3.5 Immune System

Immunosuppressive products are used to prevent the immune system from rejecting its own cells or transplanted cells. Examples of immunosuppressive drug classes include cytostatic drugs and glucocorticoids. Because of the nature of immunosuppressive products inhibiting the functions of the immune system the primary risk from occupational exposure to these products is the increase in risk of infections and infectious disease. Additional health effects from exposure to immunosuppressive drugs are highly variable to do the variety of products available in this category.

When inflammatory functions of the immune system are inhibited the body can no longer prevent infection as effectively nor can it fight existing infections. Immunosuppressive drugs can potentially aggravate any worker with existing infections or infectious disease such as hepatitis or cancers.

Example: Humira®, produced by AbbVie, is a Tumor Necrosis Factor (TNF) inhibitor that is indicated for Rheumatoid Arthritis, Plaque Psoriasis, Crohn’s Disease, Ankylosing Spondylitis, Psoriatic Arthritis, and Juvenile Idiopathic Arthritis. It is in the class of antibody immunosuppressive drugs.

Health effects from immunosuppressive drugs should be considered systemic and an inhibited immune system can affect more than a single organ. The mechanism of immunosuppression can be specific as in the case of a specific organ transplant or systemic as in the case of antibody products treating joints throughout the body affected by rheumatoid arthritis.

2.3.6 Chemotherapy Agents

Traditional oncological (tumour treatment) agents work through mechanisms that kill cells, including both cancerous and normal cells alike. Such agents are called cytotoxic drugs. They have a greater toxic effect on rapidly dividing cells (such as malignant cells) and thus inhibit their growth and proliferation. Most cytotoxics are themselves carcinogens and/or mutagens and some may exhibit other forms of toxicity e.g. reproductive toxicity (teratogenicity or sterility).

These drugs can exert biological effects even at very low levels of absorption. Also, as therapeutic dosages are high, the quantities handled by workers—and therefore the level of potential exposure—can be significant.

Example: Methotrexate was developed and continues to be used for chemotherapy either alone or in combination with other agents. It is effective for the treatment of a number of cancers. The most common adverse effects from methotrexate treatment include: ulcerative stomatitis, low white blood cell count and thus predisposition to infection, nausea, abdominal pain, fatigue, fever, dizziness, acute pneumonitis and rarely pulmonary fibrosis.
Monoclonal antibody products are an example of a therapy that is more targeted at cancerous cells. Potential occupational effects of monoclonal antibodies are severe projections of common adverse effects from therapeutic doses due to lack of information. Commonly observed health effects associated with undergoing treatment include heart failure, anemia, nephrotoxicity, reactivation of hepatitis B, and dyspnea.

**Example:** Rituxan® is produced by Genentech. Like many of the most popular oncological products, it is a monoclonal antibody. Rituxan® binds to specific sites on B lymphocytes that are commonly expressed in lymphomas (but not many other tissues). It is thought to induce cell lysis (rupture of membranes) of neoplasms and apoptosis (programmed cell death) in lymphoma cells. It is indicated for chronic lymphoid leukemia, non-Hodgkin’s lymphoma, rheumatoid arthritis, and Wegener’s granulomatosis.

Observed health conditions that may be aggravated by exposure to the oncological drugs include a variety of respiratory and cardiac conditions, as well as viral infections. Oncological products are known to cause acute toxicity to the skin, liver, kidney, and the blood (if leukemia or blood conditions exist). Some oncological products were found to have reproductive and teratogenic health effects as well.

A relatively new class of drugs that are often oncolytic agents, referred to as antibody drug conjugates (ADC), are the combination of a potent oncolytic agent attached to a monoclonal antibody by a linker molecule. These targeted warheads move directly to the cancerous tissue via the antibody-antigen response in the body to create a targeted and precise impact on the tissue to be eradicated. As a result of their precision they often produce fewer adverse side effects in the patient during and after treatment. Their production is often smaller scale and in liquid-phase for most unit operations and therefore can potentially pose a reduced hazard to the pharmaceutical worker versus large-scale formulation with powders. The occupational hazard that remains to be explored with ADCs is the potential for the linker molecule to release the oncolytic agent if an oxidizing cleanser is used in the manufacturing or downstream patient administration processes.

### 2.3.7 Endocrine System

The **sex hormones** comprise the female sex hormones, the male sex hormones and antagonists and anabolic steroids. Exposure limits for sex hormones can be extremely low, in the low μg/m³ or even ng/m³ range.

Female sex hormones include the natural and synthetic oestrogens (US spelling: estrogens) and progestogens. Natural oestrogens are used largely in Hormone Replacement Therapy (HRT) and are often extracted from the urine of pregnant mammals (horses/mares). Synthetic oestrogens are used in the treatment of breast and prostate cancer.
Anabolic steroids (which were developed from the male sex hormones [androgens]) are used in the treatment of some aplastic anaemias, but have been abused by some bodybuilders and athletes.

As well as the treatment of various conditions outlined above, the commonest use of the sex hormones is in the oral contraceptive pill. Contraceptive pills may contain oestrogen only, progestogen (progesterone and testosterone analogues) only or both. Ethinyloestradiol is the commonest oestrogen component in the pill. Desogestrel, levonorgestrel and norethisterone are the most commonly used progestogens.

A series of reports throughout the 1970s and 1980s highlighted the problems caused by occupational exposure in both men and women. Studies confirmed the prevalence of problems at very low levels of exposure.

The concern with the use of the sex hormones is the development of male traits in women and female traits in men and effects upon fertility. In women, menstrual disorders, diminished fertility and increased frequency of spontaneous abortion have been observed. In men, reduction in libido, breast growth and testicular pain have been reported. Progestogens may also inhibit spermatogenesis, resulting in decreased fertility.

The effects of occupational exposure to hormones may be severe. For male workers, exposure to oestrogens may give rise to breast development; for female workers, there may be menstrual disorders, abnormal overgrowth of the endometrium and excessive bleeding during menopause.

Exposure of male workers to progestogen may bring about a lack of sexual drive and testicular pain. On the other hand, exposure of female workers to androgens is known to cause menstrual and ovarian function disorders, diminished fertility, increased frequency of spontaneous abortions, and symptoms of masculinity. The production of female contraceptive pills using diethylstilboestrol and the use in pharmaceuticals of other natural and synthetic steroid hormones has been associated with a number of adverse health effects.

Corticosteroids are a drug class used to treat a variety of conditions ranging from generic inflammation, asthma, and allergic reactions, to more serious conditions such as hepatitis, Crohn’s disease, and rheumatoid arthritis. They are produced as creams, lotions and foams for topical application, and as powders for use in inhalers.
Many corticosteroids focus on regulating inflammation or an aspect of metabolism through their hormonal activity. Long-term overexposure to corticosteroids can affect many parts of the body:

- **Adrenals** – Causes the adrenal glands to make less natural cortisol - a condition called adrenal suppression. This can be life threatening during times of stress, such as illness or surgery
- **Immune system** - Inhibits the normal activity of the immune system, causing increased risk of infection and prolonged wound healing
- **Muscles and bones** – Causes muscle shrinkage and thinning of bones (osteoporosis)
- **Skin** - Thins and dries the skin, increases susceptibility to bruising and causes several kinds of skin rash. More frequent, severe infections and slow healing of wounds

These effects have been observed as being reversible upon employee’s removal from exposure. Occurring cases suggested that these occupational conditions can be caused by either local exposures or systemic exposures.

The most common occupational effect is steroid withdrawal rash (SWR), an acne-like rash is usually accompanied by skin dryness, redness, flaking, and a burning sensation. SWR:

- is triggered by an interruption in steroid overexposure
- occurs 2-10 days after the last exposure.
- most commonly occurs on face, neck or hands
- typically lasts for two-three weeks.
- does not usually cause long term effects
SWR is an indicator that over-exposure may have occurred and that current controls may not be effective. Skin is the most common route of overexposure. This can occur when touching a contaminated surface, such as doorknobs, tables, or the outside of a contaminated vial or metered dose inhaler, while not wearing gloves. It can also occur when you touch a contaminated glove to your neck or face. Once on a surface, glucocorticoids tend to stay there. They are sticky, greasy chemicals which are not easily cleaned away with water-based cleaners.

2.4 Hazards of Associated Materials

Similar to industries such as health care and medical research, the pharmaceutical industry has a range of material hazards capable of producing acute and chronic health affects in workers.

Skin and respiratory sensitization are common issues. Examples of chemicals or other agents used in the industry that can produce sensitization are listed in the Table following.
Antibiotics:
- ampicillins
- cephalosporins
- penicillins

Inorganic chemicals:
- chromium
- cobalt
- nickel

Organic chemicals:
- cyanoacrylates
- diazonium salts
- ethylenediamine
- formaldehyde
- glutaraldehyde

Proteolytic enzymes:
- amylase
- papain
- subtilisin

Animal materials:
- animal "dander"
- bovine (cow) urines
- egg proteins
- storage mites

Plant or microbial materials:
- castor bean dust
- latex
- tea dust
- guar gum

### 2.4.2 Animal Allergens

Within the research and development sector of the pharmaceutical industry animal research for pharmacological and toxicological studies is a critical component. The workers that care for laboratory animals are subject to exposure to allergens.

According to research references, approximately one third of laboratory animal workers have occupational allergy to animal dander, and a third of these have symptomatic asthma. Sensitization generally occurs with the first 3 years of employment. Studies have shown an exposure-response relationship to laboratory animal allergies (LAA) in the early years of exposure (Hollander, 1997). LAA symptoms develop after repeated exposure, in most cases within a two to three year period, but in some instances they first occur after many years exposure.

Risk factors include a history of dermal and respiratory allergies, as well as job description as it relates to the intensity of exposure. As with other respiratory sensitisers there is some association between atopy and the development of symptoms i.e. atopy increases risk of developing symptoms in individuals. However, 70% of atopic individuals will not develop LAA.

The common allergens are proteins from body tissue excretions and secretions. Urine, hair/fur, dander/animal dandruff, saliva and serum all contain allergenic proteins. Allergens are deposited on fur, litter, and dust particles. They can be inhaled, introduced via a break in skin caused by scratches, bites or instrumental skin punctures, or topical contact on skin or mucous membranes.
Symptoms may occur independently, and include asthma, rhinitis, conjunctivitis and urticaria. Those with symptoms due to sensitisation will continue to experience these symptoms unless allergen exposure is prevented. The symptoms may, in certain individuals, subsequently become more severe and in some cases can persist despite removal from exposure to allergens.

Depending upon the severity of their symptoms, sensitised individuals may be able continue to work with animals provided suitable RPE is worn to reduce exposure to allergens and they are closely medically supervised.

Exposure monitoring can be carried out for allergens using traditional pumped sampling coupled with Radio-allergosorbent Test (RAST) or Enzyme Linked Immunosorbent Assay (ELISA) to determine the allergen concentrations present. Highest exposures to allergens are usually found in the cage cleaning operations and bedding disposal. Increasing use of automatic cage washers and low emission bedding can significantly reduce exposures. High general ventilation rates in animal housing rooms and the use of filter topped cages also reduces exposure.

2.4.2 Latex Allergies

Throughout the scientific work environment in pharma, personal protective equipment historically containing latex-based rubber has also produced and/or exacerbated allergies to latex.

Allergy to latex was first recognized in the late 1970s. Since then, it has become a major health concern as an increased number of people in the workplace are affected. As used in this topic, latex refers to the natural rubber latex manufactured from a milky fluid that is primarily obtained from the rubber tree (*Hevea brasiliensis*). Some synthetic rubber materials may be referred to as "latex" but do not contain the natural rubber proteins responsible for latex allergy symptoms. Workers exposed to latex gloves or medical products containing latex are especially at risk. It is estimated that 8-12% of health care workers are latex sensitive. Between 1988-1992, the US Federal Drug Administration (FDA) received more than 1,000 reports of adverse health effects from exposure to latex, including 15 deaths due to such exposure.

Allergy is triggered by contact with “free" latex protein in the gloves, that is, the protein must be available to penetrate the skin. Protein that is firmly bound into the gloves and thus not bioavailable is unlikely to initiate the reaction. With high quality gloves, considerable care is taken to ensure that protein in the latex is “fixed” during manufacture. The resulting glove is then subjected to various washing, leaching and chemical treatments to form the final glove. Less expensive gloves are not washed or chemically treated and often show considerably high levels of free protein. The use of powdered corn starch to make cheaper gloves easier to don, greatly increases the risk as latex protein
binds to the corn starch, increasing skin contact and penetration. It has been suggested that a minimum standard should be use of unpowdered gloves with a maximum free protein content of 50 μg per gram of glove. (Packham, 2004/2007).

While symptoms may resolve quickly with natural rubber latex avoidance therapy, detectable IgE indicating continued sensitization remains beyond 5 years, and thus continued avoidance of latex is recommended according to the US Centers for Disease Control.

2.5 Precautionary Approach and Assumptions

The pharmaceutical research and development environment poses special considerations due to the number of unknown or little-known factors including API toxicity, containment capabilities of new formulation processes and new formulation work methods.

As a result of lack of information during early phase or early stage drug development it becomes critical that a proactive, precautionary occupational hygiene approach be employed based on the known or anticipated hazard data. Within this approach we must consider occupational toxicology, engineering controls and occupational hygiene assessment strategy and decision analysis. These topics are more thoroughly covered in subsequent chapters, but examples of a proactive approach may include consideration of only task sample data versus time-weighted average data that assumes zero exposure for the remainder of the work day, and application of provisional control bands by occupational toxicology when only small amounts of toxicological data are available.
References:

- Micromedex 2.0 (Truven Health Analytics product)
- Respective product websites for specific products for categories
- US Centers for Disease Control and National Institutes of Occupational Safety and Health sites.
- IMA Encapsulation, Fette Tablet Compression and Bohle Tablet Coating sites.
- Packham C., EnviroDerm Services, Technical Bulletin No. 6 Thoughts on latex allergy Issue, 2004/7
- ILO Encyclopaedia, Tait K. [http://www.ilo.org/oshenc/part-xii/pharmaceutical-industry/item/385-pharmaceutical-industry](http://www.ilo.org/oshenc/part-xii/pharmaceutical-industry/item/385-pharmaceutical-industry)
3 PROCESSES AND TECHNOLOGIES

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3.5 Research and Development
3.1 Introduction

The processes which are employed during the manufacture of Pharmaceutical products can be broadly classified under the environments in which they are carried out, namely:

- Active Pharmaceutical Ingredient (API) manufacture (Primary Manufacture) – Large scale manufacture of raw materials produced in high concentrations
- Formulated product (FP) manufacture (Secondary Manufacture). – Large scale manufacture and packaging of products which contain the required dose of Active Pharmaceutical Ingredient.
- Research and Development (R&D) – This is characterised by small scale laboratory type activities which are varied and involve a large number of materials.

Some of the processes which are undertaken are common to all of the stages of manufacture; however other processes are integral to particular stages. Figure 1 below broadly summarises the type of processes undertaken within the different environments.
Figure 1: Manufacturing process in the pharmaceutical industry

Source Adrian Hirst – Adapted from ILO Encyclopaedia of Occupational Health and Safety
3.2 Active Pharmaceutical Ingredient (API) Manufacture (Primary Manufacture)

The manufacture of Active Pharmaceutical Ingredients (APIs) typically involves the manufacturer of medium sized quantities of material such as tens to hundreds of kilograms of solid material and thousands of litres of liquids. The basic production of bulk API products can employ three different types of process:

- **Biological Processes** - These predominantly involve fermentation where microorganisms are cultured in a substrate to produce useful substances e.g. Antibiotics, steroids and vitamins. However other biological processes are used such as the production of vaccines and genetically modified organisms.

- **Organic chemical synthesis** – The use of chemical reactions to manufacture specific molecules.

- **Extraction from a Biological source** – The use of a solvent or other extractive mechanism to release substances from plants or other natural materials. e.g. digoxin, and opiates.

3.2.1 Biological Processes

Fermentation is the most commonly used biological process. This involves the use of specifically selected micro-organisms and microbiological technologies to produce a chemical product. The process is typically undertaken on a batch basis and involves three stages:

**Inoculum and seed preparation** - Inoculum preparation involves preparing a culture of the specific micro-organism being used. Typically spores of the micro-organism are activated with water and selected nutrients in warm conditions. The micro-organisms may be grown on agar plates, test tubes or flasks.

**Fermentation** - The cultured cells are transferred to a small vessel (seed tank) for further growth. After suitable growth has been achieved the cells are transferred to a larger fermentation tank. The tank is supplied with nutrients and heat and is normally agitated and or aerated. After the biochemical reactions are complete, the fermentation broth is filtered to remove the micro-organisms.

**Product recovery** - Depending upon the drug being manufactured the API may be present in the filtrate or within the cells which have been filtered out. The recovery of the material may involve various steps such as solvent extraction, precipitation ion exchange and absorption. A variety of solvents can be used to extract and synthesize materials, in recent years there has been an increase focus on the environmental fate of waste from the use of solvents. Figure 3 gives a list of some commonly used solvents, and their environmental preference. A schematic diagram of a fermentation process is given in Figure 2.
Figure 2: Diagram of a fermentation process

Source: Adrian Hirst – Adapted from ILO Encyclopaedia of Occupational Health and Safety
### Figure 3: Solvents used in the pharmaceutical industry

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Used in Chemical Synthesis</th>
<th>Used in Fermentation</th>
<th>Used in Extraction from a biological source</th>
<th>Environmental Preference</th>
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</tbody>
</table>

3.2.1. **Organic chemical synthesis**

Organic chemical synthesis processes use organic and inorganic chemicals in batch processes. The process normally involves a number of stages with intermediate compounds being formed before the final API is synthesized. Pharmaceuticals are becoming increasingly more complex and often require multiple stages of synthesis. Synthesis is undertaken within a series of reactors, often
multi-purpose reactors which may be used to manufacture a number of APIs. A typical process for liquid based reaction chemistry is shown in Figure 4.

Figure 4: Simplified Bulk API process

Source: Adrian Hirst
The reactors are normally reinforced pressure vessels with stainless steel, glass or metal alloy linings. The nature of chemical reactions and physical properties of materials (e.g., reactive, corrosive, flammable) determine the design, features and construction of reactors. The reactors are normally fitted with cooling/heating coils on the outside as well as Agitators on the inside. Sensors for temperature, pressure, volume and weight or normally fitted. Depending upon the type of reaction the vessels may be operated at high pressure or under low vacuum as well as being heated or cooled.

APIs and intermediates are often manufactured on a ‘campaign’ basis where the production only occurs for planned discrete periods with long breaks in between. e.g. It is not uncommon for some materials only to be made on an annual basis. In some instances, intermediate products may be manufactured in a separate facility to the final API. Intermediate compounds are often manufactured and traded as commodities.

Once the required API or intermediate has been synthesised within the reactor then it may require various stages of drying, milling and blending.

3.2.3 Extraction from a Biological Source

Large volumes of natural materials, such as plant and animal matter, may be processed to extract substances which are pharmacologically active. In each step of the process, the volumes of materials are reduced by a series of batch processes, until the final drug product is obtained. Solvents are used to remove insoluble fats and oils, thereby extracting the API. The pH (acidity) of the extraction solution and waste products can be adjusted by neutralizing them with strong acids and bases. Metal compounds are often used as precipitating agents, and phenol compounds as disinfectants.

3.3 Formulated Product (FP) Manufacture (Secondary Manufacture)

How the API is formulated into the finished pharmaceutical product is critical for both the manufacturing route and the patient.

It can have a major impact on “patient compliance”, i.e. whether the patient takes the medication reliably as prescribed. Some routes of administration and some types of formulation are more acceptable to patients, but they have to be compatible with the metabolism and absorption of the drug. For example, patients generally prefer oral doses to injections, but if the API breaks down in the stomach, oral administration may not be effective. The key considerations are usually known as:
• **pharmacokinetics** (concerning the processes of uptake, distribution, and elimination of drugs).
• **pharmacodynamics** (concerning e.g. the physiological effects of drugs)

Formulation also determines the efficiency with which the drug is absorbed by the patient. Improving the formulation can therefore reduce the amount of API that is needed, which can in turn reduce the risk of occupational exposure as less API will be handled in the workplace.

The pharmaceutical delivery route selection, whether it be oral in the form of solid, semi-solid, or liquid, or non-oral, is determined by a number of physiochemical characteristics of the API, target dose and target patients.

Formulated (or Finished) Product Manufacture involves the incorporation of the Active Pharmaceutical ingredient with other materials to produce a product with the required dose which can then be administered to the patient. The other, pharmacologically inactive, materials are called excipients. They may include binders, fillers, flavouring and bulking agents, preservatives and antioxidants. These ingredients may be dried, milled, blended, granulated and compressed in order to produce the required characteristics of the product.

Processes for formulation are driven by the product form. Typical products are:

**Oral Formulations**

• **Tablets.** A tablet is usually a compressed preparation that typically contains:
  o 5-10% of the drug (active substance);
  o 80% of fillers, disintegrates, lubricants, glidants, and binders; and
  o 10% of compounds which ensure easy disintegration, disaggregation, and dissolution of the tablet in the stomach or the intestine.
  o In addition to traditional formulations, many drugs are now available in
    o fast-dissolving versions, for quick therapeutic action
    o modified-release versions, for slow release over an extended period.

• **Capsules.** A capsule is a gelatinous envelope enclosing the active substance. Capsules can be designed to remain intact for some hours after ingestion in order to delay absorption. They may also contain a mixture of slow- and fast-release particles to produce rapid and sustained absorption in the same dose.

• **Targeted** forms for specific patient populations (e.g. chewable, effervescent)

• **Technology Enabling Dosage Forms** (e.g. Melt extrusion, Spray drying...)

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Chapter 3: Processes and Technologies
Other Formulations

- Gas propellant Inhalers, dry powder inhalers
- Vials (or phials), prefilled syringes, ampoules
- Eye drops and nasal sprays
- Liquids such as cough mixtures and medicines for children and the elderly who cannot swallow solid dose forms
- Creams, ointments

Figure 5 gives an outline of the various processes which may be required:

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Figure 5: Pharmaceutical manufacturing of dosage-form products
Source: Adrian Hirst adapted from ILO Encyclopaedia of Occupational Safety and Health
FP manufacture typically involves larger volumes with tens of kilograms of solid material and processes are conducted at relatively high speed. The most common form of Formulated Product is that of a tablet.

### 3.3.1 Compounding

Compounding involves the mixing of different ingredients in order to produce a bulk material from which individual doses can subsequently be manufactured. Compounding may involve the mixing of solids and liquids to produce solutions, suspensions, syrups, ointments or pastes.

### 3.3.2 Granulation

Dry and wet solids are processed to form granules of a desired size and morphology. The process essentially causes individual constituents within the compounded product to stick together. The design of granulation equipment varies but the equipment essentially involves the physical mixing of powders together with liquids and possibly heat and dry air or steam. Granulators are typically fully enclosed.

Wet granulation is a process of using a liquid binder to lightly agglomerate the powder mixture. The amount of liquid has to be properly controlled, as over-wetting will cause the granules to be too hard and under-wetting will cause them to be too soft and friable. Figure 6 shows a schematic diagram of a typical wet granulator.

Dry granulation processes create granules by light compaction of the powder blend under low pressures. The compacts so-formed are broken up gently to produce granules (agglomerates). This process is often used when the product to be granulated is sensitive to moisture and heat. Dry granulation can be conducted on a tablet press using slugging tooling or on a roll press called a roller compactor.
3.3.3 Drying

Solids which are wet with either water or solvents need to be dried at various stages of the manufacturing process. Dryers can be of different designs but generally involve the use of mild heating, vacuum and forced airflow to evaporate water/solvent.

- **Tray Drying** can be difficult to contain at the source, because powders must be manually spread over trays and placed into dryers. Operators have to manually manipulate the powder using scoops, and typically dump the dry powder from the trays into drums for bulk packaging. These manual manipulations and transfer can present some difficulties containing the product at source. Often for potent compounds, tray drying should be avoided. For small scale development batching may make it possible to utilize isolator technology.

- **Fluid Bed dryers** agitate the wet solids with hot air inside an enclosure. The agitation of the powder together with the heat allows the solids to be dried quickly without significant handling.

- **Spray dryers** dry material by spraying a fine mist into a hot-air chamber, the material then falls to the bottom as dry powder.

- **Freeze Dryers** dry a frozen product in a vacuum. The vacuum allows the ice to turn directly into vapour without first passing through the water stage.

- **Rotary dryers** involve rotating the material inside a drum or tumbler into which hot air is fed.


3.3.4 Milling

Dry solids are often milled to change their particle size and morphology such as when trying to produce free-flowing powders. Mills have different designs but essentially involve applying energy to materials to break them up. This energy might be applied by an impellor, hammers, rotating balls or rollers. For potent compound handling and containment at source, in line milling where possible, should be considered.

Process safety and combustible dust properties, such as minimum ignition energies of the material, needs to also be considered, especially during high energy interactions within the milling process.

3.3.5 Blending

Dry solids are blended to produce homogeneous mixtures. Blending normally involves tumbling powders within an enclosed container although the use of specialist mixers fitted with blades appropriate for powders can also be used. Figure 8 shows a V blender facility where different
materials are transferred in by pipelines at the top and then the whole unit is tumbled before removing the blended product from the bottom.

Figure 8: A 'V' blender

3.3.6 Tabletting

Tablets are manufactured by compressing the formulated dry solids. To form a tablet a precise amount of granulated material must be fed into a cavity formed by two punches and a die. The punches then press on either side of the material to form a tablet. Compression or tableting machines tend to work at high speed and can produce hundreds of thousands of tablets per hour, and involve either a single cavity or multiple punches on a rotating turret.

An alternative process is direct compression. The granulation and drying steps are replaced by direct compression, where the blended powder is dry pressed into a sheet and then “nibbled” into pieces. These pieces are then milled or micronized to smaller particles before being compressed into tablets.

The occupational hygiene factors unique to tablet production and packaging depend on the following factors. The first factor for consideration is the containment capabilities of the equipment. Many of the newer tablet presses are capable of containment and exposure control to the point of allowing reductions or elimination of respiratory PPE for less hazardous materials. Ancillary equipment should also be evaluated for dust exposure potential, such as dedusting, in process testing and discharge of reject tablets and good tablets. The second consideration is whether the tablets are coated or uncoated, as this could impact downstream processes and the potential for exposure (such as packaging, but also in pharmacies and patient populations). The coating process
for tablets seals in the API as compared to uncoated tablets and provides a relative measure of protection for post-production handling and during pharmaceutical packaging processes.

Figure 9 shows two different tablet presses, whilst Figure 10 presents a schematic diagram of the rotary press.

Figure 9 Tablet Presses

Source: Pharma-machines.com
3.3.7 Tablet Coating

Some tablets are coated with a protective layer following compression. The coating seals and protects the tablet but may also provide other characteristics which influence where the tablet is absorbed in the body, taste, ease of swallowing and aesthetics. Tablets are coated by rotating them in an open drum into which the coating material is poured or sprayed. The tablets are then rotated until an even dry coating is achieved. Figure 11 shows two tablet coating machines.
3.3.8 Capsules

As with tablet pressing, containment capabilities in production equipment are a key factor in capsule manufacturing. The newer generations of equipment prove to have greater worker protections as illustrated by exposure assessment studies for containment. The capsule production process can also include a very important post-encapsulation dedusting stage that reduces exposure to the worker who is responsible for charging containers with finished produce, as well as the worker methods and equipment containment while performing the final packaging tasks. Soft gel capsules are manufactured with typically an oil-based formulation containing the Active Pharmaceutical Ingredient. It is a relatively newer style of pharmaceutical manufacturing. From a containment at source perspective, it can significantly reduce the risk of handling potent compounds, as the dry powder is only handled in initial stages for weighing and addition to the liquid formulation.

3.3.9 Non-Oral Formulations

Whilst predominant formulations are oral as the preferred route of administration, there are some pharmaceuticals that can only be administered by other routes due to their chemical composition, bioavailability, stability and other patient factors. Other than some potentially inhaled drug products such as dry powder asthma medications, the APIs tend to be dissolved or suspended in liquids and gels and therefore carry a reduced potential for airborne exposure to the worker relative
to powder APIs. They include, topicals, and injectables and are typically aqueous-based or alcohol-based materials.

### 3.3.10 Packaging

The packaging of pharmaceutical products is essentially similar to the packaging of other products such as food. Purpose built packing lines are used to place the required amounts of products in numerous different types of packaging including; Ampoules, Bottles, (glass and plastic), Blister and foil packaging, sachets and syringes and autoinjectors, suspension syrups.

Liquids are filled into containers using closed pumping systems whilst tablets and capsules are transferred into appropriate containers using vibration and gravity feeds.

Packaging is usually differentiated from filling activities.

- **Filling** involves putting the required quantity of a product into its primary product container (glass vial, bottle, blister, foil sheet etc).
- **Packaging** involves taking the primary container and placing it in secondary packaging. These may then be further packed into boxes or trays for transport.

### 3.3.11 Cleaning and Maintenance Activities

The nature of Pharmaceutical products is such that equipment is required to be very clean before it can be used. This necessitates regular and thorough cleaning of all the equipment and the manufacturing environment. Equipment is typically cleaned between every batch manufacturing process and can account for a high proportion of workers’ time. Cleaning activities represent significant opportunities for exposure as surfaces are often contaminated with API.

Practically all sterile manufacturing processes use Formaldehyde as a fumigation agent in solid form (para-formaldehyde) or liquid (formalin solution at various concentrations). In some instances, Hydrogen Peroxide is used. Both Formaldehyde and Hydrogen Peroxide present significant chemical hazards to the worker and it would be preferable to use less hazardous materials. The industry requires effective sanitization and sterilization of equipment and although significant effort has been put into finding alternatives the chemical remain in use. Control of exposure is normally achieved by the minimization of fumigation together with strict operating procedures which include various engineering, PPE and administrative controls.
Cleaning is typically performed by washing or wiping liquids and vacuuming dusts. Dry sweeping and blowing solids with compressed air are strongly discouraged. Some equipment may be fitted with an automated ‘Clean in Place’ process where reaction vessels and pipelines are purged with air or water. Even with clean in place systems some manual cleaning may be required.

Continuous Manufacturing is in the initial phases of becoming more widely used. Essentially it is lining up all the process steps in a continuous, closed process train, and allowing small quantities of powders to continue to travel through each process step. The benefit is that scalability becomes less of an issue as the process remains small scale and the only factor is the amount of time to run the equipment. From a containment perspective it can be easier to contain smaller scale equipment and less risk of upset conditions.

3.4 Sterile production

Many ophthalmic products and those that contact open wounds generally require sterilising, as do all injectable products. Sterile production requires the highest levels of Good Manufacturing Practice (GMP) in order to minimise the risks of microbiological and particulate contamination of the product and any risk to the patient.

Both liquid and dry products are manufactured aseptically. Sterility of the product can be ensured by two main techniques:

- Aseptic preparation – maintaining sterility throughout the production process. Liquid products are sterilised on entry to the area by filtration through fine (0.22mm) filters and other components via autoclave, heat sterilisation or controlled transfer of the pre-irradiated component.
- Terminal sterilisation - after filling in a similar clean area, the product is autoclaved on exit from the area. Entry of materials to the filling area uses the same approaches as above.

3.4.1 Clean Rooms

Clean rooms of various classes are used to establish aseptic areas in which to work. Clean rooms use combinations of filtration, air exchange, and positive pressure to maintain a “clean” environment. Clean rooms typically incorporate the following features:

- HEPA/ULPA filters on ceiling
- Exhaust vents on floor
- Drains in aseptic processing areas are inappropriate
- Airlocks and interlocking doors to control air balance
- Seamless and rounded floor to wall junctions
• Readily accessible corners
• Floors, walls, and ceilings constructed of smooth hard surfaces that can be easily cleaned
• Limited equipment, fixtures and personnel
• Layout of equipment to optimize comfort and movement of operators.

There are a number of standards which specify the performance of clean rooms. Typically, compliance is assessed with measurements taken using direct reading particulate counters, air flow velocities and microbial counts. Figure 12 below summarises the requirements of different standards.

![Figure 12: Clean Room Classifications](image)

<table>
<thead>
<tr>
<th>US federal Standard 209 Classification</th>
<th>ISO 14644-1 Classification</th>
<th>WHO Technical Report Series, No. 961</th>
<th>&gt;0.5μm particles/m³</th>
<th>Viable microbes (cfu/m³)</th>
<th>Ave Airflow velocity (m/sec)</th>
<th>Air Changes per hour</th>
</tr>
</thead>
<tbody>
<tr>
<td>100,000</td>
<td>8</td>
<td>D</td>
<td>3,520,000</td>
<td>100</td>
<td>0.03 to 0.05</td>
<td>5-48</td>
</tr>
<tr>
<td>10,000</td>
<td>7</td>
<td>C</td>
<td>352,000</td>
<td>10</td>
<td>0.05 to 0.08</td>
<td>60-90</td>
</tr>
<tr>
<td>1,000</td>
<td>6</td>
<td>B</td>
<td>25,200</td>
<td>7</td>
<td>0.13 to 0.20</td>
<td>150-240</td>
</tr>
<tr>
<td>100</td>
<td>5</td>
<td>A</td>
<td>3,520</td>
<td>1</td>
<td>0.20 to 0.40</td>
<td>240-480</td>
</tr>
</tbody>
</table>

Pressure differentials are used to maintain airflow from higher cleanliness areas to adjacent less clean areas. A minimum of 10-15 Pascals should be maintained between the aseptic area and an adjacent room with differing clean room classifications (doors open).

Certain materials are not permitted in aseptic areas such as: Fiber-shedding materials e.g. cardboard and paper. Wood, Copper and Aluminium.

### 3.4.2 Sterilisation Hazards

From the occupational hygiene point of view, cleaning and in particular sterilisation of the production area may pose a significant hazard in sterile operations.

Use of formaldehyde to sterilise a facility after shut-down has been a common technique. The area is cleaned, and then formaldehyde pellets or solution are heated to produce formaldehyde gas. With the hazards associated with formaldehyde this can obviously only be performed with a facility unoccupied and strict control of entry to an area is required. Once formalisation is complete the formaldehyde is purged from the area and appropriately protected staff must confirm absence of residual formaldehyde in the area & cupboards etc using appropriate monitoring techniques.

More recently the use hydrogen peroxide vapour has gained in popularity as a means of sterilising a facility or equipment. A number of companies now make integrated systems which can be linked
directly to sterile filling isolators or rooms. These systems leak test an isolator before vaporizing a solution of hydrogen peroxide and introducing this to the area for a fixed period, in which time most of the hydrogen peroxide converts to water. After a set period the system is vented and confirmed as ready for use. Hydrogen peroxide detection systems are integrated and can alarm to abort a sterilisation cycle or evacuate an area if leakage of hydrogen peroxide is detected.

Manual cleaning methods are also used. This involves the intense manual cleaning of the areas with a number of cleaning agents. These agents themselves can pose a hazard, particularly as large surface areas (all wall, floor and machine surfaces) have to be treated. Cleaning agents containing formaldehyde and glutaraldehyde, sodium hypochlorite or other chlorine liberating cleaning agents may be used.

3.4.3 Production Hazards

In sterile areas operators pose the main risk of contamination to the product. GMP demands mean that intervention to the process is very restricted. Operators are therefore separated or remote to the process resulting in the reduction of exposure risks. However, some conflicts between the requirements of GMP and occupational hygiene can occur. For example, handling of sterile materials is often carried out under positive pressure laminar flow air that directs any contamination towards the operator. The use of any RPE, such as disposable respirators in aseptic area can be extremely difficult to gain approval for due to particle shedding and potential bioburden on the respirators. Whilst ‘surgeons’ masks are worn for product protection these are not approved for nor do they provide respiratory protection and must not be relied upon for operator protection. Compromises between these GMP and occupational hygiene conflicts can be difficult to achieve.

Where liquid products are manufactured, the exposure issues are generally simpler to manage as the majority of the process following dispensing & making the product solution is carried out with the product as (usually) an aqueous based liquid. Solvent based products are manufactured too and as well as controlling exposure to the solvent by inhalation and skin contact consideration must be given to the potential for the solvent to carry API through the skin resulting in systemic effects.

Dispensing may be done using a downflow booth or isolator as already described. Ideally the dispensed material can be made up into solution in the same containment system and added to the process as a liquid, simplifying downstream handling.

Inhaled products are widely used in the industry for the delivery of bronchodilators (b-agonists such as salbutamol) and anti-inflammatory drugs (glucocorticosteroids such as fluticasone) for the treatment of asthma. The traditional delivery system for these has been the pressurised metered dose inhalers (Ventolin etc) but dry powder inhalers are a rapidly growing dosage form.

With dry powder inhalers the hazards associated with handling the propellants do not exist but being a dry dosage form, powder handling issues provide the greater challenge especially as
products are typically micronized and so potentially very dusty. With glucocorticosteroids being highly potent, isolators are the preferred control measure for dispensing and blending of small batches. Filling processes require careful design in order to control airborne emissions - the use of isolators for addition of API to filling machine hoppers and filling cabinets maintained under negative pressure. Additionally, procedures need to be adopted and supervised to prevent the spread of surface contamination and skin contact.

Pressurised metered dose inhalers are filled with the micronized actives held in liquid propellant(s). Propellants used in these products must obviously be of low toxicity but have posed an environmental risk as they were originally CFCs but most have now been reformulated to use the less damaging HFA’s.

Careful control of the filling process is required to prevent escape of both active and propellant. Use of CIP systems with solvent recovery are extensively used but manual cleaning of smaller parts may be necessary with the associated inhalation and skin exposure risks.

3.5 Research and Development

Research and Development (R&D) within the pharmaceutical involves the Laboratory synthesis, formulation, testing and analysis of synthesised and formulated products, development of analytical methods. As such R&D involves all of the processes and activities which occur in API and FP manufacture. The main difference in laboratories is that most activities are small scale involving gram quantities of solids and millilitres of liquids. Development functions such as pilot plants can use larger quantities, in miniature versions of manufacturing equipment.

Standard laboratory processes with glassware are generally used for chemical synthesis. Preparation of active and excipients for formulation uses bench top scale equipment for particle size reduction and blending, tablet making, capsule filling etc. Low hazard activities with low hazard materials are carried out on the bench. Activities and/or materials perceived to carry a moderate risk are carried out in a fume cupboard. For materials and/or activities expected to have a higher risk bench top extraction hoods and isolators may be used dependent on the dustiness of the task. Testing uses standard laboratory methods and equipment to the highest technology levels for chemical and physical analysis.

R&D within the pharmaceuticals does however involve some activities which are unique:

- **Lack of Information**
  
  In the development phase, there can be substantial gaps in information that is available, as animal studies and in human trials may not have been completed yet. Hazard Assessments and Control Banding / Categorizations were developed to address this and allows a professional to make a judgement on which category a new compound may fall in, which then allows
appropriate controls to be put in place. This will be discussed in more detail within other Chapters.

- **Process Controls**
  At the development scale, process controls are not yet defined and may vary as the process becomes established. Therefore, flexibility is needed in batch records and documentation. As well Formulation Scientists often requires additional sampling and interactions with the production to enable better characterization of the process and the product. The goal in the end is a robust commercial process where direct interactions with the product occur less frequently. This can present a challenge for potent compound handling.

- **High throughput screening of novel compounds for new applications**
  The test compound it is added to a medium containing the bacteria or virus target. High speed liquid jets may release aerosols from which the liquid can rapidly evaporate leaving very fine particles which can penetrate deep into the lung if inhaled. Surfaces may also be contaminated which may raise the risk from dermal contact from some materials.

- **Animal testing**
  Animal skin, fur etc may cause a reaction in some people either through inhalation or skin contact. A combination of good ventilation and regular cleaning to reduce the build-up of allergens with worker personal protection (such as gloves, long sleeves, a face mask) and pre-employment screening are generally used to manage this.

- **Novel technologies**
  The application of new approaches generally starts in development with a new product or a new product type such as multi layered tablets. Examples are
    - **Liquid dispensing technology**, where the API in solution is added to a depression in the middle of a “blank” tablet and is absorbed. This avoids the need to dispense the API as a powder and is particularly advantageous with high hazard materials that have low exposure limits.
    - **Supercritical fluids**. Use of supercritical fluids such as carbon dioxide utilizes the solvent properties of fluids above their critical temperature and pressure, where they exhibit both liquid-like and gas-like properties. By replacing solvents, they can lead to improved control of product characteristics such as particle size, solubility and crystalline structure. This can lead to products that are better absorbed or more stable. It also provides a route to manufacture nanoparticulate pharmaceuticals. Eliminating organic solvents has environmental benefits.
References:

Chapter 4: Hazard Assessment and Communication

4 HAZARD ASSESSMENT AND COMMUNICATION

4.1 Hazard Assessment and the Product Development Process

4.2 Occupational Toxicology Testing

4.3 Determination of an Occupational Exposure Limit (OEL)
   4.3.1 Identification of a Lead Effect
   4.3.2 Estimated Human NOEL
   4.3.3 Allowable Daily Exposure
   4.3.4 NOEL Calculation
   4.3.5 Calculation of OELs

4.4 Acceptable Surface Limits

4.5 Hazard Banding
   4.5.1 Definition of an Occupational Hazard Category
   4.5.2 Assigning Substances to OHCs

4.6 Hazard Communication
4.1 Hazard Assessment and the Product Development Process

Toxicological studies are an important element in the evaluation of new drug candidates to determine whether they are safe to administer to humans for therapeutic purposes. Companies employ pharmaceutical toxicologists to support the drug development process. They help to screen out chemicals that will not be safe enough for use as medicines, and to identify the optimal dosage and administration routes for those that are safe enough in that the therapeutic value outweighs any side effects.

Toxicology studies can be classified as:

- **Pharmacodynamics (PD)**, which is the study of how a drug affects the body, including both therapeutic and unintended side effects.

- **Pharmacokinetics (PK)**, which describes how the body deals with a particular drug. It includes the mechanisms of absorption and distribution, as well as the chemical changes of the substance in the body (metabolism) and the effects and routes of excretion of the metabolites of the drug. Pharmacokinetic properties may be affected by elements such as the site of administration and the dose of administered drug which may influence the absorption rate.

PD and PK are often summarized by saying that pharmacodynamics is the study of what a drug does to the body, whereas pharmacokinetics is the study of what the body does to a drug.

**Figure 1** Stages in toxicology testing for new medicines (Source: British Toxicology Society)

- Early in drug development, computer models can be used to predict toxicity based on knowledge of the intended target and chemical structure or existing knowledge of the properties of the chemical or similar chemicals.
- Once chemists have synthesised potential new drugs, *in vitro* screening tests can quickly indicate if the new drug is likely to cause skin or eye irritation or damage DNA.
- Toxicologists can use computer models and *in vivo* tests to understand whether metabolism within the body is likely to affect the toxicity of the drug.
- Once a promising candidate drug has been chosen, it must be more comprehensively tested for toxicity; this involves the use of animals. The blood and tissues from exposed animals need to be carefully examined for toxicity. Later in the drug development process, it may also be necessary to determine whether the drug may cause cancer or is likely to cause developmental or reproductive toxicity, such as effects on fertility or birth defects.
- It may be necessary to design specialised studies to further investigate any toxicity. These experiments often involve sophisticated biochemical, immunological, molecular or microscopical techniques.
Before a new drug can be given to patients, the pharmaceutical company must demonstrate the safety of the drug in a series of laboratory tests. This exact nature of these tests is normally specified by toxicologists working in regulatory authorities, who will ultimately give permission for the drug to be used in humans.

Once the company is satisfied that the drug is effective in treating the disease, that any toxicity is low enough at therapeutic doses, and that the drug is likely to be commercially viable, toxicologists then collate all the toxicological evidence to submit to a regulatory body for approval. If approval is granted, the drug can then be sold for general use in patients. [Source: BTS. Needs permission]

4.2 Occupational Toxicology Testing

One of the challenges is to define what represents an adverse workplace effect for an agent that is inherently designed to modify patient biological function. This is the role of occupational toxicology.

Whilst many of the effects observed are considered desirable in a patient population being treated under medical supervision, they are not acceptable as a result of exposure at work. Current practice in most pharmaceutical companies is to consider the pharmacological properties of an active ingredient to be adverse if expressed in a healthy worker.

The development of a toxicological testing programme requires consideration of the potential for occupational exposure, likelihood of causing an adverse effect, availability of compound for testing and probability that the pharmaceutical will reach large-scale manufacture. This last point is especially important in conserving resources, since there is a high attrition rate in the industry since very few new drug candidates ever reach the drug approval process. This typically leads to the development of a tiered testing approach that is linked to the development track of the new drug substance and initially requires only small quantities of the test compound and utilizes non-animal test methods.

The initial tier of tests typically carried out on chemical intermediates or employed to supplement pre-clinical studies undertaken on the drug candidate may include: computerized analysis of quantitative structure–activity relationships (QSAR); physico-chemical characterization (e.g. pH, octanol–water partition co-efficient); automated high-throughput bacterial mutagenicity tests; and in vitro cytotoxicity tests to predict acute toxicity potential. Since these tests can be conducted relatively quickly and very small scale, they may be undertaken prior to any early medium-scale manufacture in R&D pilot plants.

The second tier of testing, typically undertaken with material obtained from the initial pilot plant campaign, may include ex vivo assays to assess skin corrosion and eye irritation potential.
Only when the drug candidate is deemed to have a good chance of progressing to market and when manufacturing scale has increased is the third tier of tests initiated. This third tier is selected on the basis of results obtained from the in silico and ex vivo studies and may include further evaluation of genotoxicity using mammalian cells in vitro, skin sensitization using the local lymph node assay, skin and eye irritation using rabbit models and an evaluation of acute toxicity. Based upon the results of the third tier and a knowledge of the likely exposures from the ultimate manufacturing process, further tests, such as in vivo genetic toxicity tests (e.g. mouse micronucleus test) and repeat-dose studies to establish target organs, may be conducted.

In order that animal studies be minimized, most pharmaceuticals employ a “3R” alternative methods approach. According to the National Institute of Environmental Health Sciences, the concept of replacing, reducing, or refining animal use in research and testing was first described more than 60 years ago and is commonly referred to as 3Rs:

- **Replacing:** A test method that substitutes traditional animal models with non-animal systems such as computer models or biochemical or cell-based systems, or replaces one animal species with a less developed one (for example, replacing a mouse with a worm).
- **Reducing:** A test method that decreases the number of animals required for testing to a minimum while still achieving testing objectives.
- **Refining:** A test method that eliminates pain or distress in animals, or enhances animal well-being, such as by providing better housing or enrichment.

Test methods that incorporate the 3Rs are referred to as new alternative methods.

Figure 2 is a diagram representing the tiered approach to occupational toxicity testing illustrating alignment to pharmaceutical development milestones.

Data generated from the occupational toxicology test battery are used to establish company OELs or generic exposure control categories defined by hazard categories or bands. The data are also communicated to those potentially handling the chemical, such as company employees, contractors, toll manufacturing partners and distributors, by a variety of hazard communication methods such as safety data sheets, labels and training programs.
4.3 Determination of an Occupational Exposure Limit (OEL)

The pre-clinical safety evaluation of pharmaceuticals is tightly regulated by national agencies. Computer models and tests are required on a variety of animal species and yield data such as acute and repeat dose toxicity, reproductive toxicity, genotoxicity, carcinogenicity and metabolism.

These data sets, as well as a wealth of human data obtained from clinical trials and adverse event profiles of marketed products, are available for the occupational toxicologist to identify potential endpoints of concern from occupational exposure to pharmaceuticals. There may be additional hazards of concern for occupational exposure that are distinct from the primary pharmacological effects.

4.3.1 Identification of a Lead Effect

While it is typical to use hazard or exposure bands and associated controls to support the safe handling of an investigational new drug, the first step in the establishment of an OEL is the identification of the "lead" or "critical" effect. This is defined as the “adverse” effect considered of most concern in relation to the working population.
The effects of increasing exposure to a therapeutic agent may be viewed in the continuum:

1. No pharmacological or toxicological effects observed.
2. Compensatory effects, early effects of dubious significance without health consequences or pharmacological effects only seen in patients exhibiting the disease being treated.
3. Minimal health impairment or signs of pharmacological effects in healthy persons.
4. Overt disease or pharmacological effects.

The effect is considered to become “adverse” during the transition from 2 to 3 (above).

If certain effects of concern have been demonstrated in pre-clinical studies and are judged likely to occur in humans they should also be considered as lead effects, e.g. sensitisation, reproductive hazard.

### 4.3.2 Estimated Human NOEL

Once the lead effect has been identified, in most cases the next step in developing an OEL is to determine a No-Observed-Effect-Level (NOEL). A NOEL may be calculated based on pharmacokinetic (PK) data from clinical trials when these parameters can be directly related to the pharmacodynamic (PD) effect. If not, an estimated human NOEL can be calculated using the equation below. NOEL values are expressed as microgram (μg) per day.

### 4.3.3 Allowable Daily Exposure

Establishing an OEL requires assumptions about the use of PK principles:

- There is a relationship between plasma concentration of a drug, receptor occupancy (or other biochemical effect such as enzyme inhibition) and PD effect.
- Data from clinical studies can be extrapolated to workplace exposure, taking into account the routes of administration. It is generally considered that absorption of material from the respiratory tract can be rapid and that kinetics might be closer to those following intravenous dosing than oral administration.

However, an Allowable Daily Exposure can be selected from clinical studies at a range of doses, or estimated from comparison of dose-response and PD / PK relationships.

Clinical studies often rely on repeated, daily doses administered over a defined period. Although providing valuable information for workplace hazard and risk assessment, this ‘bolus-style’ daily dosing may not always model well the continuous eight-hour exposure envisaged in establishing an OEL. Furthermore, use of the traditional dose metric does not allow for a reliable estimate of a
short-term limit. Infrequent, task-based exposures of much less than 8 hours are probably the most common pattern of exposure in pharmaceutical operations.

Modern drug development activities provide a detailed understanding of PD / PK relationships for active pharmaceutical ingredients. With this information, and using standard clinical PK tools, it is possible to provide a relatively robust estimate of an internal dose that can be accommodated for a particular drug, both from continuous exposure over the work shift and over shorter-term peak exposures. From this estimate, an appropriate OEL may be derived.

- Deposition and absorption of airborne material from the lung is likely to be < 100 % (perhaps only around 20%) due to the following factors:
  - Only particles < 10 mcm are likely to penetrate to the lung
  - A high proportion of even fine particles will likely deposit along the airways or be breathed out
  - Any particles depositing along the airway (>10 micron) are likely to be ingested or expelled in phlegm
  - Clearance mechanisms from the lung are relatively effective with most foreign materials being removed within 24 hours unless the particle load is excessive (significantly in excess of 5000 μg/m3)

- Where oral bioavailability is high and absorption relatively rapid, differences between inhalation and oral exposure are likely to be within the usual safety margins for calculation of occupational exposure limits. This can be verified if comparative intravenous and oral exposure data are available.

- Breathing rate will be about 20 litres/minute equating to a total volume of 10 m³ over 8 hours and 0.3 m³ over 15-minutes. This is a default assumption and is probably very conservative. Literature reference values range from 2.4m³/8 h to 5m³/8 h work day for a man of average size performing work at moderate exertion levels.

The first step in calculating an OEL is to estimate a dosing rate required to achieve the target concentration at the NOEL. The dosage rate can be calculated using the following equation (1):

\[
\text{Dosing rate} = \frac{\text{Target} \times \text{CL}}{\text{F}}
\]

Where:

- T = Target = concentration that triggers no PD activity at the target site and is expressed in terms ng/ml or μg/l
- CL = Clearance = the rate at which the drug is cleared from circulation expressed as l/hour. Clearance is routinely calculated once PK data are available.
- F = Bioavailability: % of dose absorbed. Bioavailability factors depending upon deposition characteristics. If oral bioavailability is reasonable (> 30 %) then it is usually appropriate to employ this in the Acceptable Daily Dose calculation.
The calculated Allowable Daily Dose is then used to estimate the OEL in the normal way, taking account of relevant uncertainty factors.

**Estimation of a Short-Term Exposure Limit (STEL) Using PK Principles**

Similar considerations apply in the calculation of a STEL. However, for short-term exposure a more relevant model is that based upon distribution of a finite dose around the body, accounting for the apparent volume of distribution. The formula for this is straightforward and is again based upon the concentration in plasma, giving rise to no apparent PD effect. The determination of an allowable dose for short-term exposure is described by the following equation.

\[
\text{Allowable dose} = \text{target concentration} \times \text{volume of distribution} \times \text{bioavailability (F)}
\]

- Where target concentration is in ng/mL or μg/L
- Volume of distribution is in l/kg
- Bioavailability = % of the dose absorbed.

Typically, guidance on the application of short-term exposure limits allows exposure for up to one hour, or 4 x 15-minute exposures at the STEL value (EH40). Thus, the allowable dose will be divided by 4 to allow for these multiple excursions and limit the total intake over the working day. This will also serve to reduce the potential intensity of peaks of exposure over the 15-minute time frame.

The calculated allowable short-term dose (exposure) is then used to estimate the OEL, taking account of relevant uncertainty factors. For STEL calculation a volume of air of 0.3 m³ is taken to be representative of that breathed over 15-minutes.

### 4.3.4 NOEL Calculation

\[
\text{Estimated Human NOEL} = \frac{\text{No Observed Effect Level (NOEL)} \times \text{Body Weight}}{\text{Uncertainty Factors (F1}\times\ldots\times\text{F4)}}
\]

The use of appropriate uncertainty factors is addressed below.

**Body Weight**

This factor may be necessary to estimate total doses from those quoted in dose/body weight. A value of 60 kg is typically used as a representative human body weight. 60 kg is also a conventional value used for risk assessments conducted by the World Health Organisation and other health authorities.

**Uncertainty Factors**

Relatively few resources exist to guide the development of uncertainty factors in establishing occupational exposure standards. However, consideration of hazard evaluation and risk modelling in areas such as the development of food and drinking water safety, and other public health

The identification of discrete uncertainty factors, and general approaches to the identification of the range for each factor are aligned with the recommendations of the IPCS (WHO) and other groups, but they also reflect historical experience in establishing OELs. A general scheme for the application of uncertainty factors in OEL decisions is shown in Figure 3.

Figure 3 - Use of Uncertainty Factors in OEL Calculations (Threshold Effects)
Uncertainty Factor F1: Inter-species Variation
Implicitly, \( F_1 = 1 \) when human studies are used to establish the NOEL. Also, \( F_1 = 1 \) when direct effects on the respiratory tract are suggested by pre-clinical studies reflecting inhalation exposures, e.g. respiratory irritation.

Often it is necessary to extrapolate from animals to humans. Elimination and biotransformation of a given dose of chemical is more rapid in small mammals and so may underestimate the power of a substance to cause adverse effect in humans. An adjustment factor based upon metabolic rate is used to allow for such differences between species when scaling NOELs. The use of this uncertainty factor has proved more reliable than using merely a body weight comparison between the animal test species and humans. The following values are used for uncertainty factor F1 when scaling data from routes other than inhalation, e.g. oral:

- \( F_1 = 7 \): used for extrapolating from mouse studies to humans;
- \( F_1 = 4 \): used for extrapolating from rat studies to humans;
- \( F_1 = 4 \): used for extrapolating from guinea pig studies to humans;
- \( F_1 = 3 \): used for extrapolating from dog studies to humans;
- \( F_1 = 2 \): used for extrapolating from rabbit studies to humans;
- \( F_1 = 2 \): used for extrapolating from monkey studies to humans.

On occasion, there will be sufficient drug metabolism and pharmacokinetic data for both animals and man to more accurately estimate the value of \( F_1 \). When experimentally derived values are available, these may be used to replace the default values shown above.

Uncertainty Factor F2: Intra-species Variability
This factor allows for an expression of effects that may render individuals in a species group more or less sensitive to the pharmacological or toxicological effects of certain substances.

In many cases when using pre-clinical studies or small-scale clinical studies to guide selection of the NAEI, variability in response among individuals may not be apparent, and use of a default value of 10 is warranted. However, when significant variation in biological responses to a substance is identified, whether based on pharmacokinetic variation or other susceptibility-altering factors, values ranging from 3 to 10 may be used.

Uncertainty Factor F3: Adequacy and Quality of Information
Confidence in the predictability of the hazard appraisal process for human health outcomes increases along with the amount of information that is available from Lead Effect Studies.

The magnitude of this uncertainty factor should be based upon the quality and completeness of information from which the NOEL is obtained, regardless of other information that is available.
• *F3 = 1*: This value is to be assigned to F3 when calculations based on extensive clinical data, resulting from repeated administration, indicate a definitive NOEL. This factor is also used when a definitive NOEL is available from good-quality pre-clinical toxicity studies or other studies, conducted over an appropriate time period to ascertain the nature of the hazard (e.g. developmental toxicity studies).

• *F3 = 3*: This value is suggested when results from clinical data are used that do not involve repeated administration or are not of sufficient quality to allow definitive extrapolation of results to the occupational scenario. This factor is also used when a definitive NOEL is available from pre-clinical studies in which a NOEL is established from sub-chronic exposure.

• *F3 = 5–10*: Consideration should also be given to the use of this factor when pharmacokinetic or pharmacodynamic information has been used to provide a more accurate extrapolation of animal data to man.

• *F3 = 3–10*: A value from this range should be used in cases for which data on the lead effect identify a Lowest-Observed-Effect Level (LOEL) instead of a NOEL from either clinical or pre-clinical studies.

• *F3 >> 10*: Values greater than 10 will only be used in those exceptional circumstances in which there is substantial concern regarding interpretation of studies (because of experimental design, etc) addressing a critical endpoint.

When the information available for a substance does not fit the above scheme exactly, judgement should be used in assigning an appropriate value for F3 following the scheme of the above guidelines. The rationale for the assignment of F3 should be fully documented and included in OEL criteria documents.

**Uncertainty Factor F4: Nature and Severity of Effect**

In general, the foregoing uncertainty factors (F1–F3) account for critical elements of interpretation for most study outcomes. However, certain target organ or other effects are of concern because of the irreversible or otherwise severe consequences for health. Uncertainty factor F4 provides for a level of conservatism in situations where serious effects with incompletely understood dose-response characteristics form pivotal studies in establishing an OEL.

In general, the use of F4 applies to events which are believed, or demonstrated, to have a dose threshold (e.g. adverse effects on developmental endpoints, tumorigenicity arising from non-genotoxic effects). Where such concerns exist and, when data from relevant studies are not available, F4 can be used to give an added level of conservatism to the OEL. The F4 value used will depend upon the level of concern. For example, where the concern relates to known teratogenic effects arising from a specific pharmacological class, then a value of 10 might be considered if such effects are observed with no sign of maternal toxicity. Similarly, a smaller factor (e.g. F4 = 5) may be applied to the same endpoint, if fetal effects are only observed when accompanied by maternal toxicity.
Stochastic (Non-threshold) Effects
A special set of concerns arises for some adverse effects; in particular genotoxicity, carcinogenicity and respiratory sensitisation, where it may not be possible, based on present knowledge, to define a threshold for adverse effect. In such cases it must be assumed that any level of exposure, however small, may carry some finite risk and OELs for substances possessing these properties must be established pragmatically rather than being purely based on traditional dose-response concepts. Decisions about uncertainty are made on a case-by-case basis considering the weight of evidence, available dose-response information, and other factors. However, the practical outcome of such considerations may be to establish a pragmatic OEL with the recommendation to control exposure to levels considered to carry a sufficiently low level of risk.

4.3.5 Calculation of OELs

The estimated human OEL is calculated by dividing the NOEL value by the amount of air normally breathed over an 8-hour period of moderate physical activity, assumed by default to be 10m³ as discussed above.

\[
\text{OEL} = \frac{\text{Estimated Human NOEL (mcg)}}{10 \text{ m}^3}
\]

Upper Limit for an OEL
On occasions, when chemicals are not toxic or pharmacologically potent, a very high value for the OEL may be calculated by occupational toxicologist.

Time Average Basis for OELs
OELs are usually expressed as the Time-weighted Average (TWA) over an 8-hour period, taking into account the known effects of repeated or prolonged exposure to the substance.

However, for certain substances, it is important to prevent peaks in exposure that are not controlled by application of an 8-hour TWA. Thus, a Short-term Exposure Level (STEL) may be established. A STEL is usually expressed as a TWA over a 15-minute period and takes into account the known acute effects of the substance (e.g.; pharmacological effect of acute onset, respiratory irritation, irreversible effects, etc.). It is important to understand that a STEL may be set to prevent health effects that are not the same as those which would determine the level for an 8-hour TWA OEL.

In general, STELs should be set using the available relevant scientific data to produce a control regime (level, frequency, and duration of exposure) that is useful in the workplace. However, in some cases a pragmatic approach may be taken with the STEL value being set 3-fold greater than a corresponding 8-hour TWA OEL. Inasmuch as a STEL value implies that a substance will have adverse effects of rapid onset or for some other reason requires control over short periods, excursions above a STEL value are not to be permitted.
Notation of Special Hazards

In determining OELs for proprietary substances, certain potential health hazards will be identified which require notification to staff. These effects are generally those for which the occurrence of the effect is stochastic or for which there is no well-formed basis for identifying:

- dose-response characteristics;
- any employees at extra risk;
- routes of exposure other than inhalation that could be a significant occupational hazard.

In particular, a systematic means for notation of the following effects is required, for example:

- suspected or proven human carcinogens (carcinogen);
- reproductive hazards (adverse effects on fertility, development, or lactation) (reproductive hazard);
- respiratory sensitisers (respiratory sensitiser);
- dermal sensitisers (skin sensitiser);
- corrosive substances (corrosive);
- the potential for significant skin absorption contributing to systemic dose (skin).

Such hazard notations, as appropriate to the substance, should accompany the OEL value wherever published.

4.4 Acceptable Surface Limits

For drug substances where there is a potential for skin absorption and systemic effects from skin absorption, the occupational toxicologist may have derived an Acceptable Surface Limit (ASL). The occupational hygienist should ask the occupational toxicologist questions about the derivation of the ASL similar to above.

With an OEL and ASL available, analytical methods for analyzing air and surface samples should be developed if not already available and should be targeted at 50% of the target limit (OEL or ASL) as an action limit when feasible.

Residual Cleaning Level (RCL)

The RCL is the concentration that assures that the cleaning limit guideline has been met. The RCL is calculated from the Residual Dose Level and is based upon the equipment, the subsequent batch size, and the daily dose of the subsequent drug.

Cleaning Limits Guidelines established by the committee for the divisions to follow when cleaning their non-dedicated equipment. The guidelines assist the division in preventing product cross contamination. The guidelines include a residual dose level and a cleaning statement. The divisions use the guidelines to calculate residual cleaning levels for their equipment.
The Cleaning Statement refers to the part of the cleaning limit guideline that expresses the requirement that product contact surfaces must appear clean and rinse solutions must be clear and colorless after the equipment has been cleaned.

4.5 Hazard Banding

During the early stages of drug development, the lack of available toxicological and pharmacological data makes it extremely difficult to set a numerical OEL for the pharmaceutical active ingredient. Moreover, for some materials, such as certain isolated chemical intermediates and raw materials, there are never sufficient data generated on which to establish a health-based OEL. Consequently, an alternative approach to control exposures, based upon semi-quantitative criteria for assessing compounds and knowledge of the effectiveness of containment technologies, has been adopted by most pharmaceutical companies. This generic control approach, variously known as ‘hazard banding’, “hazard categorization” or ‘exposure banding’, uses available toxicological or pharmacological properties to assign the substance to one of four or five discreet occupational hazard bands.

These bands are related to control strategies known to provide the necessary degree of workplace exposure control to protect employees. Such control banding has become a generic approach used by, for example, ILO, but originated and is much more highly developed in the pharmaceutical industry (see Chapter 7).

4.5.1 Definition of an Occupational Hazard Category

An Occupational Hazard Category (OHC), sometimes referred to as an Occupational Exposure Band (OEB), is defined as a grouping which classifies compounds based on health hazards. The specific hazards of materials within an OHC may not be comparable but to avoid ill-health following exposure all materials in an OHC require control to the same degree. In general, the least hazardous materials are classified as OHC 1; the most hazardous as OHC 4 or 5 depending on the number of bands used.

4.5.2 Assigning Substances to OHCs

OHCs are to be established for Active Pharmaceutical Ingredients (APIs), isolated intermediates, proprietary starting materials and other “key substances” used in syntheses of APIs. In general, OHCs are assigned to materials occurring as solids; as dictated by knowledge of potential health hazards liquid materials may also be assigned an OHC. In this context, the term “key substance” is inclusive of reagents and excipients used in bulk, i.e. pilot plant and larger scale manufacture. For brought-in chemicals, occupational exposure limits supplied by various external agencies (when they are available), or more rarely, limits established by companies which make or distribute the
chemicals may be adopted for use. If no occupational exposure limit has been set and if toxicity data are available, an OHC (or OEL) can be established if there is potential for exposure to employees.

Where a defined exposure standard set by another manufacturer, or similar credible value exists, those standards should be recognised. An OHC corresponding to the available OEL may be assigned to aid in guidance of appropriate workplace controls but does not supersede regulatory standards. In general, substances which are used as excipients, flavourings, colourants, coatings, etc, and perceived by occupational toxicologists to represent minimal hazard will not be assigned an OHC unless there is concern for exposure and possible ill health.

In general, the following minimal information should be available before assignment of substance to a data-derived OHC:

- basic discovery pharmacology (API only);
- structure-activity assessment;
- relevant physio-chemical information.

Business circumstances may dictate that an OHC be set on a more compact data set. In this case professional judgement should guide the selection of relevant elements of a partial data set in formulating an OHC.

As substance-specific health hazard information accrues during product development, APIs will be considered for assignment of an Occupational Exposure Limit (OEL). Isolated intermediates, raw materials and reagents generally retain only an OHC throughout the product lifecycle and do not receive consideration for assignment of an OEL, although additional health effects information (e.g. irritation and sensitisation potential) for these substances is frequently available. In circumstances where substantial information regarding adverse effects is available and there is concern for occupational exposure, an OEL may be established for an isolated intermediate, raw material, or reagent by exception.

Preliminary Data Assessment and Initial OHCs
To facilitate establishing OHCs, all newly identified substances are assigned to OHC 3 as an initial, default or provisional position. For some substances, appraisal of available data may suggest an alternative initial OHC be established other than OHC 3 (e.g. many reagent substances would be anticipated to be OHC 1 or 2). Occupational toxicologists will review available data to ensure that substances of either limited hazard (e.g. some reagents, excipients) or of high hazard are assigned to an appropriate OHC.

Methodology and Timing for Assigning Substances to OHCs
The use of categorical methods for summarising and communicating potential occupational hazards in the pharmaceutical industry has been widely discussed (for example, Naumann et al, 1996; Olson
et al, 1997, Binks, 2003). There are also hazard categorisation schemes published by regulatory agencies in some national jurisdictions (e.g.; the HSE in the UK).

The methodology and data gathering procedure differs depending on the type of substance concerned as outlined below.

**Therapeutic Substances**

An OHC is initially set at the time a substance is formally selected as a candidate for development, from among the lead substances in a therapeutic development programme. This initial OHC will be based upon the results of a structure activity prediction, screening for potential genetic toxicity, plus additional relevant information such as pharmacological potency. All substances will initially be placed in OHC 3, unless a substantial concern exists to suggest that OHC 4, or another category, is more appropriate. Occupational toxicologists should review available data to ensure assignment to an appropriate OHC.

When sufficient data become available for a relatively complete health effects review (usually when a substance is transitioned through commit to product development status and nearing a decision to engage in Phase III trials) the OHC will be replaced with a health effects-based OEL (for general timing see Figure 1). Business decisions supporting materials sourcing and facilities design may require OHCs to be established in advance of pre-set milestones.

**Isolated Chemical Intermediates and Starting Materials**

An OHC is initially set for isolated intermediate substances near the time of introduction of a process into a chemical pilot plant. This initial OHC will be based upon the results of a structure activity prediction and may be supplemented with results of a bacterial mutagenesis assay for materials with chemical structures of high concern as potential mutagens. All isolated chemical intermediates will initially be assigned to OHC 3 unless results of structure activity prediction, bacterial mutation assessment, or other considerations suggest another OHC (see Appendix 2). Occupational toxicologists should review available data to ensure assignment to an appropriate OHC.

After achieving proof of concept and when it is likely that clinical trials will progress to Phase II/III, certain *in vitro* indicator assays for endpoints, such as ocular irritation and skin corrosion, may be conducted using generally accepted methods. In general, positive results in these assessments will allow hazard labelling and exemption from further testing. Following the proof of concept decision and consultation with project managers in Chemical Development, an acute toxicity package will be initiated. Further data such as 28-day repeat dose oral toxicity, and *in vivo* clastogenicity or mutagenicity assays may be commissioned to allow further review of the OHC. Results of the package of toxicity studies will allow re-evaluation of OHCs prior to events such as manufacture of validation batches, decisions on materials sourcing, or commissioning a commercial manufacturing plant.
4.6 Hazard Communication

Monographs
Most companies have realised the importance of documenting the rationale for their Occupational Exposure Limits. This is typically done in the form of a monograph. The monograph communicates the assumptions and conclusions to other stakeholders, such as occupational hygienists, physicians, engineers and line management. It also ensures that any follow-up actions, such as the need to develop substance-specific occupational hygiene analytical methods, health surveillance procedures or workplace controls are identified.

OHC are based on the properties of the material, and therefore doesn’t change during the life cycle of the product. For example, the pure API will have the same OHC as the finished product that might only have a drug load of 1%. What can change is the associated controls.

Another consideration is that companies often focus on controlling potent compounds, and although they have a lower exposure limit, there are still hazards associated with the low potency products. A good example is a product that is a sleep aid, it is likely to be a OHC 2, however, exposure could lead to an operator becoming sleepy, which in turn could lead to a serious injury (for example if they fell asleep while driving home from work). When hazard communication is presented to employees, it is important to communicate that although exposure levels change depending on the properties of the material, it is important we are controlling products so that there are no exposures above the established limits.

Safety Data Sheets
Safety Data Sheets although are an important regulatory required piece of information, the quality of the data can be poor in some cases depending on the source of the material. For pharmaceutical manufacturing and determination of OHC, a more thorough understanding of the material is required and is generally provided by occupational toxicologists.

Potent Compounds Training
Employees working with pharmaceutical products need to have a clear understanding of the materials they are working with, how to protect themselves and how to recognize if a potential exposure might have occurred (signs and symptoms). To accomplish this, a detailed training program should be created and delivered to employees interacting with products and for those that may inadvertently come into contact with products.
References and Further Reading


### Appendix 1: Example Criteria for Allocation of Substances to OHCs

<table>
<thead>
<tr>
<th>OHC 5</th>
<th>HYGIENE GUIDE</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤1 μg/m³ (solids)</td>
<td>Substances known to be carcinogenic to humans or with very strong experimental evidence for carcinogenicity, unless potency suggests a less stringent OHC.</td>
</tr>
<tr>
<td>≤0.05 ppm (liquids, vapours)</td>
<td>Substances giving cause for concern over mutagenicity, which in the opinion of an expert, is sufficient to justify high containment, unless potency suggests a less stringent OHC.</td>
</tr>
<tr>
<td>&gt;1 - ≤10 μg/m³ (solids)</td>
<td>NCEs with predicted therapeutic dose &lt; £0.1 mg/day unless specific information indicates that lower doses may be allowed e.g. respiratory products (or higher doses when combined with evidence of irreversible effect or sudden on-set incapacitating effect)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>OHC 4</th>
<th>HYGIENE GUIDE</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;0.05 - ≤0.5 ppm (liquids, vapours)</td>
<td>Substances suspected of being carcinogenic to humans or with very strong experimental evidence for carcinogenicity, unless potency suggests a less stringent OHC.</td>
</tr>
<tr>
<td>&gt;0.05 - ≤0.5 ppm (liquids, vapours)</td>
<td>Substances for which there is reason to suspect carcinogenicity by analogy with closely related substances, unless potency suggests a less stringent OHC.</td>
</tr>
<tr>
<td>&gt;1 - ≤10 μg/m³ (solids)</td>
<td>Substances giving cause for concern over mutagenicity, which in the opinion of an expert, is sufficient to justify high containment (see next entry)</td>
</tr>
<tr>
<td>&gt;0.05 - ≤0.5 ppm (liquids, vapours)</td>
<td>Substances with high-concern structural alerts for possible mutagenicity and positive, concentration-related responses in one or more in vitro genetic toxicity tests.</td>
</tr>
<tr>
<td>&gt;0.05 - ≤0.5 ppm (liquids, vapours)</td>
<td>Substances classified as toxic to reproduction or lactation, unless potency suggests a more appropriate OHC</td>
</tr>
<tr>
<td>&gt;0.05 - ≤0.5 ppm (liquids, vapours)</td>
<td>Substances classified as causing a serious irreversible effect.</td>
</tr>
<tr>
<td>&gt;0.05 - ≤0.5 ppm (liquids, vapours)</td>
<td>Substances classified as very toxic.</td>
</tr>
<tr>
<td>&gt;0.05 - ≤0.5 ppm (liquids, vapours)</td>
<td>NCEs with a predicted therapeutic dose &lt;£ 1 mg/day.</td>
</tr>
</tbody>
</table>
| OHC 3 | HYGIENE GUIDE | Substances of unknown toxicity not allocated to another OHC (initial OHC for uncharacterised substances).
|       |               | Substances classified as respiratory sensitisers, unless potency suggests a more appropriate OHC.
|       |               | Substances classified as moderate, strong or extreme skin sensitisers, unless potency suggests a more appropriate OHC.
|       |               | Substances classified as corrosive or severe eye irritants, (where physical form suggests low potential for exposure, a less stringent OHC may be considered).
|       |               | Substances for which there is experimental evidence for carcinogenicity that is not adequate for making a satisfactory assessment (Cat 3 Carcinogens), unless potency suggests a more appropriate OHC.
|       |               | Substances giving cause for concern over mutagenicity, unless in the opinion of an expert, there is justification for a more stringent OHC.
|       |               | Substances classified as harmful to reproduction, unless potency suggests a more appropriate OHC.
|       |               | Substances classified as toxic.
|       |               | Vapours causing drowsiness or dizziness, unless potency suggests a more appropriate OHC.
|       |               | NCEs with a predicted therapeutic dose >1 –50 mg/day. |
| OHC 2 | HYGIENE GUIDE | Substances classified as harmful.
|       |               | Substances for which there is evidence of cumulative effects but not sufficient to classify as toxic.
|       |               | Substances for which there is evidence to suggest concern for sensitisation (mild sensitisers) but not sufficient to classify as sensitisers.
|       |               | Substances not classified as hazardous following acute exposure but lacking evaluation for potential effects of repeated exposure.
|       |               | NCEs with a predicted therapeutic dose >50 mg/day. |
| OHC 1 | HYGIENE GUIDE | Substances classified as an irritant.
|       |               | Substances not classified as hazardous (based on appropriate data set) and for which there is no reason to suspect hazardous properties. |
**Glossary of Terms**

**In vivo** Studies in whole, living organisms

**Ex vivo** Studies in live, isolated cells, extracted from a living organism eg. cultures from a biopsy.

**In vitro** Studies “in glass”, ie. in a laboratory environment using test tubes, petri dishes etc.

**In silico** Studies performed on a computer or by computer simulation.

**Substance** A general term which can include new therapeutic substances, pharmaceutical actives, chemical intermediates, reagents, and excipients.

**NCE** New Chemical Entity
Chapter 5: Exposure Assessment

5  EXPOSURE ASSESSMENT

5.1 Introduction

5.2 Air Sampling
   5.2.1 Selection of Sampling Equipment
   5.2.2 Sampling Methodology
   5.2.3 Practical Considerations
   5.2.4 Data Interpretation

5.3 Exposure Prediction
   5.3.1 Qualitative Expert Judgment
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5.7 Wipe Sampling
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   5.7.2 Standards for Surface Contamination

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5.9 Qualitative Exposure Assessments and Surrogate Sampling
5.1 Introduction

Characterisation of inhalation exposure in the pharmaceutical industry is dominated by measurement of Active Pharmaceutical Ingredients (APIs) and intermediates because their occupational exposure limits are typically much lower than the other materials involved.

Control of APIs usually provides adequate control of associated excipients, which tend by their nature to be of low hazard. Exposure to other hazardous materials such as solvents can usually be well controlled by normal process engineering measures such as pumped transfers. Standard sampling and analytical techniques can be applied to these materials when required.

Since APIs are most commonly powders and can generally be assumed to be totally absorbed into the body when inhaled, it is normal to measure personal exposure to inhalable particulates, following the CEN/ISO/ACGIH convention. Respirable dust measurements are seldom required (an exception being for Human Growth Hormone which is easily broken down by stomach acid).

The low concentrations involved have several consequences:

- Gravimetric analysis is rarely sufficiently accurate for personal exposure determination. Chemical specific methods are needed and the analysis can necessitate sophisticated techniques. Thorough validation of analytical methods is essential.
- Real time particle counters are of limited value because background levels of dust may be comparable to the levels of the materials being measured.
- Variations in sampling efficiency caused by choice of sampling heads can be important, and wall losses need to be accounted for.

Most pharmaceuticals are produced in relatively small quantities by batch processes. Manufacturing campaigns may be infrequent and it follows that obtaining sufficient personal sampling data to characterise exposure can be difficult. The industry has therefore become very interested in exposure prediction, both by groups of experts and by exposure modelling.

Skin exposure becomes an increasing problem with potent compounds especially for those that may be allergic sensitizers. Traces deposits may be invisible but chronic exposure can still lead to serious health effects.
5.2 Air Sampling

5.2.1 Selection of Sampling Equipment

The most widely used samplers in the industry are the 37mm Closed Face Cassette (CFC) and the IOM sampler. Other inhalable dust samplers sometimes used are the GSP and the 25 mm Button sampler.

![Diagram of Closed Face Cassette](http://www.westernsafety.com/zefon/zefonpg2.html) (accessed 16 Feb 2014)

The 37-mm diameter ‘closed face cassette’ (CFC) is a three-piece non-conductive polystyrene cassette which has a 4-mm circular aspiration orifice. It was one of the earliest designs and remains widely used because of its simplicity and low cost. It is usually operated at a flow rate of 2l/min, though some companies are known to use 4l/min to increase analytical sensitivity. It has several known limitations (inner wall losses, bypass leakage, and non-uniform deposition on collection filter) and is recognised for having a low sampling efficiency for particles >30 µm. Wall losses inside the closed face cassette are high and must be recovered by washing it out. The 37mm closed face cassette has advantages in that it is cheap and disposable.

With the IOM sampler, particles are drawn into the device through a 15-mm circular inlet orifice under a suction flow rate of 2l/min. The sampler incorporates an internal cassette, which for gravimetric sampling is weighed together with the 25-mm filter it contains. Most particles passing through the inlet orifice are collected on the filter and the remainder are deposited on the cassette inner walls.
For chemical analysis, the wall losses need to be washed out of the cassette and recovered. Pharmaceutical companies tend to use the stainless-steel version of the IOM head rather than the plastic one to facilitate recovery of API. A field study by GSK and Bureau Veritas examined wall losses for IOM sampling heads with pharmaceutical dusts and found that deposits on the cassette walls ranged from 15% to 61% of the total sample weight. It is clear that recovery of inner wall deposits is critical for API determination, at least with the CFC and IOM heads. An additional consideration for the IOM sampling head is that there is a high degree of manual handling of the cassettes to fit it in and out of the housing body. This is especially important for potent compounds where analytical methods are targeting the nano or pico gram range, and cross-contamination can easily occur. To mitigate this potential problem, frequent glove changes by the hygienist are required.

The SKC Button Aerosol Sampler is a newer device which follows closely the ACGIH/CEN EN 481/ISO 7708 sampling criteria for inhalable particulate mass when sampling at 4l/min. The higher flow rate enhances sensitivity, but a heavy-duty pump is required.
The Gesamtstaubprobenahme (GSP) sampler (also known as the Conical Inhalable Sampler) is a German design used by some European pharmaceutical companies. Inhalable particles are aspirated through a sharp-edged inlet designed for optimal inlet velocity at 3.5 l/min onto a 37-mm filter.

Ambient air movement influences the collection efficiency of samplers and should also be considered in choosing sampling equipment and interpreting data. For example, workers in downflow booths or sitting at laminar flow cabinets may experience high air movement past the sampler.

Aizenberg showed that compared with ACGIH/CEN EN 481/ISO 7708 sampling criteria for inhalable dust, the IOM, GSP and Button heads show fairly high sampling efficiency at 0.5m/s. The closed face cassette (4-mm orifice) produced the poorest performances of all the tested samplers.
Other studies generally support these findings. Görner et al. (2010) found that in calm air the efficiency of the IOM sampler compared to reference criteria for inhalable dust was 92.0%, compared with 41.6% for the CFC. Work by Sleeth and Vincent (2012) at low wind speeds has shown that the IOM and button heads over-sampled relative to the convention at 0.10 m s\(^{-1}\) and showed improving agreement with increasing wind speed. In contrast, the CFC significantly under-sampled and was considered to give results far too low for it to be of use for sampling the inhalable fraction. However, a study by Kenny et al. (1999) showed that in low ambient air movement the GSP also has significant wall losses for larger particles (>30μm) compared to the inhalable particle convention.

Care must be taken in interpreting these findings as the researchers sometimes do not specify whether internal wall losses were considered in their analysis.

5.2.2 Sampling Methodology

Sampling Location

While working with pharmaceuticals that require lower levels of containment (e.g. engineering controls), exposure typically arises from direct interaction of the operator with the process or material. Thus, employee exposure tends to be much higher than background levels in the area, and personal sampling is essential for exposure characterisation. Selection of the sampling locations are critical in all assessments regardless of level of containment. Determination of the static sampling locations is
important to any assessment and is typically performed at weak points in the system such as a pass-through port, through a split valve or at a continuous liner location on a glove box, etc. There are tools available such as using the ISPE Version 2 Good Practice Guide: Assessing the Particulate Containment Performance of Pharmaceutical Equipment. This guide was developed with experts in the industry to facilitate the most appropriate sampling techniques for pharmaceutical processes and is recognized as a best practice.

This tends to be less true for potent compounds which demand higher levels of containment and the elimination of manual intervention. In these situations, there is also a role for static sampling to identify sources of airborne contaminants and are used to assess the general process area or migration patterns. Positioning of static samples needs particular attention if they are to provide meaningful results. Trend information may be more helpful than individual results.

**Sampling Duration**

The batch nature of most pharmaceutical operations gives rise to intermittent short-term exposures. The use of task-based personal sampling protocols has therefore become ubiquitous as full shift sampling is only meaningful for those few pharmaceuticals that are made in large enough quantities to generate essentially continuous production.

Deriving full-shift exposure levels from task-based results depends on assumptions made about the duration of exposure. Whilst exposure duration can be observed directly on the day of sampling, there is no guarantee that the same exposure duration will apply on other days.

Care must also be taken to check what other materials the employee might be exposed to as interactions and additive or synergistic effects are possible. As working patterns are often unpredictable, and are liable to unexpected changes, a degree of caution is advisable in comparing estimated 8-hour exposure levels with Occupational Exposure Limits (OELs).

A common, and precautionary, approach is to compare task-based results directly with the 8-hour limit. Hence, on time weighting considerations alone, a 2-hour sample would carry a safety factor of 4, and a 15-minute sample a safety factor of 32, assuming no other exposure to the same chemical later in the day. However, if the evaluation is based on a small number of samples, the uncertainty in the estimate of true exposure reduces the safety factor quite considerably. In addition, shorter samples further increase the uncertainty of the estimate and so reduce the safety factor still more.
Another advantage of this task-based approach to compliance is that it encourages employers to provide basic containment even for short term tasks, which might otherwise be operated without controls on the strength of a calculated time-weighted average. The task-based approach also gives better information regarding the effectiveness of the containment controls. Operating without containment carries risks. It can lead to a build-up of contamination on surfaces and the attendant possibility of skin contact or absorption as well as potential for carry over to other areas of a facility. There is also the risk that operating duration may become extended over time, particularly in periods of high production pressure.

5.2.3 Practical Considerations

Several possible failure modes must be considered when planning a sampling exercise.

Sample contamination
When considering exposures in the μg/m³-ng/m³ range, extreme care must be taken to avoid contamination of the sample. Contamination may occur during sample device preparation, in the field if capping or uncapping the samples, or when removing the filter from its holder. Care and technique when removing samples is important, and frequent glove changes are required to reduce the risk of contamination of samples. The use of field blanks to check for background contamination is very important.

Product cross-contamination risks
Working in a pharmaceutical manufacturing facility requires specific precautions to be taken to ensure that the product does not become contaminated as a result of the measurement process.

During sampling it is likely that sampling equipment will become contaminated with product. This may give rise to GMP concerns if the equipment is subsequently deployed in other areas. For example, equipment used in penicillin areas may require a documented and validated decontamination procedure before being allowed into a non-penicillin manufacturing areas.

Microbial contamination
Sampling in aseptic areas poses particular problems and there are no agreed standard protocols.

- One approach has been to use vacuum lines from within the aseptic area, which is more suitable for stationary samples rather than personal samples. Valves, flow gauges and sampling lines need to be autoclavable to ensure sterility. Silicone
elastomer tubing (such as Silastic® manufactured by Dow Corning) may be suitable for autoclaving.

- For personal sampling, dedicated equipment kept in the aseptic area may be necessary to reduce the possibility of the sampling equipment bringing microbial contamination into the area. Any sampling equipment to be taken into the area will need to be cleaned and disinfected beforehand. It may be necessary to cover parts of the sampling equipment in a protective material such as a plastic film or bag. Sampling equipment for aseptic areas may also require special modification such as HEPA filtering the exhaust of the sampling pump. Any modifications to pumps should be discussed with the manufacturer to ensure that safety or operating performance is not compromised. Some companies limit the taking of exposure measurements to the production of technical (non-production) batches so that aseptic technique is not required.
- Surface sampling using sterile swabs, and passive sampling using autoclaved petri dishes placed in the aseptic area as settling plates, are also possible.

Before carrying out any air sampling work in cGMP areas you should discuss your proposals with the local manager to ensure that cGMP will not be compromised during your survey. Hygienists will need to be cGMP trained to go into certain areas and must follow in full the local gowning and decontamination procedures.

**Observations**

For Pharmaceutical applications, and potent compound sampling, it is critically important for a Hygienist to monitor and observe the progress as much as possible and take specific notes on the various activities being conducted in the area. This is important, because the exposure limits are very low, below the visible range, and if the results come back higher than expected, these observations may be able to help identify the weak points in the process and enable further improvements.

**Sampling in Flammable atmospheres**

When working in areas where flammable liquids are used, sampling equipment may need to be certified as intrinsically safe to the relevant standard. These situations are common in primary manufacturing facilities and pilot plants.

**Sampling workers who are using Respiratory Protective Equipment**

When workers are wearing RPE (including airline breathing apparatus), personal samples outside the RPE are still appropriate unless it is physically impracticable to attach the sampler. The result represents the exposure that would have occurred in the absence of respiratory protective equipment. If a sample is ever taken inside of
RPE, it must be clearly noted in the sampling paperwork and report, as the result is biased low in relation to the OEL.

It is not appropriate to divide the measured concentration by an Assumed Protection Factor for the RPE and quote the result as the exposure. Even if the RPE performs according to specification, high airborne levels can lead to exposure by indirect routes. The target is to limit exposures to below the exposure limit with engineering or work practice controls and to utilize respiratory protection as a redundant protection. Respiratory protection, and PPE in general, should not be relied on as the sole control.

5.2.4 Data Interpretation

There are many reasons for undertaking air sampling, one of which is demonstration of compliance with an exposure limit. Different countries have different requirements for demonstrating compliance with exposure limits. These are normally based on Time Weighed Averages (short or long term) and involve the use of statistics to calculate the probability of exposures being below the relevant exposure limit.

Individual pharmaceutical companies tend to choose their own internal criteria for demonstrating compliance. Overall, these criteria tend to be more stringent than the formal requirements specified by individual countries. For example, in many pharmaceutical companies there is a convention that task-based exposures are compared directly with the exposure limit. This adds a margin of safety to the compliance process.

There is increasing use of Bayesian Decision Analysis (BDA) to test for compliance for the more hazardous APIs. BDA combines measured exposure data with expert judgment to determine the most likely level of exposure. When data is sparse, Bayesian analysis produces a better estimate than using data alone. An alternate to using BDA when data is limited, is to use a rules-based approach to data interpretation, such as EN 689. These rules apply an additional safety factor by requiring all data to be under a specified percentage of the occupational exposure limit, depending on the number of samples available.

If the data plentiful, descriptive and parametric statistics should be used to draw conclusions. Commonly, the 95th percentile of the data set is used as a comparison to the occupational exposure limit. As an example, one major company allows a 5% error in decision making and adopts a statistical approach to sampling. The fewer samples collected, the higher the safety factor employed. The closer to the exposure limit, the more frequent the monitoring is required, and the more samples collected.
Monitoring strategies are discussed further in Chapter 7.3.3 and AIHA’s IH Stat tool is a resource available for statistical analysis of data sets.

Some companies differentiate between “compliance testing” (i.e. testing against regulatory requirements to determine legal compliance) and “conformance testing” (i.e. testing against internal or industry standards to assess performance). Compliance testing will then follow strictly the relevant national requirements, whereas conformance testing may be more pragmatic.

5.3 Exposure Prediction

The intermittent nature of most batch manufacturing operations and the labour-intensive nature of personal sampling make it difficult to obtain sufficient samples to characterise exposure adequately. Being able to predict exposure levels from a given process does not replace the need for measurement but does allow the hygienist to target sampling resources more effectively. A number of approaches to exposure prediction have been developed, including

- expert judgment
- exposure modelling
- application of control matrices

5.3.1 Qualitative Expert Judgment

Typically, a panel of hygienists familiar with the industry is asked to predict the exposure from a particular operation. Research has shown that individual hygienists can make very different judgments and are unreliable predictors (e.g. Gurumurphy et al. 2003, Logan et al. 2009). Judgment can be improved with training and by taking a group average.

5.3.2 Exposure Modelling

An alternative approach to exposure prediction is to model exposure mathematically. Mechanistic models have been available since the mid-1990s based on a source-receptor approach. Pharmaceutical companies have been active in promoting the development and adoption of such models.

A simple theoretical model (Cherrie, 2009) comprises a source term that is dependent on the intrinsic properties of the contaminant (e.g. the dustiness of a solid), the way the material is handled (e.g. careful scooping of a powder), and finally, the efficiency
of local controls. These three parameters are multiplied together to provide the active emission of the source.

The model then makes assumptions about the dispersion of contaminants in the near-field, close to the worker whose exposure is being investigated; and in the far-field based on room volume and ventilation rates. It can also consider passive emissions from other sources.

Initial quantification of modifying factors is based on expert judgment, but this can then be calibrated against real data.

Attempts to apply this model to pharmaceutical situations have given encouraging results (see Figure 6).

![Figure 6: Scatter plot of assessed exposure level in relation to the observed mean exposure level for a range of pharmaceutical scenarios. (Source: Cherrie et al. 2009)](image)

Cherrie’s exposure model has been greatly refined in the Advanced REACH Tool (ART) based on Tielemans et al. (2008). ART is available online at [www.advancedreachtool.com.](http://www.advancedreachtool.com) The ART exposure model has been validated for pharmaceutical industry (Schinkel, 2014a). Figure 7 illustrates the ability of ART to predict exposure for a range of processes, including pharmaceuticals. Training in the use of ART improves agreement amongst a group of hygienists, but not necessarily the accuracy of the prediction.
The ART can produce exposure estimates in the absence of measurements, but now features a Bayesian engine which can combine the modelled data with real exposure data to produce the best possible estimate (McNally, 2014). The precision of the estimates improves as more data become available. The software links to a library of exposure scenarios with associated measurements. Summary statistics and a brief description of the exposure scenario are provided for each scenario in the library and the source of the measurements (the relevant study) is referenced. Based upon the exposure scenario described by a user, the ART identifies related exposure scenarios which a user may utilise (see Figure 8).

It is important to remember that ART is a statistical tool aimed at predicting broad patterns of exposure as a basis for prioritising sampling programmes. It is not capable of predicting the exposure of an individual at a particular time, which can be affected by personal behaviour or the failure of controls.
5.4 Method Development and Validation

The very small quantities of complex materials to be analysed often require sophisticated analytical techniques, such as liquid chromatography (LC) to separate the materials combined with mass spectrometry (MS) to identify the compound of interest. They also mean that the results are very sensitive to losses or contamination. Thorough validation of the sampling and analytical methods is therefore very important.

In selecting a laboratory to conduct the analysis, it should be remembered that in-house quality assurance labs usually deal with much higher concentrations in different media. It cannot be automatically assumed that they will have the competence to handle occupational hygiene samples.

Criteria for assessing a qualified laboratory should include:

- 3rd party accreditation for trace analysis, e.g. from AIHA Industrial Hygiene Laboratory Accreditation Programme, or a national accreditation scheme such as UKAS in the UK. Note that ISO 17025 is primarily a quality management system standard and does not address the competency of staff.
- Participation in relevant “round robin” testing schemes using spiked and blank filters. Even spiking is not straightforward – there are issues over spiking samples in solution rather than as powders. Hygienists need to be trained in how to spike a sample before attempting it.
Analytical methods should be evaluated for:

- **System suitability**, e.g. for a chromatographic method, retention time and sharpness of the peak are important.

- **Sensitivity**. A detection or quantitation limit of one-tenth of the Occupational Exposure Limit for a 15-minute air sample at 2l/minute is desirable, but not always practicable. High molecular mass biomolecules with low Occupational Exposure Limits can present analytical challenges because the Limits of quantification by traditional ELISA (Enzyme-Linked ImmunoSorbent Assay) techniques are often inadequate.
  - This should not be underestimated, as the exposure limits for potent compounds are so low, that it can be difficult to have a method sensitive enough. A report that indicates results are below detectable limits, but when calculated through show that the OEL is lower than the detection limit doesn’t provide any value. The Hygienist to should always double check this prior to sampling.

- **Linearity of response** (judged from the calibration curve).

- **Specificity** determined by comparison with library compounds.

- **Accuracy**, when analysing samples containing potential interferents.

- **Stability in solution**. Stored and fresh standards are compared after standing overnight.

- **Precision**. Typically, 6 repeat measurements are required to evaluate method repeatability.

- **Reproducibility**, taking into account different analysts, analysis on different days, analysis on separate machines).

Issues can also arise with the sampling method. For instance, it is well known that some penicillins degrade on the filter unless it is made alkaline. Enzymes are another product that can present some challenges. Proteolytic enzymes in particular have very low exposure limits, and therefore require very low analytical limits of detection. As well, since they are proteins, other proteins in the air (skin / hair particles) can cause false positives.

Validation of the sampling method should consider:

- Filter media selection;
- Recoveries from spiked and blank filters
- Storage stability spikes
- Sampling stability, by drawing air through spiked samples
• Sample collection efficiency
• Potential for False Positives, for example, if a product contains more than 1 active ingredient, there could be interferences. Or if sampling in another area to show no migration of product to another area, the method should be evaluated to consider if other products in the area might trigger a false positive.

In the past, the actual number of spikes and blanks needed for a survey depends upon the size of the study. A minimum of 3 field spikes must be used per survey, with an additional spike for every 10 samples. Spikes and blanks are paired.

An example of a quality control package for a large validation study might be:
• 3 lab spikes and 3 lab blanks ... these don’t leave the lab.
• 3 shipping spikes and 3 shipping blanks ...these are shipped from the laboratory to the site but are not used.
• 3 remote spikes and 3 remote blanks ...these get put somewhere that the analyte is not present.
• 6 or more field blanks and 6 or more field spikes ...these go into the area where you know you have the material present.

Blanks are important to confirm that handling of the samples did not contribute to any contamination in the field, but also in the lab, keeping mind the very low quantity, we are looking for. In some cases, the lab wants blank samples labelled as blanks, however, there is value in sending blanks labelled the same as other samples. The rule of thumb I know is a field blank for every 10 samples and a media blank per sampling batch.
• NIOSH suggests 3 field blanks and 3 media blanks per batch and recommends using spikes: https://www.cdc.gov/niosh/docs/2014-151/pdfs/chapters/chapter-sa.pdf
• OSHA Technical Manual states 1 field blank for up to 20 samples: https://www.osha.gov/dts/osta/otm/otm_ii/otm_ii_1.html

Storage and transport of samples need special care as degradation of some APIs can occur due to heat, light, moisture or contact with cleaning agents such as chlorine given off from bleach. Field spikes should pick up these issues. Depending on the analyte, samples may need to be kept refrigerated, in the dark, humidified or dehumidified, and to be analysed within a specified time period. Specific methods may require filters to be pre-treated with preservatives. Losses during transport can be minimised by avoiding overloading of the sample and by recovering the full contents of the sampling cassette.
5.5 Direct Reading Instruments

Use of light scattering instruments to measure airborne concentrations is limited by their lack of chemical specificity, but can be helpful:

- in sterile suites where background levels of particulate are very low. It may be possible to assume that the peak levels measured relate directly to the pharmaceutical materials being handled.
- for checking equipment for leaks. This can help with selection of locations for further monitoring by more specific techniques and can help to trouble shoot containment solutions.

A powerful approach is to combine direct reading instruments with synchronised video recording. This allows the causes of exposure peaks to be determined visually and can be very effective as an educational tool to show operators the working practices that generate high exposures.

Some chemical-specific, portable instruments are starting to appear based on mass spectrometry, Fourier Transform Infra-Red (FTIR), and Ion Mobility Spectrometry. Instruments are currently being developed for quality checks on tablets and to monitor progress of chemical reactions and could potentially be applied to occupational hygiene. At present they are applicable mainly to surface measurements and are not suitable for direct measurements of airborne particulates. However, they can be used to analyse air filters much more quickly than conventional analytical techniques. The range of detection is often a lot narrower, so the sample may need to be diluted and the analysis repeated. Yet, these instruments can still be considered as research tools rather than mainstream.

5.6 Skin Exposure

Skin exposure can arise:

1. From uncontained handling of powders. In addition to direct contamination of the worker, dust can accumulate on surfaces leading to secondary contact. Skin rashes are a common outcome.
2. During maintenance and cleaning operations where enclosure is breached, and exposure can be gross. This typically presents with OHC 1-3 materials where a degree of uncontained working is permitted. Outcomes may include skin rashes and sensitisation.
3. From leakage around seals and valves in more highly contained systems. Dust on surfaces may not be visible. Skin rashes are less likely but potent compounds that can be absorbed through the skin may present a systemic risk.

4. From handling of finished product (e.g. in healthcare environments). This is a recognised issue, for example, with cytotoxic drugs in cancer wards. NIOSH has issued guidelines and USP 797 and USP 800 are effective standards for the safe handling of hazardous drugs to minimize the risk of exposure to healthcare personnel. This topic is covered in Chapter 9.

Skin exposure becomes more important with highly hazardous APIs where even small amounts can trigger serious health effects.

5.7 Wipe Sampling

Most pharmaceutical companies employ wipe sampling to some degree. It is conventionally done by wiping a measured area of a surface with filter papers and subjecting them to laboratory analysis.

There is a prospect of being able to map surface concentrations in real time using direct reading instruments as discussed above. This could offer great advantages by providing rapid feedback on contamination levels but there are issues still to be resolved concerning range, sensitivity and specificity.

5.7.1 Applications of Wipe Sampling

Wipe sampling has been used for a variety of purposes for Hygienists as well as for Quality Assurance groups:

- **Map surface contamination** in a workplace. Wipe samples can identify the path of contamination without necessarily quantifying exposure, which can be useful in identifying a source of contamination and the route of travel. A common application is in facilities where a physical segregation is made between process and non-process areas to prevent the spread of product cross-contamination. For example, wipes from doorknobs on changing rooms might indicate ineffective changing or washing procedures. Typical wipe test sample locations are:
  - Process areas:
    - handrails on staircases
    - valve handles (pipework, sample points, etc.)
    - adjustable LEV hoods or dampers
    - door handles
• **Check integrity of control measures.** It may be impractical to detect low level, intermittent leaks by air sampling, but the accumulation of deposited dust on proximal surfaces can be detected by wipe sampling even if they are invisible to the eye.

• **Raise awareness.** Wipe samples can be a useful educational tool to teach process operators and supervisors about the effectiveness of control measures and the need to adhere strictly to procedures. For example, samples may be taken from the inside of Personal Protective Equipment to check for adherence to changing and cleaning procedures.

• **Assess surface cleanliness.** Validation of cleaning activities may be needed for decommissioning purposes before disposal of equipment or for maintenance. There may sometimes be opportunities to combine a hygiene assessment with swab sampling for quality assurance purposes.

• **Assess or predict personal exposure.** Surface wipe tests provide an indicator of the potential exposure by skin contact which might then lead to skin absorption or inadvertent ingestion. A lot of research work is underway to develop methods of direct monitoring of skin exposure, using for example fluorescent dyes. However, no generally accepted method is yet available.

### 5.7.2 Standards for Surface Contamination

It is difficult to set standards for surface cleanliness, and several methods have been used to establish acceptable levels:
• One approach is to use relative levels, e.g. the percentage removal achieved based on tests before and after cleaning, or the ratio of levels in a process area to those in a non-process area.

• Another approach is to establish a baseline by testing after a thorough cleaning process.

• A third approach sometimes used is to try to define health-based surface exposure limits, usually expressed as a mass of contaminant per decimetre squared (μg/dm$^2$) of the surface area. Such standards depend on assumptions made about the contact frequency and area, transfer efficiency, skin absorption rate and ingestion. Guidelines for acceptable cleanliness in process areas may be higher than non-process areas as they consider the operating controls and protective equipment in use.

A health-based limit for surface contamination can be calculated, assuming a rate of transfer from the surface to the person and uptake via skin absorption or ingestion. Depending on the regulatory agency may be called something different. Acceptable Daily Intake (ADI), Allowable Daily Dose (ADD) or Acceptable Daily Exposure (ADE). Hygienists & Occupational Toxicologists sometime used these limits to facilitate determination of an acceptable level. Often 100% transfer and uptake are assumed, which will give a conservative standard. If an ADD is not directly available, it can be back-calculated from an established air concentration limit by assuming a daily respiratory volume (conventionally 10m$^3$ though there is some evidence that 5m$^3$ may be a more accurate for the level of physical activity typical in the industry).

5.8 Biological Monitoring

Given that a great deal is known about the materials which pharmaceutical workers are exposed it is conceivable that biological monitoring might provide useful data. In particular, biological monitoring may provide a way of monitoring total exposure when skin is a suspected route of absorption. For example, Van Nimmen et al. (2006) identified skin exposure as the primary route of absorption in a study of the manufacture of potent opioid narcotics.

Biological monitoring has been used successfully for research on oncolytics, where white blood cell counts can provide early warning of unsuspected exposure. It has also been used together with air monitoring to monitor solvents such as dimethylformamide (DMF) where skin absorption may occur.
Case Study: Biological Monitoring for Oncolytics

Sessink et al. in 1993 studied exposure to methotrexate in a secondary manufacturing site. Atmospheric levels as high as 182 μg/m³ were found in the area in which the powders were dispensed. Urinary excretion of methotrexate was used as a method of determining absorption and an average level of 13.4 μg in a 24 h period was found. The workers in the area wore a high level of respiratory protection and the authors concluded that skin absorption was a major factor.

In 1994, Sessink studied exposure to 5-fluorouracil by the measurement of a metabolite. Again, significant exposure in the dispensing area was found and significant contamination of the work surfaces within the work area was detected.

In practice, though, biological monitoring is not often used to assess exposure to APIs within the pharmaceutical industry. Concerns are often expressed by occupational physicians about creating unnecessary fears when elevated levels are detected without known clinical significance. Proposals for the use of biological monitoring therefore need to be evaluated carefully by occupational health and hygiene professionals before starting a monitoring programme.

5.9 Qualitative Exposure Assessments and Surrogate Sampling

Although quantitative data collected through air sampling provides a much more accurate assessment of potential exposure, a qualitative assessment should not be ruled out. Early stage development work often will not have an established exposure limit nor an analytical method. However, useful information can be gathered by doing an assessment of the area by an experienced hygienist. Work practices and technique can be identified to improve and in some case improvements on equipment and / or local ventilation can be identified as areas to improve by assessing the area. As an example, we know that the exposure limit for potent compounds is below the visible range, therefore when conducting the assessment if we dust is observed, we already know there is an area to improve.

Surrogate sampling in some cases can be conducted in the absence of a specific analytical method for the API or when it is important to evaluate engineering controls with a surrogate prior to use with a potent API. In some cases, this can be done with one of the excipients that may already be in the batch at a known concentration. Alternatively, a process can be evaluated by using a known surrogate, often naproxen sodium, mannitol, or lactose, and mimic a process. It is important to be aware of the particle size and % of surrogate in the formulation and try to match with the typical
products manufactured. Often other considerations for surrogate selection include quality concerns of using an API as a surrogate and the analytical sensitivity required to obtain meaningful data.
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6 CONTROL OF EXPOSURE

6.1 Exposure Control Principles and Containment in the Pharmaceutical Industry

6.1.1 The Case for Containment
6.1.2 Process Activities Giving Rise to Concern
6.1.3 Developing a Scheme of Containment

6.2 Engineered Containment

6.2.1 Performance of Engineered Containment
6.2.2 Layers of Protection
6.2.3 Facility Specification
6.2.4 Equipment Specification
6.2.5 Barrier Walls and Surfaces
6.2.6 Pressure Zoning
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6.2.8 Drainage Systems

6.3 Maintenance Concerns

6.4 Cleaning and Disinfection

6.5 Verification Testing – FAT, SAT and SMEPAC

6.6 Use of RPE and PPE

6.7 Control in Healthcare Settings

References and Containment System Vendor Examples

Annex 1: Types of Engineered Containment Systems
6.1 Exposure Control Principles and Containment in the Pharmaceutical Industry

6.1.1 The Case for Containment

The purpose of containment is to limit the emission and spread of material. It is important within the pharmaceutical industry for four reasons:

- prevention of occupational exposure. A wide range of engineering control strategies and specific hardware systems have been developed to maintain material segregation from the operator.
- prevention of cross contamination, as required by Good Manufacturing Practice (GMP).
- prevention of environmental harm due to material ecotoxicity.
- prevention of financial losses.

The use of “open” operations on multiple product facilities would give rise to an elevated risk of cross-contamination. In single stream facilities (i.e. those manufacturing one product at a time on a campaign basis), there is significant cost in carrying out and proving complete facility cleans between product campaigns.

Pharmaceutical intermediates and APIs are extremely expensive, with values frequently in the $1000s per gramme. Open manufacturing leads to increased risks of losses and reduced yields through spillage and inadvertent emission in routine operation. Costs of these losses are difficult to quantify but may be significant when added to the costs of cleaning greater areas due to their occurrence.

6.1.2 Process Activities Giving Rise to Concern

The risks of airborne exposure are created for the most part in a number of specific key activities: typically activities requiring manual access to or open handling of hazardous material, or where contaminated systems are opened or separated. Common areas to consider are:

a) Manual activities, such as:
   - Sampling
   - Material handling e.g. dispensing and weighing
   - Charging of API and excipients
   - Solid liquid separation (e.g., centrifuge)
   - Drying – Dyer unloading (tray dryers, fluidized bed dryer)
   - Equipment set-up e.g. calibration
   - On-line maintenance
   - Off-line maintenance (if prior cleaning or decontamination is not carried out*).
   - Manual cleaning
b) Anticipated failures

- Make-break connections
- Vent systems
- Drainage liquors

c) Unanticipated failures

- Spillage or leakage
- Equipment failures leading to a requirement for manual access to rectify the problem.

* Note that certain items, such as HEPA filters, product filter bags and cartridge filters may not be clean when they are removed for maintenance or replacement.

Where extensive operator handling of processing material is required, for example through charging, discharging, sampling, packing and cleaning operations, it will result in potentially higher levels of exposure unless containment systems are installed.

It should be noted that some apparently non-process activities may also carry a risk of exposure, for example sampling for material identity in a receiving warehouse.

6.1.3 Developing a Scheme of Containment

Creating effective containment requires an understanding of the mechanisms of emission, transmission and reception. It also needs a good cross-functional and multidisciplinary team working within an organisation to define the parameters required for containment design and the methodology for performance verification.

The methodologies to control exposure follow classical occupational hygiene principles, including the use of risk assessment and application of the hierarchy of control.

Where exposure is a concern, the first choice of action should be to eliminate or reduce need for containment. Wherever possible process technologies should be selected that inherently minimise exposure and so avoid the need for additional containment.

- If processes can be specified such that open handling or make-and-break transfers can be avoided, then operating staff exposures will be significantly reduced. This may involve the use of directly coupled systems relying on gravity or pneumatic transfers, and/or automated feeding and packing systems. For example, bulk handling or vacuum transfers are usually preferable to drum handling.

- Consideration should be given to alternative processing methods, such as single pot granulation and drying, rather than separated granulation, delumping and drying equipment requiring intermediate transfer. The adoption of continuous processing should be encouraged where appropriate. SoftGel processing may also be appropriate and can reduce the risk of airborne exposure, as the process typically only handles powders at the weighing stage and then goes
into solution. This also reduces the risk during downstream operations such as packaging, and even handling in health care facilities by pharmacies, nurses, caregivers and patients. In practice, such process modifications may not be possible due to product registration (GMP) constraints, but the option to integrate or “telescope” operations should always be considered before considering detailed engineered control systems.

- It may be possible to source raw or intermediate materials in appropriately dispensed weights, ready for use.
- Opportunities to handle materials in less hazardous forms giving rise to reduced levels of airborne dust should be considered, for example by keeping the product as a slurry or damp solid between stages or by using coated particles. As above, the scope to do this may be constrained by product registration.

In many cases, the higher levels of the hierarchy of control (elimination or substitution) cannot be applied in the pharmaceutical setting. Often the materials of concern and their physical form are specifically required for the purpose of product effectiveness. There may be scope to combine, reduce or remove specific process steps, such as intermediate dry product recoveries, but these are typically limited to the chemical processing part of drug manufacture.

As a result, control is commonly achieved by the use of closed equipment, engineered local exhaust (extract) systems, special engineered containment systems, procedural controls, or the use of Personal Protective Equipment (PPE).

The selection of containment equipment should be based upon the requirements identified through the risk assessment. The individual capabilities of the various available control systems must be understood in terms of their impact on exposure, the effect of the control on mitigation of the risk, and the impact on other aspects of the process, e.g. accessibility, ergonomic concerns, ease of cleaning, production costs, efficiencies etc.

It is also necessary to have an understanding of the likelihood of failure, the implications of it occurring, and the tolerability of measures required to achieve recovery. This will help define the need for, and scope of, secondary and tertiary systems to provide an ‘onion skin’ layered approach to containment.

The development of a high level scheme of containment is a useful method of identifying areas and materials of concern, agreeing how they will be controlled and providing a common record of the basis of control selection for future reference. The key elements of the control philosophy are as follows:
a) Definition of process activities including all process, cleaning, maintenance and breakdown activities as far as they can be defined.
b) Definition of hazardous materials, including basis of determination—including health based criteria (e.g., Categorization / Band, OEL) and identification of other effects (e.g., dermal).
c) Identification of major risk areas where significant exposure to hazardous materials might occur. This should be developed from a risk assessment approach. These risk areas should be identified for all processes including manufacture, cleaning, maintenance, and failure recovery. The method used for establishing exposures should be stated.
d) Definition of generic control methodologies, for example barrier and contained transfer systems or extract based approaches. These will be developed from the identification of any gaps in the risk analysis and equipment selection processes. Targeted levels of containment should be defined in this process.
e) Requirements for HVAC system and room design including pressure control regimes, filtration requirements, recirculation or once-through and the need for dedicated Air Handling Units.
f) The nature and role of PPE in the process under routine conditions of operation, with consideration for non-routine or upset conditions.
g) Cleaning methodologies required for safe cleaning of equipment and other contaminated surfaces including building and equipment surfaces. The requirement for PPE in such applications should be clearly identified.

6.2 Engineered Containment
The terms ‘contained’ and ‘open’ are commonly used in the pharmaceutical industry to describe typical conformations of equipment and the associated control measures.

Open System
- Generally describes relatively uncontained process systems with no physical barrier between the operator and material, sometimes incorporating the use of engineered extract containment systems.
- Exposure potential exists and hence open systems are not protective for handling OEB 4 and 5 compounds.

Contained System
- Contained systems can be considered as any having physical barriers between operators and the material. There is a very wide range of equipment systems available for such systems, the performance of which varies depending on the specific application, and the detail of the equipment installed.
Exposure potential is minimal and are protective for OEB 4 and 5 compounds when designed and maintained properly and particulate containment is validated for handling of OEB 4-5 compounds.

There are two basic approaches to engineering containment:
a) Interruption of emission/transmission through the use of barriers.
b) Interruption of transmission by use of capture airflows (extraction).

Traditionally, most containment systems in the industry have used airflow to control emissions (e.g. extract booths, benchtop cabinets, fume cupboards, downflow booths, custom ventilated enclosures and capture hoods). These were satisfactory because the control requirements were relatively low, and they have the advantage of restricting access to the process only to a small degree.

As APIs have become more hazardous, there has been a growing trend towards barrier systems such as isolators and flexible containment systems, with some extreme materials requiring containment to levels previously only found in the nuclear industry.

Engineered containment is typically used in two ways:
- to provide primary/secondary containment of specific process equipment.
- to provide ‘clean-break’ coupling mechanisms to allow transfer of material to or from individual process equipment or processes.

Combinations of both can be used. For example, an isolator fitted with a bag-out port to allow contained removal of waste, product containers or other equipment.

Annex I at the end of this section gives details of the different engineering containments which can be employed. These include:
- Extract Hood/Cowl
- Horizontal Flow Booths
- Downflow Booths
- Clean break coupling systems
  - Simple Butterfly Valve Systems
  - Split Butterfly Valve Systems
  - Cone valve systems
- Rapid Transit Port (RTP) or Alpha-Beta Door Arrangements
- Sealed Liner or Bagout Systems
  - Single Standard Liner Systems
  - Tailored Bag Systems
  - Continuous Liner Systems
- Contained Transit Systems
6.2.1 Performance of Engineered Containment

When considering exposure control and the performance of control equipment, it is important to recognise that technology contributes only one element of the containment performance of the system. Of equal importance is the training of operating and support staff, and the application of effective maintenance protocols. It is unreasonable to expect that improperly operated or maintained equipment, however highly engineered, will continue to operate satisfactorily over an extended period, and may in fact lead to a false belief in an individual’s protection.

The specific characteristics of the process to be contained affect the performance of the containment and whether the system will be effective or not. Selection of particular types of containment systems is therefore challenging. While general guidelines on the capability of specific equipment types have some benefit to the inexperienced user, actual performance may still require verification following installation.

In general, containment performance in a given situation is a function of four elements:

a) Process detail (Process equipment type/form)
b) Material properties (Quantity handled, physical form, duration)
c) People (number, location, operating methods)
d) Containment equipment type

The probability of exposure also depends on the ambient environment in the operating area, e.g. room size and general ventilation, as this influences the dispersion of any contaminant that escapes from the containment.

Looking at the four elements of containment in more detail, the level of performance achieved in practice is a function of many factors, including the following:
a) Process Detail
   - Activity to be carried out with the material, including the energy input, and the access requirements (degree of intervention e.g. for charge/discharge/sampling/blockages/cleaning) and associated technology.
   - Environmental conditions (e.g. relative humidity, which may affect material dustiness, temperature).
   - Frequency of operation (high frequency of use may create high background levels or repeat exposures).

b) Product/Material
   - Physical Form
   - Particle Size
   - Density
   - Morphology
   - Static charge
   - ‘Dustiness’ (often an aggregate property defined by factors above)
   - Quantity handled
   - Flow characteristics

c) People and Systems
   - Operator proficiency – incorrect or poor operation gives increased risk of emission and exposure.
   - Implication of user physical conformation (shape, height, handedness) on effectiveness of system ergonomics
   - Maintenance and inspection regime – poor maintenance often gives poor performance.
   - Operator position relative to sources – distance and duration

d) Containment Equipment
   - Type of system (degree of inherent containment, demands on operator)
   - Specific details of containment engineering control system installed
   - Access to process and implications on operational access and ergonomics.
   - Control approach and impact on location of operator/exposed individual

As a result of this wide range of potential factors affecting emissions and control performance, it is difficult to generalise on specific equipment performance with any degree of accuracy. It is however possible to give some broad ‘rules of thumb’ as to the typical capabilities of systems in common applications that may be practically useful in the majority of situations found in the Pharmaceutical Industry. These form the basis for Control Matrices (see Chapter 7).
6.2.2 Layers of Protection

Engineered control strategies tend to concentrate on containment at source as far as possible. Different systems have more or less effective containment capabilities giving rise to the risk of background concentrations of material outside the primary containment system. The possibility of unforeseen failures and leaks may also present the possibility for external contamination or release to the environment, especially for potent compounds where exposure limits are below the visible range. In order to control such contamination and to prevent its egress to other areas of a facility and into other process units or support areas, it is common to install secondary systems to prevent material migration. A layered approach to exposure or emission control for a facility may be defined:

Primary Systems
Systems that contain the material at source, typically including process vessels, pipework, clean-break couplings, IBCs, etc. The material is generally not visible to the operator and the operator is not required to physically contact or otherwise access the material.

Secondary Systems
Systems that prevent egress from the locality of the source of emission. These include local extract, laminar flow booths and isolator systems.

Such systems may be combined with primary systems to create enhanced containment systems where the secondary system reduces the effect of failure or inadequate performance of the primary system.

These are often installed at weak points in the system, such as connection points, or in areas where troubleshooting may need to occur.

Tertiary Systems
Systems external to the secondary system, that prevent egress of material from the primary/secondary systems into other areas of the facility. These will include containment rooms with airlock, gown/degown and decontamination facilities in entry/exit, room air flow sweeping from high at the door to low level return and air pressure cascades to prevent airborne egress. Such systems are frequently subject to rigorous operating procedures such as entry/exit protocols and gowning/degowning procedures to prevent material egress on contaminated clothing and equipment as well as by airborne vectors. Personal Protective Equipment and administrative controls can also fall into this area.
6.2.3 Facility Specification

Three types of movement within the process facility/building must be controlled:

- **People** – operators, supervisor staff, other technical staff (e.g., quality, EH&S), maintenance staff.
- **Materials** – raw materials, intermediates, product, equipment, tools, waste materials
- **Air** – especially if pressurised or contaminated.

The systems and equipment installed within the facility must support the control of these movements; the main concern being the prevention of the movement of hazardous materials to areas where they are not desired (or conversely outside of areas in which they can be contained and controlled).

The vectors by which material can be moved should be understood and protected. Specifically, mechanisms should exist to prevent the inadvertent movement of materials via the following methods:

<table>
<thead>
<tr>
<th>Mechanism of Movement</th>
<th>Possible prevention methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Airborne dispersion and laydown</td>
<td>- Barrier walls</td>
</tr>
<tr>
<td></td>
<td>- Air Flow in the room (sweeping high to low level)</td>
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<tr>
<td></td>
<td>- Air pressure zoning</td>
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<td></td>
<td>- Filtered HVAC extract systems (filter in room)</td>
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<tr>
<td>Surface contamination by operators</td>
<td>- Gown/Degown procedures</td>
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<td></td>
<td>- Change airlocks (preferably separate in/out).</td>
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<tr>
<td></td>
<td>- Decontamination or misting Showers in personnel airlocks</td>
</tr>
<tr>
<td>Surface contamination of Containers</td>
<td>- Transit airlocks to process area (possibly separate entry and exit)</td>
</tr>
<tr>
<td>and Equipment</td>
<td>- Container valeting procedures.</td>
</tr>
<tr>
<td></td>
<td>- Local cleaning facilities in process area</td>
</tr>
<tr>
<td>Waste materials – Solid</td>
<td>- Waste handling and secondary enclosure (over bagging) procedures</td>
</tr>
<tr>
<td>Waste Materials – Liquid</td>
<td>- Sealed drain systems in rooms</td>
</tr>
<tr>
<td></td>
<td>- Dedicated drains to treatment or disposal system</td>
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</tbody>
</table>

Care must be taken with maintaining the cleanliness of operator gowning away from designated contaminated areas, as clothing contamination can lead to ‘tracking’ where hazardous material can be transported to supposedly ‘safe’ areas such as changing rooms. Furthermore, de-gowning rooms must be operated with the philosophy that they must be clean at all times such that clothing is decontaminated prior to entry to the de-gowning room to prevent operator secondary exposure from the act of removing contaminated clothing. Building details are important to support such control mechanisms.
6.2.4 Equipment Specification

The specifications of the equipment requirements are a direct function of the following fundamental questions:

- **What is known about the material to be handled?**
  - Identified health based criteria for control (e.g. band, OEL/STEL)
  - Any other specific toxic concerns (Skin notation, respiratory or skin sensitizer, reproductive toxicity, ecotoxicity).
  - Any other specific safety concerns (flammable, explosible rating).
  - Any other specific GMP concerns (specific groups such as steroid hormones, Beta Lactams, “cytotoxic” compounds) requiring dedication/segregation by regulation.

- **What is known about the process?**
  - Quantities (Per batch, per day?)
  - % active in the batch
  - Physical Form (powder/dust/granule/lyophilized or spray dried powder etc.)
  - Physical Properties (dustiness, particle size etc.)
  - Frequency of operation
  - Complete spectrum of operations required (including processing, sampling, cleaning, on-line and routine maintenance)
  - Operator access requirements

- **What are the installation facility details?**
  - Equipment space availability
  - Local environment quality (humidity/temperature/particle quality/pressure regime)
  - What is local support capability (technical support, technology availability, local confidence with high level technology)

- **Are there any specific business constraints?**
  - Capital costs/Revenue costs constraints
  - Facility/product lifecycle duration?

The selection of equipment is driven by the constraints inherent in the answers to the question above. Design of containment systems is essentially a subjective activity, often based on limited knowledge of the installed system or similar systems working with materials of (hopefully) similar physical properties to extrapolate data to an anticipated value.

Guidance can be gleaned by studying similar systems and identifying what has been installed to control exposure and the degree to which it has been successful. If such ‘copying’ is to be carried out, the following questions should be considered as to whether the comparison is appropriate or not.
Are the design and performance requirements of the comparison system understood?

Material handled – toxicity, physical form?

Are there specific process requirements, e.g. nitrogen inertion, present in the comparison system that may affect equipment selection.

Available data on equipment containment performance and possibility of extrapolation?

It should be clearly understood, that whilst such copying, if carefully applied, may give satisfactory results, great care must be taken in extrapolating information from one installation to another as very significant variances in performance can be found through apparently trivial differences in circumstances including differences in the physical properties of the materials.

The availability of the above data may be variable, it is not unusual to have little data on material form and flow characteristics, and operator requirements may be driven by equipment selection leading to an iterative process of equipment selection.

It is critical that all available expertise is called on to establish the impact of all the above parameters, including engineers, operators, safety, health and environmental professionals, quality and maintenance staff. The most balanced solution is most likely to be developed by such a multifunctional team, as it is unlikely that any one individual will have sufficient expertise in all areas to fully understand the impact of all the factors affecting system specification.

Pharmaceutical companies have used a number of different approaches to overcome the difficulties of selecting appropriate equipment on a case-by-case basis:

Setting global standards for key equipment types. The standards may include detailed engineering specifications, equipment layouts and validated performance data. They may also include standard procedures for operating, training, commissioning, validation and maintenance and an implementation checklist. They may be referred to as “Pre-Engineered Solutions”.

Cataloguing engineering designs. Company catalogues may document examples of good or best practice, showing the equipment used and containment performance achieved in particular situations. They typically document the design intent and might include such details as operation, batch size, OEL, OHC, dustiness, volatility, photographs, drawings, unit cost, performance data, training requirements, hints on work practices, lessons learned and vendor contacts.

Use of Control Matrices. Control matrices tabulate the requirements to achieve a given level of performance and allow initial decisions to be made on the basis of very limited hazard and process information (see Chapter 7).

Vendor guarantees with Acceptance Testing. When the containment equipment required is available as a standard package from a commercial supplier, companies may seek guarantees of
performance from the vendor. Generally, the contract will require validation of performance via Acceptance Testing in the supplier’s facility, on the user’s site, or both. Guarantees can be difficult to uphold as many processes involve ancillary equipment that can contribute positively or negatively to containment.

- **Mock-ups.** When the situation is novel and the effectiveness of controls is unclear, mock-ups may be built to test the capabilities and ergonomic constraints of proposed systems. This can be especially important to determine the functionality of the equipment. If containment is achieved but operators can’t perform necessary tasks, the success of the equipment will be limited.

Where such resources are not available, the following guidelines illustrate the basic method for selecting equipment.

**Primary Containment System Selection**

The method for Primary/Secondary equipment selection is as follows:

1. Establish key operating parameters:
   - Hazard Band / Category / OEL (plus any other hazard information e.g. skin sensitiser).
   - Process requirements (primary and supporting).
   - Batch size and % active
   - The likely degree of variance of exposure from safe levels in uncontrolled condition (defining the degree of control the containment system is required to deliver).

2. Define a Cleaning and Maintenance Strategy.

3. Define a Spillage and Decontamination Strategy.
   The latter two items will be defined by the nature of the material, the ease of cleaning, and the requirement to recover/rework spilt materials. For all equipment types, there is a finite probability of failure, both minor and catastrophic. Strategies for clean-up in all cases should be considered ranging from minor leaks (for example flange drips) through to full batch loss (e.g. ruptured transit vessel). The decontamination systems, ranging from full room sprays through to manual HEPA vacuuming and ‘mop and bucket’ activities will have a major effect on the design requirements of secondary and tertiary systems.

4. Identify possible equipment systems that meet all strategies above (based on experience, supplier data, other users, literature etc.).

5. Confirm required size of equipment to meet process requirements.
   The size of some systems may limit their applicability in certain situations, for example, large scale powder processing clean-break couplings may require large diameter connections to prevent blockage. This may not be available for some systems.
6. Evaluate basis of containment performance data
The basis of any containment performance data from similar systems needs to be carefully
evaluated for applicability by experienced hygiene specialists. Care needs to be taken in the reuse
of suppliers or other users’ data.

7. Check acceptable solutions against space requirements
Much engineered containment equipment is bulky and is frequently very difficult to retrofit into
existing installations. Care must be taken to ensure that access and other process activities are
not compromised, and that sufficient ceiling height is available.

Secondary System Selection
The likely (or actual) containment performance and inherent variability of the primary system
determines the performance requirements of the secondary system. Correct choice of secondary
system may allow the use of a primary system with intrinsically inadequate containment
performance. An example might be the use of a simple split valve with local extraction as an
alternative to an expensive, complex high containment split valve.

Even if the primary system is adequate in normal operation, a secondary system is needed if failure
of the primary system might produce an intolerable risk. An example might be a liner-based drum-
filling system within an isolator or extract booth. The purpose of the secondary system is to minimise
the spread of material in case of spillage and to reduce the requirements for decontamination and
cleaning. An understanding of potential failure modes and potential frequencies is required to
understand the degree to which such a secondary system might be challenged in the event of
primary system failure.

The options for secondary system fall broadly into two types; those presenting a hard-physical
barrier, or those relying on airflows to prevent material egress. The former includes glove bags and
isolators while the latter, which are more common, include extract booths and local extract
ventilation.

Tertiary System Selection
The requirements for the tertiary system are determined by the requirements to control movement
in and out of the area, as well as by the primary and secondary systems. Tertiary systems typically
rely on physical walls, with controlled differential air pressures and airlocks to prevent airborne
egress. Changing facilities are needed to prevent surface contamination leaving the process area on
operator apparel or transit vessel surfaces.

Such airlock and change areas are expensive, due to the building space that they take up, and the
high-quality surfaces required to support decontamination and cleaning. They are also difficult to
retrofit into existing facilities because of space constraints.
The presence of tertiary systems reduces the risk of cross-contamination with other processes that may be operating within the same facility and thus helps with GMP compliance.

Interesting paradox is that the better that primary containment that is achieved the less the need for tertiary systems. However, need to consider the potential for upset conditions as well as the ability to monitor an upset condition. For example, a potent compound has an exposure limit below the visible range, therefore a failure of a valve may occur, and no one would know, therefore secondary and tertiary controls become more important.

6.2.5 Barrier Walls and Surfaces

The purpose of barrier walls is to restrict personnel access to specific routes and to prevent airborne or waterborne material egress to uncontrolled areas. Barriers may be permanent (of rigid construction) or temporary (eg. from PVC sheeting). It must be assumed that loss of containment may happen within the process area and hence mechanisms to decontaminate the barriers must be available, either through cleaning or disposal.

Permanent barriers should be impervious and sealed at joints to floors and ceilings. They should be smooth and finished such that they can be readily cleaned. They should be robust to exposure to the required cleaning methods, such as solvent wiping. Floors, walls and ceilings should be similarly specified to allow ease of cleaning.

An alternative to cleaning is to use disposable polymer sheet materials supported on a framework. Spillage removal is by dry cleaning of the area, followed by encapsulation of remaining contamination by fog and mist sprays with limited wet cleaning, then finally dismantling and disposal of the enclosure. The inner surface of the enclosure should be smooth and sealed to ceiling and floor elements and care should be made to ensure that the system is suitably earthed through the use of dissipative films.

A critical area of barriers is the design of doors. These should be designed to be close fitting and sprung hinged to ensure that they cannot be left open inadvertently. There is some evidence to suggest that air flows through brush door seals (see zoning below) has some cleaning effect on the air by trapping particles by impact and the air quality in a process room can significantly improve over time due to this cleaning effect as long as seals are routinely checked and cleaned. The hinge mechanisms, and any powered actuation mechanisms, should be specified for cleaning; ideally, they should be located outside the process area to reduce the risk of contamination in the event of spillage.
6.2.6 Pressure Zoning

The use of pressure zoning is a common technique to control airflows and thereby prevent airborne material egress. The basis of design is to maintain the process room at a negative pressure to adjacent rooms to encourage airflows from the latter into the former. Where airlocks are fitted to rooms, the option exists to create pressure cascades with a series of pressure drops from corridor to airlock and then to process room. The size of the pressure differential is limited by the force required to manually open the door between zones: typically a differential of 15 Pa is used; a practical maximum is around 25 Pa unless automated openers are used, in which case the possibility of failure and mechanisms for escape in the event of failure should be considered.

Pressure zoning is achieved either by controlling the leakage around door seals, or through connecting ducts with counterbalanced dampers to maintain pressure differentials. It is critical that rooms are as well sealed as possible to aid pressure control, and to prevent uncontrolled air ingress from adjacent areas. This is particularly critical where 'black' (i.e. potentially contaminated) technical areas are located adjacent to process areas with equipment mounted or driven through barrier walls. The risk of technical area contamination, or process area contamination with potentially dirty air from such technical areas, should be reduced as far as possible.

Pressure differentials are achieved by extracting air from the process room via the main plant Heating Ventilation and Air Conditioning (HVAC) system. It is good practice to mount High Efficiency Particulate Air (HEPA) filters on extract vents in the wall of the room with the capability to safe-change filter elements into the room. This reduces the risk of ductwork and HVAC system contamination in the event of a spillage when air changes in the room may be used to clean the air prior to wet decontamination. The classification of HEPA filters (see ISO 29463-1:2011) is difficult as performance depends strongly on particle size. It is however common to fit either type H13 (99.95% efficiency) or H14 filters (99.995%). There is a standard test of installed integrity available using a liquid or solid aerosol and particle counter technique.

Finally, design of pressure cascades should take note of other extract systems in process areas, for example extract booths and LEV systems. In extreme cases, it may be impossible to open room access doors when extract booths are operating due to reduced pressure in the room.

6.2.7 Airlocks

Airlocks provide intermediate transit areas between transit corridors and individual process rooms or suites of rooms. At the extreme, airlocks can be provided for each process room; alternatively several rooms can be served by a single airlock to reduce cost, at the expense of having larger areas to clean in the event of a spillage in one of the rooms.
Airlocks provide a mechanism to prevent material egress by air movement (see zoning above), and provide mechanisms by which migration of material by mechanical contact (tracking) on clothing and equipment can be controlled. Normal practice is to have two airlocks: one for personnel, one for material/equipment. In some cases where higher protection is desired, separate entry and exit locks may be provided for personnel to segregate gowning and decontamination/ungowning activities. The method of operation is for the operator to move material and equipment into the airlock from the transit corridor, then to enter the process room via the (entry) personnel airlock. The equipment and material can then be brought into the process area from the material/equipment airlock via the process side door.

Exiting of personnel and material/equipment is the reverse process of the above.

Airlock doors should be interlocked to prevent simultaneous opening, this avoids a direct air route from the process area to the transit corridor with a resultant risk of losing pressure cascades. Local room pressure differentials can be observed through the use of local displays such as Magnahelic® differential pressure gauges marked with red and green zones for easy visual interpretation. Alarms tend to have delay timers built in to allow pressures to re-establish in the event of a door being only open for a short period which is normal practice.

The purpose of the personnel airlock, in addition to aiding zone pressure control, is that it allows specific personnel gowning and degowning and decontamination activities to be carried out in a controlled environment. Where such facilities do not exist, there is the potential for a build-up of material to occur in centralised change areas leading to a risk of uncontrolled exposure to other operators and potential contamination of external equipment. The airlock also allows the provision of controlled decontamination facilities, e.g. showers and mask air points, for use in the event of spillage and clean-up, without the risk of external area contamination.

The material airlock allows the contained transfer of material and mobile equipment into the process room without opening a direct route from process area to transit corridor. It also allows a facility to clean/valet contaminated surfaces of containers or equipment prior to their movement back into the transit corridor. It also allows the facility for clean secondary covers to be placed on material or waste containers where surface cleaning may not be possible.

Decontamination potential API contaminated material is needed to reduce contamination of corridors and other areas. For example, wheels of cart coming from API handling areas need to be wipe cleaned and decontaminated.
6.2.8 Drainage Systems
Hazardous materials are not necessarily decomposed by solution or suspension in cleaning fluids. There is a risk that such liquid waste streams might leak and leave a solid residue of hazardous material following evaporation of the solvent or suspending liquid. Liquid waste streams should be treated as hazardous until the hazardous component is destroyed or rendered safe.

Drains should be of sealed construction with floor grids having sealed removable covers for room clean down. Open drains are generally unacceptable in GMP rated facilities due to risk of microbial and chemical contamination potential from the drains.

Environmental hazards such as potential aquatic toxicity may create the need to segregate highly contaminated waste streams for specialised disposal rather than via site effluent systems. Such material may be stored in collection tanks, which should be suitably bunded to ensure containment in the event of leakage.

6.3 Maintenance Concerns
Containment systems are generally bulky and technically complex. For example, they may include systems such as split valves that incorporate a large number of sensors for accurate positioning, and secondary cleaning systems. Containment systems should therefore be treated as additional plant items that need the appropriate technical and financial resources applied to maintain performance to desired levels.

Some systems, for example split butterfly valve, are highly engineered mechanical devices and tolerances for operation are very tight. Care must be taken, especially in reassembly, to ensure that the appropriate tolerances are achieved and it may be necessary to test them to ensure that the containment performance of the system is re-attained.

A lot of containment equipment is bulky and heavy with restrictions on access. Fixed or mobile lifting system may be needed for parts removal. For example, 250 mm diameter active split valves can weigh up to 30 kg once removed from docking systems. Cone valve assemblies weigh a similar amount.

The weight of bolted on components on systems should also not be ignored, the fitting of a split valve or Rapid Transfer Port to the base of an isolator may require significant additional stiffening in the isolator base to avoid distortion.

Given that it is human nature to modify difficult processes to make them simpler, care should be taken in design to ensure that all tasks are made as simple as possible to reduce this tendency to ‘cut corners’.
Maintenance of downstream processes should also be considered, such as house vacuums, portable vacuums, dust collection systems, duct work, equipment maintenance etc.

6.4 Cleaning and Disinfection

Ideally, cleaning should not require a breach of containment, for example by manual disassembly. This would require the use of a CIP or ‘Clean in Place’ system. CIP is widely used in the food and drinks industry to allow rapid plant turnaround. It is not so widely used in the pharmaceutical industry due to the cost, the difficulty of incorporating CIP into standard pharmaceutical processing equipment, and the difficulties encountered in removing many pharmaceutical residues.

The next best form of cleaning is WIP, or ‘Wash in Place’. In this case, the system is essentially rinse clean by an external wash system using spray balls (or spray discs) but requires final manual disassembly to clean small parts or areas that are inaccessible to effective cleaning by fixed spray devices. Isolators are provided with spray ball for cleaning. Programmed spray cleans isolator and dried air injected dries the isolator also.

Finally, the worst case is manual disassembly and cleaning following no or incomplete decontamination. This is not uncommon in equipment not designed for wetting, such as primary packing equipment. In such cases, it must be considered that a breach of containment will occur and all staff working in the ‘at risk’ area will need to use appropriate PPE, and follow appropriate room, equipment and personal decontamination procedures.

Techniques and training should be provided to minimize the risk. For example, HEPA vacuum of all powders, wet wiping should be the next step. Where possible wetting equipment / residue down reduces the risk of the dust becoming airborne.

6.5 Verification Testing – FAT, SAT and SMEPAC

To verify that the design actually meets the design intent, it is necessary to carry out some form of proving trial. These initially include simple mechanical function tests, such as;

- Pressure hold tests
- Leak tests (including filter integrity and glove leak tests)
- Air pattern testing to confirm required air flows.

The next commonly applied level of testing is surrogate testing to confirm performance, using an inert or low-hazard surrogate material to initially check for visual performance, backed up by sampling and analysis of airborne and surface contamination. Process operations are typically simulated rather than real and there may be differences in particle characteristics that affect the containment performance compared to the real process. The results cannot therefore be compared directly with the OEL of the real API. A margin of safety (perhaps 50%) must be allowed.
Commonly used surrogate materials include micronized lactose, naproxen sodium, mannitol, acetaminophen (paracetamol).

- Lactose is a sugar with an OEL of 10mg/m³ and the latter 2 materials are non-potent APIs with OELs in the region of 2-5mg/m³.
- Naproxen sodium is a soluble, crystalline API with high dustiness quotient and challenging electrostatic properties. This surrogate provides a robust challenge to the containment. It is readily detectable in air at low concentrations (0.2ng detection limit using HPLC), which allows the assessment of exposure on a task-oriented basis, even for brief duration tasks.
- Lactose powder has low toxicity and is one of the more difficult surrogates to contain because of its flow characteristics; good containment with this surrogate can go a long way to prove engineering controls. It is also cheap to buy and analyse but has a higher detection limit of 2.5ng. A benefit to using lactose is that it is considered an excipient, and therefore has less risk of contaminating products. It also typically wouldn’t trigger the need for a cleaning method to be created. One caution however, is that lactose may already be in the facility, and therefore could create false positives when air sampling is conducted. It is important that rooms are properly cleaned prior to performing surrogate testing with lactose. As well, confirm that handling of the lactose raw material containers and bags were done utilizing high potency techniques, if they weren’t the small amount of powder on the outside of bags / containers, could be enough to trigger a false positive during surrogate testing.
- Acetaminophen is a moderate solubility material with a detection limit of 0.5ng.

Finally, in process monitoring with ‘real’ API material with a number of different operators should be carried out, wherever this is possible.

**Factory Acceptance Testing (FAT)** – FAT is testing the performance of plant and equipment in the factory where it is being fabricated. Full Factory Acceptance Testing can be time consuming and expensive since it involves setting up all the equipment in the same way it will be used following installation at the customer’s premises. Often equipment is set up as part of a process, and therefore ancillary equipment may not be present during the FAT.
Site Acceptance Testing (SAT) – SAT is the testing of the performance of plant and equipment after it has been installed. This is the final stage in a project before the equipment is signed over to the customer.

To establish a standardized methodology for measuring the performance of containment systems, the International Society for Pharmaceutical Engineering (ISPE's) Standardized Measurement of Equipment Particulate Airborne Concentration (SMEPAC) Committee created a good practice guide titled "Assessing the Particulate Containment Performance of Pharmaceutical Equipment." This guide describes how to undertake testing and describes the main factors affecting test results for specific contained solids handling systems, including material handling, room environment, air quality, ventilation, and operator technique.

Ongoing monitoring
It is sensible to routinely check the performance of containment systems to ensure that they continue to operate as intended. There are so many variables to consider as identified earlier, and although a piece of containment equipment may pass a SAT or a FAT with a surrogate, the performance may differ with actual products. It is recommended that active specific air monitoring be conducted on a routine basis to confirm that the containment can be achieved, and also that the process / techniques / maintenance doesn’t change over time where it negatively impacts the containment performance. In specific cases, this may be a legal requirement, for example the requirements for a full and thorough routine test and examination under UK COSHH regulations.

For routine testing, there are a number of levels available for consideration:

- Visual inspection of system and identification of variances.
- Mechanical function testing eg. valve operation, tell tales, airflow testing, pressure differentials, leak testing.
- The use of settle plates or other passive sampling techniques to identify where problems may be starting to occur before they become visible.
- Routine full performance testing based on regular air monitoring. This approach is a potentially expensive and time consuming activity requiring the full analysis of samples taken from personal and static monitors as a repeat of the original performance test.
6.6 Use of RPE and PPE

Selection of PPE to prevent permeation of API and chemicals is very critical. Glove manufacturers such as Ansell provides glove selection chart. Latex gloves are not suitable for APIs and chemicals. Nitrile gloves are suitable for many APIs and chemicals.

Preventing API contamination of contact surfaces such as cart handle, doorknob, pen used for data entry, key pad on weighing balance is critical. Two pairs of gloves are needed while working with high potent compounds. Contaminated outer pair of gloves is replaced with fresh gloves before touching above surfaces to prevent surface contamination.

The use of RPE and PPE within the pharmaceutical is similar to that in other industries but has some unique elements:
- The potent compounds used in the industry mean that the equipment often has to provide a very high level of control. This is particularly true of Respiratory Protective Equipment. Air supplied equipment is frequently used as is powered air purifying respirators with a double bibbed hood and HEPA filter.
- There is a significant risk from exposure during the removal and cleaning of PPE. Thorough training and proper facilities for storage and cleaning are critical. Often misting showers are utilized to cause the powder to stick to the PPE and reduce the risk of becoming airborne during degowning.
- Use in sterile environments imposes restrictions on the type of equipment which can be selected. The equipment must be capable of being sterilized and/or must be sterile when first supplied.
- Some materials are readily adsorbed through the skin or can enhance the adsorption of other APIs. For example, the solvent dimethyl sulphoxide (DMSO) increases the rate of absorption of some compounds through the skin. It is used as a vehicle for topical application of pharmaceuticals, as well as having some medicinal properties itself.

These elements can be controlled by employing techniques such as:
- Cleaning using fogging, mists and water deluge
- Ensuring washing does not redistribute dust.
- Ensuring equipment is cleaned appropriately, paying attention to places where material can get trapped in PPE even after showering, e.g. treads of boots, zip flaps, in between fingers of gloves.
- Use of visualisation materials such as UV fluorescent riboflavin to help evaluate cleaning efficiency.
- Ensuring shower walls and door are cleaned to prevent transfer.
- Carrying out maintenance operations under controlled conditions eg. RPE filter changing.
6.7 Control in Healthcare Settings

Major customers for prescription only medicines are the large hospitals. Concern over exposure to pharmaceutical actives in hospitals has focused mainly on the handling of cytotoxic products and anaesthetic gases. Other reports have been made of adverse reactions in healthcare staff making up large numbers of doses of antibiotics, exposure to drugs via emissions from nebulisers and skin absorption of opioids.

Cytotoxins

A number of studies have been carried out to investigate the effects of exposure to cytotoxic drugs in hospital staff. Increased mutagenic activity in the urine of nurses administering cytotoxins was reported by Falck et al (1979) and similar effects have been reported in other hospital workers handling cytotoxins (e.g. pharmacists, pharmacy technicians, etc). More recently, adverse pregnancy outcomes were reported in nurses who prepared and administered cytotoxic drugs during their pregnancy. Monitoring of pharmacies detected measurable concentrations of cytotoxins in the air. Detectable levels of cytotoxins have been found on the outside of vials and on surface around isolators used for dispensing (Mason et al 2003). Some reports have indicated that skin contact with cytotoxins was the best predictor of symptoms.

A number of reports of poor controls and working practices exist: pharmacy staff not wearing gloves when preparing doses, and nurses administering drugs and handling faeces of patients undergoing chemotherapy without the use of gloves.

More recent reports have shown considerable improvements compared to previous studies (Mason et al 2005) and that simple procedures could reduce the risk of contamination (Touzin et al 2008), although any controls should focus on the prevailing equipment and procedures (Acampora et al 2005).

The exposure of healthcare staff to these materials can be controlled to a level where no mutational effects can be observed by the application of good occupational hygiene techniques.

The use of Class II (open-fronted, ventilated cabinets) or Class III (sealed cabinets with glove ports) microbiological safety cabinets during the preparation of cytotoxic drugs is recommended. These can provide protection of both the product and the operator. For GMP purposes, Class III cabinets may have to be maintained under positive pressure whilst for occupational hygiene purposes negative pressure is desirable. The exhausts from such cabinets should be passed through a HEPA filter and routed outside the building. Recirculation of the filtered air is not recommended as some drugs may volatilise and so pass through the filter.

Use of these cabinets has been demonstrated to adequately control exposure by inhalation. Gloves and disposable aprons are still needed to provide adequate control of skin contact.
Anaesthetics
The main anaesthetics of concern are nitrous oxide and halogenated agents, such as halothane and enflurane. All operating theatre staff are at risk of exposure.

The HSE has set Workplace Exposure Limit for nitrous oxide (100ppm, 8-hour TWA), halothane (10ppm, 8-hour TWA) and enflurane (50ppm, 8-hour TWA) and measurement of these anaesthetics is possible by pumped or diffusive sampling onto molecular sieve (nitrous oxide) or charcoal.

Nitrous oxide is considered to cause developmental effects and inactivation of vitamin B<sub>12</sub>; these effects may be interrelated. Effects of halothane and enflurane are liver and kidney toxicity.

Measurements taken in operating theatres have shown that exposure to the halogenated anaesthetics can be readily controlled. Exposure to nitrous oxide can be higher than the OEL without the use of scavenging devices, but with scavenging, exposure can be controlled to below the OEL.

Some reports of skin reactions to betalactam antibiotics in healthcare workers exist following preparation of large numbers of doses without the use of gloves. Use of gloves and fume cabinets, if large numbers of samples are being prepared, will provide adequate control.

Other drugs
Exposure to aerosolised drugs, notably Ribavirin and Pentamidine, have been reported. Ribavirin, a synthetic nucleoside with antiviral activity, is usually administered to the patient in aerosol form via a mask or oxygen tent. While measurable exposures have occurred, no adverse reactions have been reported.

Pentamidine is used for the treatment of pneumonia, and it is administered as an aerosol after being reconstituted from a lyophilised powder. Reports of side effects in staff administering the drug include coughing, sneezing, mucous membrane irritation, headache and bronchospasm.

Opioids such as fentanyl (a potent morphine analogue) can be readily absorbed through the skin.
References:


Farris et al. History, implementation and evolution of the pharmaceutical hazard categorization and control system, Chimica Oggi (Chemistry Today), Vol 24 nr 2. March/April 2006

NIOSH, Preventing Occupational Exposures to Antineoplastic and Other Hazardous Drugs in Health Care Settings, DHHS (NIOSH) Publication Number 2004–165 September 2004


Many manufacturers have useful illustrations of containment systems on their websites. The following are examples of some of the companies. This is a partial list and additional suppliers may be available and user may consider getting details on additional supplier. These links are provided for familiarisation purposes only and do not constitute an endorsement of the products or services on offer.

EHS Solutions https://ehsnow.com/


GEA Pharma Systems:

http://www.gea-ps.com/npsportal/cmsdoc.nsf/WebDoc/misy6lmeqe

Pharmaceutical Containment Technologies: http://www.pctamericas.com/

Containment Technology Services: http://www.containment-technology.co.uk/


Annex 1: Types of Engineered Containment Systems

- Extract Hood/Cowl
- Horizontal Flow Booths
- Downflow Booths
- Clean break coupling systems
  - Simple Butterfly Valve Systems
  - Split Butterfly Valve Systems
  - Cone valve systems
- Rapid Transit Port (RTP) or Alpha-Beta Door Arrangements
- Sealed Liner or Bagout Systems
  - Single Standard Liner Systems
  - Tailored Bag Systems
  - Continuous Liner Systems
- Contained Transit Systems
  - Drums
  - Intermediate Bulk Containers
  - Big Bags
- Barrier Containment Systems
  - Rigid Shell Glovebox Isolators
  - Half-suit Rigid Isolator Systems
  - Flexible Wall Glovebags
Extract Hood/Cowl – *e.g. Flanged Slot type extract on excipient dispensing application*

The purpose of LEV is to remove airborne dusts from a local area by the use of high velocity extracted air into a cowl or exhaust hood, through a duct to a recovery system, either a filter or scrubber system. The air velocity is critical to the successful performance of the hood as there is a minimum velocity – known as the capture velocity – required to divert airborne dust into the hood. Typical velocities of around 0.6 m/s are quoted for capture though this will depend on particle properties and initial velocity prior to capture.

**Benefits**

<table>
<thead>
<tr>
<th>Easy to retrofit</th>
<th>Especially into existing facilities if a local filter and fan system can be accommodated.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inexpensive</td>
<td>Compared to barrier based containment options (if a local exhaust system is installed in the facility)</td>
</tr>
<tr>
<td>Ergonomics are good</td>
<td>The operator can have very good access all around the work area</td>
</tr>
</tbody>
</table>

**Concerns**

<table>
<thead>
<tr>
<th>Cross Contamination</th>
<th>Air pulled from outside the processing area over the product risking contamination from other materials unless tertiary controls are provided. In addition, ductwork will become contaminated if transport velocities are too low and may be a source of concern in multi-product facilities with common ducted extract systems.</th>
</tr>
</thead>
<tbody>
<tr>
<td>System Performance</td>
<td>The performance of the system is strongly dependent on maintaining airflows; any reduction in the exhaust source or filter performance will significantly affect performance, and may increase the risk of ductwork explosions (see below). Other strong air currents may also affect system performance in the facility. Each system is specified with a design flow and any decay will significantly reduce system performance. Operator compliance is an issue as such systems are typically very short-range and it is necessary to place the collection hood very close to the aerosol source.</td>
</tr>
</tbody>
</table>
Explosion Hazards

Most pharmaceutical dusts are explosible and care should be taken to ensure that unsafe dust clouds are not formed in ductwork or filter systems. All systems should be:

- fully earthed,
- the duct velocities sufficiently high to prevent particle deposition (typically >18 m/s at all times),
- filters are suitably designed for the risk of explosions, especially during reverse jetting activities.

Performance may need to be proven for insurance and risk management purposes.

Surface contamination

The operator will come into contact with hazardous material due to physical contact, though inhalation may be avoided by the LEV. The risk of transporting contamination on apparel to other locations should be noted and solutions such as the use of gloves considered.

LEV duct systems can release particulates back into the processing areas if shut down for energy saving considerations during off-hours when residual material does not have sufficient time and/or transport velocity to travel to the filters.

Typical Applications

LEV systems are commonly used where there are occasional dust or vapour emissions, for example vessel loading points, small bag emptying areas, low risk benchtop activities

Horizontal Flow Booths

The horizontal flow booth is a development of the extract cowl that improves the performance of simple local hood designs by creating an air swept enclosure to prevent lateral air ingress and flow interruptions. This frequently leads to a box-like structure of various sizes over the source commonly called a booth. The booth may be small, located around the emission source allowing only hand access into the booth area (for example a sack tip extract hood) through to a large booth that the operator stands within to carry out the operations. As with the extract cowl, the performance of the booth depends on the attainment of airflows at capture velocity and it is should be anticipated that such systems are not effective outside the booth volume.

The enclosure walls must be smooth, step-free, aerodynamic and parallel to promote streamlined flow. The perforated distribution plate which may be mounted in the rear of the booth should have
a free area of no more than 5% and hole diameters greater than 15 mm to avoid whistling and to provide even flow distribution.

All air taken into the booth comes from outside the booth, the system is essentially ‘once-through’ and air quality within the booth will reflect that in the area outside the booth. The effect of operating the booth and the volume of air it will remove from the room needs to be included in the design of the facility ventilation system to ensure that elevated negative pressures are not generated in the room leading to wall/ceiling panel damage, or difficulty opening doors.

It is critical to consider the effect of operator and equipment positions relative to the booth and airflows, and to prove effects, for example through the use of smoke testing.

**Benefits**

<table>
<thead>
<tr>
<th>Reasonable access to work area</th>
<th>Ergonomics may be restricted in small booths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flexible</td>
<td>Can be upgraded through use of secondary barrier systems such as flexible or mobile rigid screens with glove ports</td>
</tr>
<tr>
<td>Capital Cost</td>
<td>Cheaper than more highly contained systems</td>
</tr>
<tr>
<td>Easy to clean</td>
<td>Booth working area is highly visible though access to ductwork and filter sets may be problematic.</td>
</tr>
</tbody>
</table>
## Concerns

<table>
<thead>
<tr>
<th>Concerns</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cross Contamination</td>
<td>The large volume of air pulled into a man-sized extract booth results in an increased risks of cross-contamination from other sources, and also the risk of affecting tertiary room air balances.</td>
</tr>
<tr>
<td>System Performance</td>
<td>System performance is strongly dependent on maintaining airflows; changes to the airflow pattern or filter resistance will significantly affect containment performance, and may increase the risk of ductwork explosions (see below). The presence of operators and equipment within the capturing airflow path may disrupt the air flow and hence the effectiveness of capture, possibly creating eddy currents from the work area to the breathing zone increasing hazards. System performance may also be affected by other strong air currents in the facility</td>
</tr>
<tr>
<td>Explosion Hazards</td>
<td>All systems should be fully earthed, the duct velocities sufficiently high to prevent particle laydown (typically &gt;18 m/s at all times), and that filters are suitably designed for the risk of explosions, especially during reverse jetting.</td>
</tr>
<tr>
<td>Surface Contamination</td>
<td>The operator may come into contact with hazardous material due to physical contact, though inhalation may be avoided. The contamination risk is increased if the operator work position is inside the booth.</td>
</tr>
<tr>
<td>Ergonomics</td>
<td>The booth may restrict access and create ergonomic problems especially on smaller booth systems. Large extract booths may improve access but require greatly increased airflow and space requirements. The working position of the operator inside the booth relative to the source can have a major impact on exposure.</td>
</tr>
<tr>
<td>Noise</td>
<td>Flow booths typically move far larger volumes of air than local extract systems and the noise generated by air moving equipment can be significant.</td>
</tr>
</tbody>
</table>
**Typical Applications**
Primary protection of low emission activities such as sampling, small volume weighing and dispensing and cleaning. Manual handling of low hazard materials (e.g., sack dump stations).

Secondary protection of primary systems with inadequate containment performance or intolerable risk of failure, for example drum liner filling and other pack off activities.

**Downflow booths**
The downflow booth is a development of the extract booth where the airflow is recirculated from the rear of the booth, via a local filter and fan system and back into the booth via a plenum located in the booth ceiling. The advantage of this system over the extract booth is that the air quality can be carefully controlled by the filter specification and the air fed back into the booth will not be contaminated which may be critical for product quality. The system will not be totally recirculated, there is a need to purge and make up a proportion of the recirculated flow (typically 10%) for fresh air makeup, higher proportions or once-through operation may be required where high background concentrations of solvent or hazardous materials are anticipated.

The downflow booth does not rely on air acceleration into the booth to affect capture, the particles are carried in the bulk movement of air at a minimum of 0.5m/s in the booth.
Benefits

<table>
<thead>
<tr>
<th>As extract booth</th>
<th>Downflow booths are generally larger and hence ergonomics are improved. The downflow of air helps to prevent contaminants from rising into the operator’s breathing zone.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk of cross contamination reduced</td>
<td>System is designed to blow clean air away from contaminated booth area preventing ingress of foreign material.</td>
</tr>
</tbody>
</table>

Concerns

<table>
<thead>
<tr>
<th>Worker proximity</th>
<th>The operator is inside the control device and can be in very close contact with the materials.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limited Effectiveness</td>
<td>Downflow booths typically cannot contain below air concentrations of 50 µg/m³ unless equipped with primary containment devices such as barriers (screens), custom LEV capture hoods, glove bags etc.</td>
</tr>
</tbody>
</table>

Clean Break Coupling Systems

It is usual for sequential process steps to be connected in one of two ways: either by direct linework for blown, gravity or vacuum transfer, or through the use of transit containers. The connection and disconnection of these containers is a major potential source of loss of containment and much development has recently been carried out into coupling systems that do not create a localised hazard during such operations. Examples of such systems are as follows:

**Simple Butterfly Valve Systems**

The simplest mechanism for containing powder flow is a simple butterfly valve. If two of these are located in close proximity, then breaking linework between them will only expose material contaminating the area between the valves (including the valve flap surface) to be potentially released to create a potential for exposure. Further improvements including the provision of dry (air wash systems) and wet (water/solvent based) cleaning of this contaminated area before breaking the linework will give improved performance.

The system performance will rely heavily on the efficiency of this inter-valve cleaning protocol – dry cleaning is generally ineffective at removing all surface contamination, and wet systems may leave residual moisture on surfaces that may affect subsequent transfers.
Benefits

<table>
<thead>
<tr>
<th>Benefit</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cheap simple solution</td>
<td>Uses established, off the shelf components. Integral wash in place increases complexity</td>
</tr>
<tr>
<td>Can be automated</td>
<td>Allows remote operation removing operator from source of hazard.</td>
</tr>
</tbody>
</table>

Concerns

<table>
<thead>
<tr>
<th>Concern</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Performance</td>
<td>Large problem of surface contaminant release in transit unless expensive secondary washing or cover systems included</td>
</tr>
<tr>
<td>Bulky</td>
<td>Requirement for two valves for transfer can create tall combination.</td>
</tr>
<tr>
<td>Cleaning</td>
<td>Dry cleaning systems using air are usually not effective and wet cleaning systems may not be effectively dried leading to lumps and flap sticking.</td>
</tr>
</tbody>
</table>

Double valve systems are relatively rare; the reduced cost of the valves is balanced by the cost and complexity of the cleaning systems. Typical uses are on IBC discharge activities to process vessels.

**Split Butterfly Valve Systems**

The split butterfly valve is a relatively recent development from the double butterfly system. The basis of operation is that the inter-valve distance is reduced to nil and the two valves operate together from a common shaft actuator following docking and locking of the two valve segments. Alternatively, a split valve can be considered as a single valve that has been sliced in half through the flap and one half is fitted to the filling vessel, and the other to the receiving unit. Neither half will operate until the two halves have been brought together and locked.

The benefit of the split valve is that the two mating faces of the flap seal together to prevent powder ingress and when the valve is closed and the halves separated, the exposed surfaces should be clean.
In practice, the cleanliness of the surfaces is dependent on the mechanical tolerances and stresses imposed on the valve, the nature of the material handled, and the frequency of valve operation since the previous full cleaning cycle was applied.

There is a wide range of proprietary systems available, with a variety of docking systems and features including air and liquid washing when the valve is partially undocked. Performance is variable but essentially the greater the cost, the better the performance. Performance is also heavily dependent on powder physical properties and methods of operation, cleaning and maintenance.

Source: Adrian Hirst

**Benefits**

<table>
<thead>
<tr>
<th>Simple Retrofit</th>
<th>Relatively easy to fit onto existing standard flanges</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wide range of sizes and materials</td>
<td>Available in appropriate materials and sizes to suit most applications</td>
</tr>
<tr>
<td>Wide Range of performance</td>
<td>Valve type can be selected to suit the material and containment requirement</td>
</tr>
<tr>
<td>Complete range of accessories</td>
<td>Cleaning and other support equipment developed for most types. Clean-in-place technology is sometimes incorporated.</td>
</tr>
<tr>
<td>Can be automated</td>
<td>Allows remote operation removing operator from source of hazard.</td>
</tr>
</tbody>
</table>
Pressure Rated Versions
Some models are available as pressure rated systems, others require in line ball or similar process valves to maintain pressure integrity.

Concerns

<table>
<thead>
<tr>
<th>Concern</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capital Cost</td>
<td>Prices range from 15K EU up to 70K EU for active/passive pair depending on size and materials. Cleaning and other supporting equipment are extra.</td>
</tr>
<tr>
<td>Size</td>
<td>Mechanical docking and locking requirements add height to the equipment stack-up. Equipment is heavy (300mm active ~ 35kg) due to sensors and actuator elements.</td>
</tr>
<tr>
<td>Mechanical Complexity</td>
<td>Systems rely heavily on close tolerance fit and high quality seal systems. The valves are often controlled by PLC systems including multiple position sensors to ensure correct operation. Multiple potential failure modes leading to failure to operate and potential loss of containment and a degree of outage due to peripheral failures, for example position sensors, should be anticipated.</td>
</tr>
<tr>
<td>Rapid Development</td>
<td>Devices are in rapid development as learning on performance becomes available. Care should be taken when selecting a valve to ensure that any new developments are fully established and possible impact on containment performance is understood.</td>
</tr>
<tr>
<td>Poor flow enhancement</td>
<td>Active/passive flap assembly forms large bluff body to obstruct flow creating greater risk of bridging with cohesive materials than normal butterfly valve. Discharge aids integral to split valves are being sold to aid discharge, but care should be taken with external vibrator systems, that may put excessive stress on the docking/locking mechanism of the valve.</td>
</tr>
</tbody>
</table>

**Typical Applications** Split valves are widely used for connections to transit vessels of all sizes (bottles, bags, kegs and IBCs) to process systems, both for filling and discharge. The availability of a range of sizes and materials of construction enables the split valve to be considered for all phases of pharmaceutical manufacture.
Cone Valve Systems – e.g. Cone valve docking system and opening

The contained cone valve system is a development of the cone valve system widely used in the chemical and powder processing industries for discharging powders from vessels or hoppers.

The basis of operation is the engagement of an actuator on a discharge station with the base of a cone fitted to the bottom of an IBC. As the actuator lifts the cone, powder flows around it, through a hopper and into the feed chute below the hopper. The base of the cone and the top face of the actuator are kept clean through the use of seals and close tolerances, similar to the split valve principal. The benefit of the cone valve system is the lifting of the cone reduces the cohesion of the powder bulks aiding powder flow, reducing the risk of blocking and the potential requirement to break containment to free the blockage. In addition, the cone can be lifted in cycles and vibrated to further aid flow. When not docked to the actuator, the cone is held in place by the weight of the material and can be clamped with an additional travel cap to provide greater security. The other benefit of the cone valve over equivalent systems, such as the split valve, is that the valve can be closed against powder flow, allowing the valve to be used as a metering or dispensing device when integrated to a suitable weighing system.

The containment performance of the valve is similar to less developed split valves though this is improved by the inclusion of air wash systems. The system can be operated remotely using an appropriate level of automation. The major problem with cone valve systems is the large size of the cone seal face and the difficulty in fabricating such large circular systems to a very high level of accuracy resulting on a need to rely heavily on deep soft seals.

IBC filling systems based on cone valve type technology are also available, these usually have the actuator fixed to the cone in the feed hopper with the cone sealing to the side of the hopper. On docking, the cone mates with and secures a flat lid in the top of the IBC and lifts in into the hopper. Again, powder flows around the cone from the hopper into the IBC. The system is sealed again by the cone being lowered, relocating the flat lid in the IBC filling port and then lifting out and sealing the hopper. As with discharge, such systems are reliant on close tolerances and the effectiveness of air wash systems and do not reduce the risk of blockage in hopper feed elements such as feed chutes which may be of reduced diameter.
Source: Servolift

**Benefits**

| Excellent flow promotion properties | The cone valve prevents bridge formation with cohesive powders and presents the best option for handling ‘difficult’ powders. |
| Established Technology | Basic design has been available for many years and many enhancements have been introduced |
| Can be automated | Allows remote operation removing operator from source of hazard. |
| Cleaning | Automated CIP can be built into discharge stations |
Concerns

<table>
<thead>
<tr>
<th>Cost</th>
<th>Specialist discharge and/or filling stations are expensive</th>
</tr>
</thead>
</table>

| Size | Valves are only available in large scales suitable for large-scale manufacture, not small development units.  
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Equipment is generally bulky as a result requiring large layout areas.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Performance</th>
<th>Containment performance is strongly dependent on frequency of cleaning, repeated operation leads to material tracking around base of IBC.</th>
</tr>
</thead>
</table>

| Availability of Support | Due to patent issues, limited number of suppliers with no interchangeability.  
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Complexity of systems requires local support availability.</td>
</tr>
</tbody>
</table>

Typical Applications

Cone valves are widely used with large scale powder IBC systems where material flow characteristics may be poor, where preset weights of powder may be required, or where rapid feeding is required.

Rapid Transit Port (RTP) or Alpha-Beta Door Arrangements

The alpha-beta door is a development from the nuclear industry created to allow the contained docking of vessels containing hazardous materials to other systems, typically rigid isolator units, to allow transfer of the hazardous material without loss of containment. The basis of operation is similar in some respects to the split valve; the door is made up of two elements, the alpha and beta parts.

The alpha element includes locking and opening devices and is typically fitted to the isolator. The beta unit is essentially a plug that fits to the transport container. The mechanism of operation is for the beta unit to be docked into the alpha unit and the two units to be clamped together such that the mating faces are tightly sealed against each other, forming an ‘alpha-beta’ seal. The sealed elements can only then be opened as a single door to allow the material to be passed from the transit container into the isolator. The alpha-beta door can then be closed and the units unlocked/undocked. Both mating faces will remain clean and the only area of concern may be the peripheral seal of the door, often known as the ‘Ring of no Confidence’.

Since the system essentially consists of a door, it is not usual to feed powder directly through such systems, unless the door peripheral seal faces can be protected, they are typically used to pass containers of material or change parts into isolators, or to allow the transit of flexible sleeves, for example from big bag systems, for connection to systems located within the isolator.
Benefits

<table>
<thead>
<tr>
<th>Well developed</th>
<th>Standard equipment sizes are available from a number of manufacturers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanically interlocked</td>
<td>The inclusion of mechanical interlocks prevents the risk of operator maloperation leading to a breach of containment.</td>
</tr>
<tr>
<td>Wide range of materials of construction</td>
<td>Available in plastic, stainless steel with a wide range of sealing materials. Disposable beta forms are becoming available</td>
</tr>
<tr>
<td>Sterilisable</td>
<td>Designed for use in sterile isolator systems and can withstand chlorine-based sterilisation.</td>
</tr>
<tr>
<td>Wide range of connecting devices.</td>
<td>The Beta door can be fitted to a wide range of transit containers such as bottles, bags or canisters to allow materials to be transferred in a contained manner into an isolator or similar system, and for a single port to have multiple uses (waste bagout, material introduction etc.)..</td>
</tr>
</tbody>
</table>

Concerns

| Cannot be used as a direct transfer device | The system is essentially a door, not a valve. Access to the alpha-beta combination is required to enable the door to be opened. Direct contact of system with powders is not encouraged as seals are difficult to clean when a system is docked. |
| Dependence on seal cleanliness | The containment performance of an alpha-beta door system is strongly dependent on maintaining the cleanliness of seal faces. The presence of powder on these seals during undocking will lead to visible loss of containment. |
| Cost | Systems are expensive and all connecting containers must be fitted with beta element. |
| Size limitations | Max available diameter is 450mm, which may preclude use with large item or material transfers. |

Typical Applications

Most commonly used for the transfer of equipment or material containers through a solid barrier in a containment device, generally an isolator. They can be used for the direct transfer of powder
material if secondary protection over the seal face is provided (a flexible sleeve for example) to prevent seal face contamination.

**Sealed Liner or Bagout Systems**

**Single Standard Liner Systems**

It is usual for bulk API powder material to be moved between processing sites in lined drum kegs of various sizes. This allows the use of simple inexpensive technology whilst enabling specific material requirements for the product contact material (e.g. moisture barrier, light exclusion, dissipative or anti-static properties to be a function of the liner material in the keg. The filling of such liners is a key element of the manufacture of API materials and the containment of such operations is commonplace in the industry.

The simplest systems use single bags that are sealed to the external atmosphere during filling by the use of inflating seals, or O-rings compressing the liner to the discharge chute. Once the liner is filled, the seal is deflated or removed, the liner is tied off and a second liner is secured over it. The liners are then pushed into the base of the keg/drum and the drum is lidded and clamped.

**Benefits**

<table>
<thead>
<tr>
<th>Simple technology</th>
<th>Simple pneumatic controls, standard systems can include bag inflation and inertion and bag deflation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cheap</td>
<td>Systems are well developed and standard systems are not expensive compared to split valve or other systems</td>
</tr>
<tr>
<td>Can be used with simple liners</td>
<td>Does not require any modification to standard flexible sack liner.</td>
</tr>
<tr>
<td>High tolerance level</td>
<td>Can absorb variations in manufacturing tolerances in liners – especially with O-ring systems.</td>
</tr>
<tr>
<td>Can be integrated with other packing off peripheral systems</td>
<td>Use with flexible liners allows the use of weighscales for controlled filling.</td>
</tr>
<tr>
<td></td>
<td>Simple end of line solution that can easily be integrated into secondary systems such as isolator or flow booth.</td>
</tr>
</tbody>
</table>

**Concerns**

| System is open for much of changeover process | Liner is open as bags are changed and potential exists for major emission if operator squeezes bag to remove air before tying off. |
Contaminated chute is open to environment during entire liner changeover period.

<table>
<thead>
<tr>
<th>Systems fail to danger</th>
<th>Failure of the inflating head or the O-ring create an emission case</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recovery from overfill is difficult</td>
<td>Systems cannot be closed against overfilled liner. Manual intervention is required to remove overfill, usually resulting in spillage situation.</td>
</tr>
<tr>
<td>Sampling</td>
<td>Sampling of material from such systems requires the use of tailored liners (see 2.1.5.2) or in line mechanical samplers which can be problematic in operation</td>
</tr>
<tr>
<td>Liner materials can cause problems</td>
<td>Liners need to be capable of withstanding solvent attack and prevent static ignition. Inertion or the use of dissipative liners are most common methods of dealing with static risk.</td>
</tr>
<tr>
<td>Discharge from liner is problematic</td>
<td>Liner has to be split to access material for discharge unless specialist port or docking device is integrated. Position where liner is split open requires containment with extract booth or isolator.</td>
</tr>
</tbody>
</table>

**Typical Applications**

Can be used for any process where dry or wet solids are loaded into flexible liner systems, either in FIBC systems or liners into drums.

**Tailored Bag Systems**

A development of the single bag system is the tailored bag where the bag includes a separate sleeve on the inlet. The purpose of this is to allow the bag to be sealed to the feed chute using an O’ring and then filled in a contained manner. After filling, the bag is tied off below the end of the chute with two cable or similar ties located approximately 50 mm apart. If the liner is then cut between these ties, then two exposed ends are left, one on the sealed product liner, one on a ‘shower cap’ still covering the end of the chute, secured with an O’ring. The product liner is overbagged, the secondary container (FIBC or drum) closed and the next bag brought in. The new bag is fed over the ‘shower cap’ and sealed to the chute with an O’ring above that of the ‘shower cap’. The operator can then reach into the bag using the sleeve on the inlet to grab the ‘shower cap’ and pull it off the end of the chute into the sleeve that can then be tied off to isolate it from the product flow. The
system is now ready to fill the next bag. The sequence can be repeated for a many times as it takes for the O’rings to reach the top of the outside of the chute. Special cleaning bags are available which can be attached over the system to allow the exterior of the chute to be cleaned and the O’ring brought down to near the lower end.

Benefits

<table>
<thead>
<tr>
<th>Benefit</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wide range of sizes</td>
<td>A wide range of liner sizes and configurations are available</td>
</tr>
<tr>
<td>Simple to use</td>
<td>Basic operating principle is simple.</td>
</tr>
<tr>
<td>Flexible design</td>
<td>The addition of additional sleeves and the design of additional ancillary bags for cleaning for example is simple and relatively inexpensive compared to ‘hard’ systems.</td>
</tr>
<tr>
<td>Easy to clean</td>
<td>Basis of system is simple chute and O‐ring clamp.</td>
</tr>
<tr>
<td>Hardware is cheap</td>
<td>No automation is required and there are no moving parts other than isolation valves that may be required to isolate the process.</td>
</tr>
</tbody>
</table>
| Can be used for contained charging | The integration of sleeve systems into the bottom of the liner allows the connection to a chute, essentially using the filling process in reverse, to allow the contained discharge of the liner into a process.  
                          | The ability to manipulate the liner means that materials with poor flow capabilities can also be discharged without breaching containment. |
| Integral sampling             | Sampling sleeves can be fitted to each liner to allow contained sampling during filling. Separate sleeves on each liner mean that there is no cross-contamination between samples from different liners. |

Concerns

<table>
<thead>
<tr>
<th>Concern</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Materials</td>
<td>The requirement to weld sleeves prevents the use of some materials due to weaknesses that welding creates. Allowable materials may have problems with solvent attack.</td>
</tr>
<tr>
<td>Cost</td>
<td>Liners are individually tailored and scarcity of suppliers results in significant cost per bag unless large numbers are used.</td>
</tr>
</tbody>
</table>
Operator Dependent | There are no operator interlocks and performance and prevention of spillage is totally dependent on the correct operation of the system by the operator.

Multiple operator Requirement | The double tie, twist, tape and cut of the liner can require three hands to complete. Systems are in development to enable single operator operation.

**Typical Applications**

Can be used for the packing off and storage of wet or dry powder materials from a wide range of processes, where containment of the material and further total discharge of the material into a later process is required.
Continuous Liner Systems

The furthest development of the sealed liner system is the continuous liner. This is essentially a continuous tube of liner material loaded onto a cartridge fitted over the outside of, and sealed to, the discharge chute. The operation of the unit uses the double tie and cut arrangement of the tailored bag system but uses the ‘shower cap’ to form the lower end of the next bag.

A typical sequence of operation is:
- Locate open drum with single liner fitted below filling chute.
- Pull sealed end of continuous liner into base of drum.
- Inflate liner – nitrogen can be used as part of purging sequence.
- Fill liner – liner fill can be detected with load cells or visual inspection.
- Deflate liner to remove nitrogen/air.
- Double tie and cut between ties.
- Close outer liner and seal.
- Lid drum and remove.
- Locate next open drum with liner fitted and repeat sequence until batch discharged.

The capability to change cartridges when continuous liner is exhausted is possible using similar methods to the single tailored bag technique with the residual ‘shower cap’ being disposed of into the bottom of the new continuous liner rather than a side sleeve.

The operation of liner based systems is extremely operator sensitive. The benefits of liner-based systems are their relative cheapness and the ease of incorporation into secondary systems, for example extract booths. The areas of concern are around the reliance on operator technique, the robustness of the liner material, especially with the presence of sharp devices to cut liners, and the ergonomics of carrying out the manual tying and cutting activities in specialised secondary containment devices.

Liner based systems are used in all processing stages in the Pharmaceutical Industry where material needs to be discharged as a powder from a processing stage (such as drying or milling) prior to storage or transfer to another location away from the manufacturing plant.
### Benefits

<table>
<thead>
<tr>
<th>Benefit</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cheap</td>
<td>As tailored liners, hardware is simple chute and O-ring. Liner material is typically cheap blown tubing.</td>
</tr>
<tr>
<td>Simple to operate</td>
<td>Well-designed systems with good access are easy to operate and the use of cartridge systems allows simple changeover when liner is exhausted.</td>
</tr>
<tr>
<td>Integrate with filling peripherals</td>
<td>Can easily be integrated into secondary containment systems such as extract booths or simple isolators. Weighscales can be integrated to monitor filling activities.</td>
</tr>
<tr>
<td>Lack of complexity</td>
<td>System incorporates no instrumentation or moving parts to effect containment.</td>
</tr>
</tbody>
</table>

### Concerns

<table>
<thead>
<tr>
<th>Concern</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liner robustness</td>
<td>Manipulation of the liner to make new bag can risk tearing. Care in operation is absolutely essential to obtain best containment performance.</td>
</tr>
<tr>
<td>Operator dependence</td>
<td>System is totally manual, the performance of the operator in manipulating the liner, performing twist, tie tape and cut and replacing cartridges is critical in achieving routine containment performance.</td>
</tr>
<tr>
<td>Recovery from overfill is difficult</td>
<td>Systems cannot be closed against overfilled liner. Manual intervention is required to remove overfill, usually resulting in spillage situation.</td>
</tr>
<tr>
<td>Sampling</td>
<td>Sampling of material from such systems requires the use of tailored liners (see 2.1.5.2) or in line mechanical samplers which can be problematic in operation.</td>
</tr>
<tr>
<td>Liner materials can cause problems</td>
<td>Liners need to be capable of withstanding solvent attack and prevent static ignition. Inertion or the use of dissipative liners are most common methods of dealing with static risk.</td>
</tr>
<tr>
<td>Discharge from liner is problematic</td>
<td>Liner has to be split to access material for discharge unless specialist port or docking device is integrated. Position where liner is split open requires containment with extract booth or isolator.</td>
</tr>
</tbody>
</table>
Typical Applications

Can be used for the packing off and storage of wet or dry powder materials from a wide range of processes, where containment of the material is required. Widely used for discharge from API filters, dryers, centrifuge, or size reduction systems

Contained Transit Systems

The transfer of powder and other solid materials within and between facilities is a common problem in the operation of contained facilities. Whilst it is desirable to minimise coupling points by directly connecting equipment, this is not always possible due to problems of layout. In addition, the requirements of process cycle times may require processes to be decoupled to allow optimal equipment utilisation. As a result, it is necessary to store materials in transit or storage containers, the benefits and concerns of which are reviewed in the following sections.

The containment performance of such systems is commonly a function either of a liner (see section 2) or a docking device on IBCs, such as a split or cone valve system.

Drums

Often also called ‘kegs’, these are cylindrical containers with clamped lids on the top, and occasionally on the base. A large range of sizes is available ranging from below 30 litres up to 220 litres. They are available in a range of material, usually steel (stainless or coated mild steel) or fibreboard. They are cheap, UN registered allowing their use for international transport, and can be disposed of after a single use.

They can be provided with liners to allow additional containment and to provide additional properties, such as static dissipation, moisture exclusion and light exclusion.

The problems with drums are that they cannot be opened, discharged or filled in a contained manner without the use of additional systems, typically isolators or extract booths, which entails significant additional capital cost. These systems require tight control over drum sizes and care must be taken to ensure that a prescribed drum size is specified to avoid proliferation of drums of different dimensions but similar volume.

Drums are typically used where small volumes and intermittent usage make bulk transfer containers infeasible. Vacuum wands often provide the safest means to transfer the contents into the process equipment. Hand scooping should generally be avoided, though there are flexible containment options available.
Intermediate Bulk Containers (IBC)

Also known as ‘bins’, IBCs are traditionally stainless steel or plastic vessels of volumes of 25 – 2000 litres. They will typically include a top filling point and base discharge, though some IBCs have a single filling and discharge point and rely on inversion for discharge. At the simplest level, filling is through an open chute, possibly with LEV to minimise dust cloud growth. Discharge would be via a standard butterfly valve into a chute through a simple seal arrangement.

At the next level, the IBC is fitted with contained make/break couplings for filling and discharge, typically split valve and/or cone valve systems. These improve the level of containment to that provided by the coupling system, albeit at the cost of requiring a passive valve section to be fitted to each IBC connection point which may double the cost of the IBC and more.

The benefits of IBCs are that they provide a simply handled storage facility that can be handled automatically using pillar lifts and other automated docking system. They are available in a range of volumes and the cost of the items justifies specific modifications that may optimise performance with specific materials.

The major problem with IBCs is the cost, which does not warrant single use operation as per drums. This means that IBCs are usually cleaned and reused, in a contained environment, this requires the installation of automated wash facilities with integrated systems to open and close containment couplings within a wash booth. The cost of such systems and the space requirements associated with storage areas, wash cabins and service skids is significant.

In addition, most IBC systems are not UN registered and cannot be used for inter-site transfer; as such it is most usual to see them used solely for internal plant transit and storage.

Finally, sampling from IBCs is very difficult; some scope for material identification using external probes (e.g. Near Infra Red spectroscopy) is being developed but is not yet in common application.

Big Bags

Big bags (also called flexible IBCs or FIBCs, or Super Sacks in USA) are large flexible containers (up to 2000 litres) used for the transfer of large volumes of bulk powders. They usually consist of an internal liner with top and bottom connections, and a woven robust outer cover which reduces the risk of punctures. They are typically inexpensive enough for single use and are generally UN registered, but most common types do not incorporate contained connection details, relying on inflating or O-ring seal systems with local extract or surrounding isolation at the docking point to achieve containment.
An alternative is the DoverPac® system developed by ILC Corporation and Eli Lilly, which uses a tailored liner system and outer woven restraint to provide big bag operation with contained transfer. The liners are single use, though the outer covers can be reused.

The concerns with big bags are the robustness of the liner; whilst the outer levels are generally robust, there is always a fear of sharp edges causing cuts and loss of containment. In addition, big bag systems cannot be easily sampled in a contained manner and partial discharge is not easy. The advantages of big bags is that they can be sized to have a single container for a complete batch, and the discharge of difficult powders is eased because the flexible liner can be manipulated to break bridges or other flow problem.

**Barrier Containment Systems**

**Isolators**

Isolators (also known as gloveboxes) are essentially barrier systems which enclose the source of emission. The operator can only access process equipment or materials within the unit via gloved sleeves or half-suit assemblies, thus ensuring that there is no direct contact between operator and process. Isolator technology originally developed out of the nuclear industry. As such, extremely high levels of containment can be achieved with such systems and there is a well-developed understanding of critical design parameters and standard methodologies for overcoming specific process requirements, such as bringing materials into and out of the isolator in a contained manner.

Containment isolators are typically operated at negative pressures of between 50 to 150 Pascals relative to the external environment. The maximum pressure differential is limited by the stiffness that the differential pressure creates in the glove sleeves, which can make operation extremely clumsy and tiring in extreme cases. The pressure differential is created by an exhaust fan protected by a filter set to prevent contamination breakthrough into the fan itself. It is usual to provide a prefILTER backed up by one, or more usually two, HEPA grade (H13 or higher) filters with condition monitoring differential pressure measurement systems. These filters are also usually specified to have safe-change capability to protect the technician replacing them.

Airflows within the isolator may be maintained by installation of an inlet air filter to provide a constant airflow into the isolator to aid differential pressure control. A prefILTER is provided to prevent gross room particle contamination of the backup HEPA. The quality of the air inside the isolator is usually far better than the external room, which may be of relevance for Quality Assurance where open product handling in the isolator is required.

The external fan is sized to maintain pressure differentials and to generate a velocity of >0.5 m/s across the largest orifice that could be created in the event of a failure, typically this is across a
gloveport. To enable this, the fan is often fitted with a variable speed drive with control from a pressure transmitter. Alternatively a second emergency fan might be fitted to operate in the event of low chamber negative differential pressure.

As an alternative to air purging, it is possible to purge the isolator with closed nitrogen circuits or specially conditioned air as necessary.

The ergonomics of isolator layouts are critical to the safe and effective operation. There are a number of ‘rules of thumb’ for design, which are detailed in standard texts and design guides and should be followed in initial design to ensure a reasonable chance of successful installation. In all cases where bespoke design of a system is being attempted, it is critical that there is a review of a mock-up of the design, either using a full-scale model, or through the use of a 3-d design walkthrough. It is also critical that operating and maintenance staff reviews this mock-up; this will aid ownership of the design, and will identify key operating activities that may not be obvious to non-operating staff.

Ideally the mock-up should include all internal elements within the isolator, preferably at the correct weight and size so that full ergonomic assessments can be completed at design review. In extremely complex cases, it may be necessary to have the actual equipment installed incorporated into the mock-up to ensure a totally authentic review of ergonomics. The implications for total system delivery timescales should be included in project programmes if prior delivery of processing hardware in time for such trials is required.

Finally, prior to delivery, it is necessary that the assembled isolator be fully tested at FAT including all safety systems and filters and extract systems. It is very difficult to modify installations on site and full acceptance of the unit prior to delivery is critical.

**Rigid Shell Glovebox Isolators**

Rigid shell glovebox isolators are the classic isolator configuration. They are typically fabricated from stainless steel with glass windows and flexible gauntlets. Materials are introduced through airlocks, rapid transit ports, or special docking arrangements, and removed through bag-out facilities. Gloves can be manufactured from a range of materials to suit specific applications and solvent or chemical resistance requirements.

Lighting is provided through externally mounted windows (typical light requirements for safe operation are >500 lux at all points) and drive motors for internal moving equipment are also mounted externally with shafts being taken through sealed bearings in the isolator shell.

Isolators can be made from multiple cells, this is usually to separate highly contaminated processing areas from docking zones to ensure that the area of highest contamination is separated from the
areas of greatest risk of loss of containment, typically a transit point for materials through the isolator shell.

Standard designs are available for common applications such as sampling, simple benchtop dispensing and small-scale laboratory scale chemistry applications. Larger isolators tend to become bespoke designs due to the high cost of such systems thus ensuring optimal design for the cost.

**Benefits**

<table>
<thead>
<tr>
<th>Description</th>
<th>Detail</th>
</tr>
</thead>
<tbody>
<tr>
<td>High level of security</td>
<td>The rigid isolator shell is resistant to damage and the automated protection systems reduce the risk of failure to a dangerous condition.</td>
</tr>
<tr>
<td>Bespoke Design</td>
<td>The isolator system can be designed to specifically meet the requirements of a particular process or item of equipment.</td>
</tr>
<tr>
<td>Allows manual handling of hazardous materials</td>
<td>Manual dispensing or charging of materials from containers that otherwise cannot be discharged in a contained manner (e.g. lined drums). It also allows the use of uncontained process equipment (for example check weighing systems on tablet presses) with High Hazard materials.</td>
</tr>
</tbody>
</table>

**Concerns**

<table>
<thead>
<tr>
<th>Description</th>
<th>Detail</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost</td>
<td>Isolators are very expensive and may have long delivery times due to bespoke design, model testing and assembly requirements.</td>
</tr>
<tr>
<td>Size</td>
<td>Isolators essentially form a cordoned area around the process contained within. The area taken up by the isolator shell, filter and fan systems will be far greater than the process equipment contained.</td>
</tr>
<tr>
<td>Easy to get wrong</td>
<td>The access of all elements via glove sleeves is difficult to design to suit all heights and sizes of staff. It can be difficult to make ergonomically difficult activities safe without recourse to additional manual handling aids as access to systems via gloveports can restrict the use of major muscle groups.</td>
</tr>
<tr>
<td>Difficult to clean</td>
<td>Design of isolators for cleaning and ensuring that surfaces maintain the required finish to aid cleaning is difficult. The installation of equipment within isolators frequently leads to the creation of dead spaces or blind spots for CIP systems and</td>
</tr>
</tbody>
</table>
requires the use of manual cleaning using spray lances and wipes.

Only as good as the weakest component

Containment is a function of all elements of an isolator, including window seal, pass-through and pass-out port, container docking system, and gloveport designs. Failure to maintain all these systems can lead to inadvertent external contamination and risk to operating staff.

**Typical Applications**

Applications where process equipment containment cannot be obtained, or where there is a requirement for routine breaches of containment, for maintenance and cleaning for example.

Glovebox isolator systems can also be used as secondary containment systems for particularly hazardous operations where a contained transfer system, might otherwise be considered to constitute an intolerable risk. An example might be the charging of a container of extremely hazardous dusty material via a split valve system.

**Half-suit Rigid Isolator Systems**

The half-suit rigid isolator is a version of the glovebox isolator where an operator protected by a half suit accesses the contained materials and equipment. The performance of the system is essentially similar to a glovebox but with improved ergonomics as major muscle groups can now be used by the operator for lifting, and the reach of the operator is enhanced. The downsides of such systems are that the isolators are far larger (and hence more expensive) than an equivalent glovebox, require far larger fan and filter sets to achieve the 0.5 m/s velocity through the half-suit port rather than a gloveport, and there is an argument that the half-suit is effectively a form of PPE rather than a containment device.

**Benefits**

<table>
<thead>
<tr>
<th>As glovebox isolators</th>
<th>Reach and manual handling is better than a glovebox isolator allowing more complex systems to be contained.</th>
</tr>
</thead>
</table>

**Concerns**

<table>
<thead>
<tr>
<th>Cost</th>
<th>More expensive due to increased size requiring larger fans, filters (to meet air in-rush requirements) and isolator shells</th>
</tr>
</thead>
</table>

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Chapter 6: Control of Exposure

51
(to enclose halfsuit connection rings). Halfsuit costs are not trivial..

<table>
<thead>
<tr>
<th>Size</th>
<th>Halfsuit isolators require larger area within the facility increasing building costs and may not be feasible for tight retrofits.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Considered as PPE</td>
<td>Some SHE professionals question whether half-suits are PPE and should be operated as such. The halfsuit has the benefit of not requiring decontamination prior to operator exiting as would be required for an equivalent air fed suit and hence performance would be considered to be superior.</td>
</tr>
</tbody>
</table>

**Typical Applications**

High containment requiring applications where there are significant manual handling, ergonomic or access problems. Containment performance may not be as good as an equivalent glovebox but operator acceptance may be better.

**Flexible Wall Glovebags**

Flexible wall glovebags are simpler than rigid systems in that the barrier to the material is usually a PVC or similar film, tailored and welded to form a ‘bubble’ over the emission source. Whilst there is scope to install air movement systems, it is more usual to operate at ambient pressures to avoid the requirement to support the film against a negative pressure. Airlocks can be created with zips or simple sealable doors for material entry, whilst bagging out is almost universally used for material removal.

Glove design is similar to the hard isolator and similar glove materials can be used.

More advanced designs have been created to allow attachment to hard process systems, allowing the generation of temporary containment systems in areas that would otherwise be impossible to isolate with a hard system.
## Benefits

<table>
<thead>
<tr>
<th>Cost</th>
<th>The price of glovebag systems allows them to be treated as a disposable item, avoiding the requirements for validated cleaning.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flexibility of design</td>
<td>The low cost of the items means that design development can continue after installation of initial systems to incorporate operator input and experience into future purchased designs. Additionally, simple systems can be create to contain occasional activities which might present a hazard such as on-line filter changing and sampling and for which the provision of hard isolator systems might be prohibitively expensive.</td>
</tr>
<tr>
<td>Improved ergonomics over hard isolators</td>
<td>The operator can move the glovebag wall to extend the reach of glove sleeves. The ability to move gloveports up and down also means that operators of different shapes and sizes can operate the system without discomfort.</td>
</tr>
<tr>
<td>Visibility of internals</td>
<td>Glovebags are routinely manufactured from clear transparent films allowing total visibility of all internal components.</td>
</tr>
</tbody>
</table>

## Concerns

<table>
<thead>
<tr>
<th>Near-total reliance on operator care and technique</th>
<th>The attachment of the glovebag to the system to be contained, and the correct operation of the glovebag are essential to maintain satisfactory containment performance.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glovebag robustness</td>
<td>Glovebags can be punctured with sharp materials and incorrectly made connections may leak. It is important to ensure that a glovebag is not damaged or ruptured before use.</td>
</tr>
<tr>
<td>Solvent Resistance</td>
<td>Glovebag materials may be susceptible to solvent wet materials. The use of antistatic PVC materials may mitigate this to some degree.</td>
</tr>
<tr>
<td>Difficulty in integrating equipment into barriers</td>
<td>Whilst hard isolators can include equipment driven by shafts through the isolator wall, for example feeder systems, this is harder to achieve with glovebags. An alternative is to create a hybrid hard/soft glovebag with a rigid base incorporating drives and other equipment requiring support, and containing it with a flexible glovebag canopy sealed along the periphery of the base.</td>
</tr>
</tbody>
</table>
Typical Applications
Pilot or development plant where product changes are frequent. Retrofitted containment to systems where space or budgets do not allow the installation of hard systems. Also used in laboratory environment for small benchtop containment.
7 Control Banding

7.1 Background and the Industry Structure

7.2 Developing a Containment Strategy

7.3 Pharma Process Activities with the Greatest Exposure Potential

7.4 Industry Control Banding Models
7.1 Background and the Industry Structure

Banding programs, sometimes termed as Performance-Based Limits of Exposure Control, began in the pharmaceutical industry in the 1980s. Exposure and control banding are a process whereby a compound is assigned to a hazard category or exposure band that corresponds to a range of airborne concentrations as well as the appropriate engineering, administrative and personal protective equipment controls. Banding programs have been adapted for use in general industry but were initially developed by pharmaceutical companies for safe handling of potent compounds.

The advent of high potency drug products in the 1980’s created a number of issues for the industry. Primary containment infrastructure needed expensive upgrading at facilities and high potency/low volume products drove a new manufacturing model. Long term reliance on personal protective equipment (PPE) became a norm in many companies.

Since OELs were typically established later in the drug development process after proactive decisions on controls needed to be taken, a systematic approach was needed to evaluate and control exposures to pharmaceutical compounds. The combination of Hazard Banding (see Chapter 4) and Control Banding allowed preliminary decisions to be taken early to protect development and small-scale production staff and to anticipate preferred larger-scale manufacturing locations.

A wide range of engineering strategies have developed to maintain material segregation from the operator, usually defined as ‘containment’. The purpose of containment is to limit the emission and spread of material, reducing the potential for operator, environmental and product exposure, and also reducing potential product losses.

The use of “open” operations in multiple product facilities gives rise to an elevated risk of cross-contamination. In single stream facilities manufacturing multiple products on a campaign basis, there is significant cost in carrying out and verifying complete facility cleans between product campaigns to ensure there is no or limited cross-contamination between campaigns.

Pharmaceutical intermediates and APIs are extremely expensive, with values frequently in the $1000s per gram. Open manufacturing leads to increased risks of losses and reduced yields through spillage and inadvertent emission in routine operation. Costs of these losses can be significant when considered with the costs of cleaning greater areas due to their occurrence.

It is critical to have a cross-functional and multidisciplinary team working within an organisation to define the parameters required for design and the methodology for performance verification of containment equipment. An understanding of the mechanisms of emission, transmission and reception is critical.

Control Banding schemes help guide occupational hygienists, or other health and safety professionals, identify appropriate control solutions where limited health hazard data is available and/or guide in the development of control systems for entirely new facilities. While they can
support and guide a professional in the appropriate selection of control measures, professional judgement is still required in order for the most appropriate solution to be selected.

Most pharmaceutical companies have their own control banding schemes. These usually adopt a four or five level approach to hazard banding of materials and providing subsequent guidance on appropriate containment solutions. Examples are shared in later sections of this chapter.

### 7.2 Developing a Containment Strategy

The development of a containment strategy is a useful method for identifying areas and materials of concern, agreeing how they will be controlled and providing a common record of the basis of control selection for future reference. The key elements or risk factors to be considered part of the control strategy are as follows:

- **Definition of all process activities, including cleaning, maintenance and breakdown activities as far as they can be defined.**
- **Definition of hazardous materials, including the basis of selection given the health-based criteria e.g. Hazard band, OEL, identification of other effects, e.g. Skin.**
- **Identification of major risk areas where significant exposure to hazardous materials might occur.** This should be developed from a risk assessment approach. These risk areas should be identified for all processes including manufacture, cleaning, maintenance, and failure recovery. The method used for establishing exposures shall be stated.
- **Definition of generic control methodologies, for example barrier and contained transfer systems or extract based approaches.** These will be developed from the identification of any gaps in the risk analysis and equipment selection processes.
- **Requirements for Local Exhaust Ventilation (ventilation rings, backdraft hoods, laminar flow hoods etc.)**
- **Requirements for HVAC system and room design including pressure control regimes, filtration requirements, recirculation or once-through and the need for AHU dedication.**
- **Cleaning methodologies required for safe cleaning of equipment and other contaminated surfaces including building and equipment surfaces.** The requirement for PPE in such applications shall be clearly identified.

### 7.3 Pharma Process Activities with the Greatest Exposure Potential

The major risks of airborne material exposure are often associated with open handling of hazardous material, processes with insufficient engineering controls, or where contaminated systems are opened or separated. Higher exposure levels can also result from activities where extensive operator handling of processing material is required, e.g. charging, discharging, sampling, packing and cleaning operations, unless containment systems are installed. However, it should be noted that
non-process activities may also carry a risk of exposure, for example sampling for material identity in a receiving warehouse.

- **Manual Activities including:**
  - Sampling
  - Scooping
  - Weighing
  - Manual activities e.g. dispensing
  - Equipment set-up e.g. calibration
  - On-line Maintenance
  - Off-line Maintenance (if prior cleaning or decontamination is not carried out*).
  - Manual Cleaning
  - In Process testing

- **Anticipated Failures**
  - Make-Break Connections
  - Transfer ports
  - Gloves (within Isolators)
  - Seals
  - Vent systems
  - Drainage liquors
  - Dedusting Operations

- **Unanticipated Failures**
  - Spillage/Leakage
  - Improper Use of Equipment and/or Controls

- **Catastrophic equipment failures leading either to:**
  - Major Leaks due to equipment connection breach
  - Minor leaks at seals and connections for Potent Compounds
  - Requirement for manual access to rectify equipment failure

- If processes procedures can be specified such that open handling or make-and-break transfers can be avoided, then operating staff exposures will be significantly reduced. This may involve the use of directly coupled systems relying on gravity or pneumatic transfers, and/or automated feeding and packing systems.

- Consideration should also be given to alternative processing methods, such as single pot granulation and drying, rather than a separated process for granulation, de-lumping and drying that requires intermediate transfers. In practise, such process modifications may not be possible due to product registration (GMP) constraints, but the option to integrate or telescope operations should always be considered before considering detailed engineered control systems. Starting with contained equipment early in the development process and continuing
through scale-up can help to avoid the problems of modifying registered processes. For existing processes, filings should be reviewed as there are often opportunities to make some changes, for example going from V-Blending to Bin Blending may be considered a minor change in a filing, however, can have a significant improvement on containment, as it can reduce some transfer steps.

An attempt to handle materials in less hazardous forms giving rise to reduced levels of airborne dust, for example wet pastes or coated particles, should be considered unless the scope to do this may be constrained by product registration.

The key to successful engineered control strategies is containment at the source. The containment performance of each system varies, giving rise to the risk of background concentrations of material outside the primary containment system. The possibility of unforeseen failures and leaks may also present the possibility for external contamination or release to the environment as well as improper procedures being followed for use of the containment equipment. In order to control such contamination and to prevent its egress to other areas of a facility, it is common to install secondary systems to prevent material migration. These systems include negative pressure in the work area, filtration of air, and once through air. A layered approach to exposure or emission control for a facility may be defined through primary, secondary and tertiary containment systems.

The selection of containment equipment should be based upon the requirements identified through the risk assessment. The individual capabilities of the various available control systems must be understood in terms of the impact on exposure, the effect of the control on mitigation of the risk, and the impact on other aspects of the process, e.g. accessibility, ergonomic concerns, ease of cleaning, production costs and efficiencies etc.

In order that appropriate selection and design of containment equipment occurs to achieve appropriate control of worker exposures, there are several factors that should be considered:

- **Material characteristics**
  - Physical characteristics including cohesion, form, size, adhesion and viscosity
  - Chemical characteristics such as flammability, combustibility, reactivity and explosivity
  - Occupational exposure limits that account for health effects

- **Process factors**
  - Concentration of the active pharmaceutical ingredient in the drug product
  - Quantity of the material handled
  - Product sampling during manufacturing

- **Equipment and facility factors**
  - Valves and containers
  - Cleaning process
  - Maintenance and inspection history

- **Environmental, health and safety considerations**
• Relative humidity and temperature
• Waste stream containment
• Occupational exposure limits

o People and Systems
  • Operator proficiency and work practices
  • Implication of user physical conformation such as shape, height, handedness on the effectiveness of system ergonomics
  • Operator position relative to sources such as distance to the process and duration of exposure

As a result of this wide range of potential factors affecting emissions and control performance, it is difficult to generalise on specific equipment performance with any degree of accuracy. It is however possible to give some broad ‘rules of thumb’ as to the typical capabilities of systems in common applications that may be practically useful in most situations.

7.4 Industry Control Banding Models

The methodologies to control exposure follow classical Industrial Hygiene principles, including the use of risk assessment and application of the hierarchy of control. It is a common theme that the hazard (toxicity/ecotoxicity) of the material is fixed and that control can only be maintained by control of the variable exposure potential.

In many cases, the higher levels of the hierarchy of control (elimination or substitution) cannot be applied in the Pharma setting as the materials of concern and the physical form are specifically required for purpose of product effectiveness.

There may be scope to combine, reduce or remove specific process steps, such as intermediate dry product recoveries, but these are typically limited to the chemical processing part of drug manufacture. As a result, control is commonly achieved using closed equipment, special engineered containment systems, local exhaust ventilation, procedural controls, and/or the use of Personal Protective Equipment (PPE). Note, as with following the principles of the hierarchy of controls, PPE should never be relied on as the sole control. It is commonly used as supplemental protection.

It is also necessary to understand the likelihood of failure, the implications of it occurring, the warning signs, and the tolerability of measures required to achieve recovery. This will help define the need for, and scope of, secondary and tertiary systems to provide a layered approach to containment.

A risk-based approach is often considered in pharmaceutical manufacturing that combines both exposure banding with control banding to address many of the above factors. One model for consideration is displayed below. This control banding model, meant primarily for solids manufacturing, guides the engineer and occupational hygienist through three steps to arrive at examples for control strategies. This example process includes consideration for material exposure.
potential, the material characteristics and amounts handled, as well as the manufacturing task durations. It is based upon a 5-Tiered Exposure Banding system typical of most potent compound pharmaceutical manufacturers.

### Step #1 – Choose the Potential For Exposure (PFE)

<table>
<thead>
<tr>
<th>Dustiness Potential</th>
<th>Low (Tablets, Capsules, Lentils)</th>
<th>Medium (Granular)</th>
<th>High (Powders)</th>
<th>Minutes</th>
<th>Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quantity of Material Handled</td>
<td>Small (g) to Medium (kg)</td>
<td>PFE-1</td>
<td>PFE-1</td>
<td>PFE-2</td>
<td>PFE-3</td>
</tr>
<tr>
<td></td>
<td>Medium (kg) to High (ton)</td>
<td>PFE-1</td>
<td>PFE-2</td>
<td>PFE-3</td>
<td>PFE-4</td>
</tr>
<tr>
<td></td>
<td>High (ton)</td>
<td>PFE-3</td>
<td>PFE-4</td>
<td>PFE-4</td>
<td>PFE-4</td>
</tr>
</tbody>
</table>

### Step #2 – Choose the Control Band

<table>
<thead>
<tr>
<th>Potential for Exposure (PFE)</th>
<th>PFE-1</th>
<th>PFE-2</th>
<th>PFE-3</th>
<th>PFE-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposure Band</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OEL is &gt;100 mcg/m³</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>OEL is 10-100 mcg/m³</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>OEL is 1-10 mcg/m³</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>OEL is 0.1-1 mcg/m³</td>
<td>4</td>
<td>4</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>OEL is &lt;0.1 mcg/m³</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

### Step #3 – Choose the Control Strategy

<table>
<thead>
<tr>
<th>Control Band 1</th>
<th>Control Band 2</th>
<th>Control Band 3</th>
<th>Control Band 4</th>
<th>Control Band 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control Strategy Examples</td>
<td>• Open transfers • General room ventilation</td>
<td>• Independent Powder Enclosures • Downflow Booths • Open transfer w/ LEV</td>
<td>• Flexible Containment • Wet-in-place (WIP) or Clean-in-place (CIP) process</td>
<td>• Split butterfly valve • Closed transfer • Wet-in-place or Clean-</td>
</tr>
</tbody>
</table>
Another example of a control banding scheme is displayed in the following two tables. This example directs the user from characterizing the material with hazard banding to then reference bands of handling recommendations.

Example Control Banding Scheme. (Farris et al).

Table 1. Hazard Banding System.
## Table 2. Handling Recommendations

<table>
<thead>
<tr>
<th>Category 1</th>
<th>Category 3</th>
<th>Category 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Open handling is acceptable for low dust-generating operations or solutions.</td>
<td>• Wear appropriate gloves, lab coat, nylon coveralls or disposable Tyvek suit; safety glasses, safety shoes, and disposable booties. Use good manufacturing practices (i.e., cGMPs).</td>
<td>• Wear appropriate gloves, lab coat, nylon coveralls or disposable Tyvek suit; safety glasses, safety shoes, and disposable booties. Use good manufacturing practices (i.e., cGMPs).</td>
</tr>
<tr>
<td>• Wear appropriate gloves, lab coat, nylon coveralls or disposable Tyvek suit; safety glasses and safety shoes. Use good manufacturing practices (e.g., cGMPs).</td>
<td>• Protective garment (coveralls, Tyvek, lab coat) is not to be worn outside the work area.</td>
<td>• Protective garment (coveralls, Tyvek, lab coat) is not to be worn outside the work area.</td>
</tr>
<tr>
<td>• Wear a certified Dust/Mist filtering facepiece respirator or a higher level of respiratory protection for high dust-generating operations. If exposure monitoring indicates exposures are below the OEL, respiratory protection may not be required.</td>
<td>• Clean/dirty/decontamination areas are to be established. Establish a means of personnel decontamination prior to entering the decontamination room such as a misting shower.</td>
<td>• Clean/dirty/decontamination areas are to be established. Establish a means of personnel decontamination prior to entering the decontamination room such as a misting shower.</td>
</tr>
<tr>
<td>• Use local exhaust ventilation and/or enclosure at dust-generating points in the process.</td>
<td>• Negative/positive air pressure relationships and buffer zones required (i.e., ante-room/decontaminating room/airlock).</td>
<td>• Negative/positive air pressure relationships and buffer zones required (i.e., ante-room/decontaminating room/airlock).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Category 2</th>
<th>Category 3</th>
<th>Category 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Wear appropriate gloves; lab coat, nylon coveralls or disposable Tyvek suit; safety glasses and safety shoes. Use good manufacturing practices (i.e., cGMPs).</td>
<td>• Area access is to be restricted.</td>
<td>• Area access is to be restricted.</td>
</tr>
<tr>
<td>• Use a powered, air-purifying respirator (PAPR) with HEPA cartridges or a supplied-air respirator (SAR), unless air-monitoring data has shown that a lower level of respiratory protection is adequate.</td>
<td>• High-energy operations such as milling, particle sizing, spraying or fluidizing should only be done within an approved emission control or containment system.</td>
<td>• Separate and dedicated work areas should be established.</td>
</tr>
<tr>
<td>• Protective garment (coveralls, Tyveks, lab coat) is not to be worn in common areas (e.g., cafeterias) or out-of-doors.</td>
<td>• Develop cleaning procedures and techniques that limit potential exposure.</td>
<td>• A highly specialized ventilation system should be installed with failure protection.</td>
</tr>
<tr>
<td>• Use local exhaust and/or enclosure at dust-generating points. Emphasis is to be placed on closed material transfer systems and process containment, with limited open handling of powders.</td>
<td>• Powders Handling</td>
<td>• High-energy operations such as milling, particle sizing, spraying or fluidizing must be done within an approved emission control or containment system.</td>
</tr>
<tr>
<td>• High-energy operations such as milling, particle sizing, spraying or fluidizing should be done within an approved emission control or containment system.</td>
<td>Emphasis is to be placed on closed material transfer systems and process containment, with no open handling of powders. Use enclosures and containment measures to reduce potential exposures.</td>
<td>• Clean-in-place systems should be in place.</td>
</tr>
<tr>
<td>• Develop cleaning procedures and techniques that limit potential exposure.</td>
<td>Use a powered, air-purifying respirator (PAPR) with HEPA cartridges or a supplied-air respirator (SAR) until processes have been monitored to show that respiratory protection is not required.</td>
<td>An emphasis on process automation and fail-safe systems should be employed.</td>
</tr>
</tbody>
</table>

### Solutions Handling
- Enclose systems where possible.
- Processing tanks are to be kept covered.
- Process samples should be taken from sample ports if feasible.
- Wear a certified Dust/Mist filtering facepiece respirator or a respirator supplying a higher level of protection until processes have been monitored to show that respiratory protection is not required.
- Ensure gloves are protective against solvents in use.
8 MANAGEMENT OF OCCUPATIONAL HYGIENE

8.1 Business Case for Occupational Hygiene

8.2 Organisational Structure

8.3 Occupational Hygiene Programmes
   8.3.1 Hazard Assessment
   8.3.2 Hazard Communication
   8.3.3 Exposure Assessment and Monitoring
   8.3.4 Health Surveillance
   8.3.5 Control Measures
   8.3.6 Training of Employees

8.4 Business Processes
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8.5 Corporate Responsibility
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Further Reading and Resources
8.1 The Business Case for Occupational Hygiene

In the pharmaceutical industry, the business case for occupational hygiene rests on the fact that pharmaceuticals are:

- high value products
- intended to improve health
- designed to have biological effects
- often extremely potent.

The industry produces thousands of different APIs that are inherently biologically active materials. Many of them have airborne exposure limits below 0.1mg/m³ (that is <100μg/m³), which is a level typical of the exposure limits associated with toxic metals. Some have limits as low as 10ng/m³ (that is 0.01μg/m³), which is 4 orders of magnitude lower. A very high standard of exposure control is essential to protect the health of workers. Occupational hygiene is therefore a critical foundation for the pharmaceutical industry. For many managers, particularly those at a senior level, this will often be sufficient justification to act. Naturally though, managers will want to be assured they are obtaining good value for money.

Occupational hygiene can also be leveraged to reduce costs and improve business performance. Improvements will need to be transmitted throughout the supply chain to ensure business continuity, minimise liabilities and meet expectations of corporate responsibility. Professional occupational hygienists should be able to contribute towards securing competitive advantage. Doing so will present both opportunities and challenges as the hygienist becomes more closely involved with business issues.

The arguments to be deployed will depend on the precise nature of the product, investment proposal and corporate culture. Some of the most common are listed below.

Risk avoidance

- **Product cross-contamination.** Containment at source minimises the risk of cross-contamination of products, which is a critical patient-safety issue for the industry and a key element of GMP.

- **Reputational risk.** Adverse health effects on workers impact on the company’s reputation as an employer but can also reflect on the safety of the product responsible for the health effects, leading to loss of sales and much wider reputational damage.

- **Reduced liabilities.** Good occupational hygiene programmes will reduce the risk of prosecution with resulting fines and penalties for non-compliance, and the likelihood of lawsuits or insurance claims for adverse health impacts to employees or the public.
Benefits

- **Healthy, high performing employees.** Workers who feel well and are free to perform their jobs without worrying about health effects are likely to be better motivated and more productive, particularly if they are able to work safely without the need for cumbersome protective equipment or lengthy procedures to avoid danger.

- **Reduced waste.** Prevention of leakage and spillages, and minimisation of waste residues in processes and containers, simultaneously reduce occupational exposures while saving expensive product, avoiding the need for specialised cleaning procedures and reducing waste disposal costs.

- **Efficiency and productivity.** Occupational exposures often occur at points where manual process interventions take place, e.g. when there are blockages, or cleaning is needed. Designing equipment and processes to avoid these issues eliminates the exposure and at the same time makes the operations more efficient.

Synergies

Occupational hygiene is both aided by and supports other areas of business improvement.

- **Occupational safety.** Ergonomic injuries including back pain and repetitive strains are major causes of lost time and increased healthcare costs in the industry. It is important that hygiene control measures such as glove boxes are designed and tested for ergonomic acceptability.

- **Process safety.** Many APIs are combustible powders and accumulated deposits can create dust explosion risks. Good occupational hygiene practices will normally eliminate such situations. Hygiene expertise can also assist with the issues raised by inerting of flammable materials.

- **Quality.** Choice of protective clothing and changing procedures need to be suitable to protect both product quality and the operator. Containment at source reduces the risk of cross-contamination and may allow reduction of ventilation rates, personal protective equipment, or cleaning schedules. Hygienists should be familiar with Risk-MaPP, which was developed by the International Society for Pharmaceutical Engineering (ISPE) to provide a risk-based approach to manage the risk of cross contamination in order to achieve and maintain an appropriate balance between product quality and operator safety.

- **Environment.** Stringent environmental regulations can often provide opportunities for hygiene improvements. Environmental measures to eliminate toxic substances, improve mass efficiency, and reduce energy consumption can benefit occupational hygiene through substitution, elimination and reducing the scale of hazardous material use. They can also introduce new occupational risks if not carefully considered.

- **Business efficiency.** Manufacturing innovations such as bio-transformations and continuous production are often beneficial for occupational hygiene by avoiding the use of hazardous materials,
and reducing the quantities of materials stored and processed. Hygiene issues can provide a catalyst to investigate production improvement opportunities.

- **Corporate responsibility.** Occupational hygiene issues can impact on corporate image, e.g., for graduate recruitment and for business reputation (see below). Similarly, a company with a good reputation in these areas is likely to be keen to maintain high standards of worker health protection.

- **Business development.** As pharmaceutical companies seek to diversify their business as third party manufacturers, sound occupational hygiene programs that can demonstrate proven containment capabilities will directly contribute to pharmaceutical business development.

### Example: Respirator-Free

A “Respirator-Free” environment is a workplace where:

- containment at source is the primary form of control rather than respirators (RPE) or protective clothing (PPE)
- airborne exposures are below the Occupational Exposure limit (OEL)
- skin exposure is prevented by the containment.

Reducing exposure to a level where respiratory protective equipment is not required is particularly beneficial: not only does it save the costs of the equipment, fit testing and training costs, plus ongoing waste disposal, cleaning and maintenance costs, but in addition it saves the time taken to don and remove the equipment each time it is worn. With air suits this can easily amount to a time saving of 30-60 minutes per shift. In addition, the unencumbered operator is freed to move more efficiently and to do his or her best work for the organisation.

A business case for a Respirator-Free programme might therefore include such arguments as:

- **Protects workers’ health**
  - reduces the risk from leakage of Respiratory Protective Equipment
  - avoids contamination of other Personal Protective Equipment
  - protects other people in the area

- **Improves processes and quality**
  - addresses causes of process interventions
  - prevents contamination of the workplace
  - avoids risk of quality issues

- **Reduces costs**
  - avoids costs of respirator programmes
  - reduces workplace cleaning requirements
  - improves productivity by eliminating/reducing washing changing time
Ensures legal compliance

To be robust, a business case will also need to identify possible risks arising and how they can be mitigated. For example, what would happen if there was a failure of engineering containment? How quickly would it be detected and controlled and what harm to health might result from the exposure? Additional measures may be needed to mitigate the risk, eg. continuous monitoring of air pressure differential inside processing equipment with an audible/visual alarm if the containment is broken.

Making the case

The approach to making a business case is fundamentally similar in all industries. Yet individual pharmaceutical companies demand approaches that vary from a simple statement of direct costs with a qualitative justification, through to a formal Return on Investment (ROI) analysis. One formal tool which has been widely used in the pharmaceutical industry, is Return on Health, Safety and Environmental Investments (ROHSEI). The ROHSEI software provides a process for the preparation of a business case and calculates commonly required financial metrics such as Return on Investment, Net Present Value, and Discounted Payback Period.

Regardless of the tools used, certain general steps are always applicable in developing a business case:

- **Understand the organisational culture.** What is the accepted way to present investment proposals in the company? What processes need to be followed? What timelines must be adhered to for budgets and for meetings? Seek advice from experienced managers in other fields, such as finance or quality.

- **Understand the business drivers.** What is the business strategy and what are the current priorities? Develop a solid understanding of the objectives, requirements and constraints of the proposed investment. What are the costs involved and how significant are they to the organisation? Check what else is likely to be on the agenda for decisions: timing of the proposal can be critical, particularly if the idea is novel or contentious.

- **Prepare the ground.** Identify who are the key players with an interest in the issue and talk to them. Who is likely to support the proposal and who is likely to oppose it? It is unwise to make an investment presentation to an audience that is not aware in advance of what is going to be proposed. Testing your proposals with the key players in advance allows you to assess likely objections and amend your proposals accordingly.

- **Aim to find win-win solutions** to issues rather than compromises. Always ask yourself what is in it for the other parties and try to ensure their needs are met.
All these steps are made easier by routine networking and relationship building. It is important that the hygienist gets to know line managers and other function specialists, and keeps in touch with business developments. Proposals can then be made in context. Moreover, the increased visibility that the hygienist will secure from networking will improve credibility when making the investment proposal.

**Key learning points:**

- The business case rests on pharmaceuticals being high value products which are: intended to improve health, designed to have biological effects and are often extremely potent.
- Occupational hygiene can be leveraged to reduce costs and improve business performance.
- Supporting benefits include reduced product cross-contamination, reduced reputational risk, reduced waste, increased efficiency and productivity.
- There are synergies with many other areas of business improvement.
- The approach to presenting a business case is organisation specific but should always follow the general process of understanding the organisational culture, understanding the business drivers, preparing the ground, and aiming to find win-win solutions.
- These steps are underpinned by business awareness created through routine networking and relationship building.
8.2 Organisational Structure

The pharmaceutical industry is highly regulated and this is often reflected in the organisational structure and culture. It is common to have hierarchical structures for both line and function management and a considerable degree of formality to business processes. Each area of the company is likely to have its own vision statement and objectives, which may be cascaded from corporate ones.

Recent attempts to improve communications and efficiency have identified these “siloed” structures as barriers. There have been many initiatives to introduce more cross-functional teams and streamline management systems. These programmes, often championed by the Human Resources or Operational Excellence functions, will have an impact on expected behaviours and ways of working. They may penetrate all the way down to individual objectives. Individual accountability can be high, with all professional staff having annual reviews of performance against their agreed objectives.

The extent to which individual hygienists can influence organisational decisions and processes will depend on their position in the company. Corporate, group or regional hygienists are likely to have more influence than site hygienists. These days it is unusual for occupational hygiene to be a standalone department: more commonly it will be an element within a larger function such as Occupational Health and Safety, or Environment, Health and Safety. The positioning of the hygiene team can have a profound impact on its priorities and programmes. It is worth developing a formal statement of the organisational structure and goals as it will often be necessary to communicate them and ensure that the goals are meaningfully supported by the very top management.

As with making a business case, it is important that the hygienist is keenly aware of the organisational context and positions his or her activities appropriately. Key factors to consider in developing the organisation are:

- **A clear definition of the role for the occupational hygiene team.** This may be focussed purely on protecting health but is more likely to include a statement of the business rationale.

- **Access to the relevant decision makers.** There will usually need to be a link with manufacturing, though many hygienists consider it important not to report directly to production (ie. not to be line managed by production) because of the potential conflict of interest. A group hygiene function will need access to the company’s executive team, usually via a sponsoring senior manager.

- **Good links with supporting functions.** Building allegiances with functions such as engineering, quality and occupational health with allow hygienists to penetrate more deeply into the organisation’s business processes and will increase their influence.

Benchmarking and sharing knowledge with hygienists in other companies is both necessary and strongly to be encouraged. Caution is needed to avoid breaching competition law, which prohibits exchange of commercially sensitive information. Most occupational hygiene information is shared openly within the industry in the interests of protecting health. A number of established mechanisms are available:
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8.3 Occupational Hygiene Programmes

Many different health risks can arise, depending on the company’s products, facilities and manufacturing processes.

- Most important usually are the effects of workers being exposed to the active ingredients in pharmaceutical products. These APIs are designed to have biological effects. While they may be beneficial for patients, they can be very dangerous for workers who are exposed to them.

- In primary manufacturing, workers can also be exposed to a wide range of hazardous chemicals including solvents and intermediates.

- The nature of pharmaceutical operations with high throughputs of materials and products also creates risks that workers will suffer damage to their backs through lifting or poor working positions, and to their hands and arms through repetitive movements.

- Noise levels can sometimes be high enough to be harmful, especially with high speed filling of glass bottles or vials. Machines may need to be enclosed and acoustically treated to reduce noise levels.

Key learning points:

- Organisational structures and cultures reflect the highly regulated nature of the industry.
- Hygienists should expect a high degree of individual accountability for performance.
- The positioning of the hygiene team in the organisational structure can have a profound impact on its priorities and programmes.
- Hygiene managers need to ensure they have a clear definition of the role for the occupational hygiene team, access to the relevant decision makers, and good links with supporting functions.
- Benchmarking and sharing knowledge with other companies provide important insights.
For most of these issues, standard occupational hygiene programmes will provide satisfactory solutions. We focus here on the special issues raised by working with exposure to active pharmaceutical ingredients.

8.3.1 Hazard Assessment

Whilst APIs are designed to have an effect on the human body, they also have the advantage that more data is available on their biological effects than for most other chemicals. Also as the materials are proprietary, the company that invents or discovers the API may be the only one with an interest in that particular material. The research-based pharmaceutical industry is therefore geared towards making comprehensive risk assessments of APIs and setting in-house exposure limits.

In most large companies these processes are led by an Occupational Toxicology function. Centralised hazard assessment ensures expertise, efficiency and consistency. It may be done ‘in-house’ in companies that have their own facility or outsourced to a reputable company that provides toxicology services. Generic companies will often have less resource available for hazard characterisation but should be able to draw on published information.

Involvement and interaction on a project team can help to design a contained process earlier in the development of a product/process. Hygienists will need to have an understanding of:

- How hazard assessment is conducted in the organisation, including the key toxicological tests used and the stages in product development where the information is generated.
- The company process for setting Occupational Exposure Limits, including monograph development and how OELs are approved. It is helpful to know the differences from public OEL setting and how they affect interpretation of the OEL values.
- Any other parameters that the company uses, eg. Health Hazard Categories, Surface Target Values.

Hazard assessment processes are being influenced by two important recent pieces of international regulation:

REACH

The European “REACH” Regulation (REACH is an acronym for Registration, Evaluation, Authorisation and Restriction of Chemicals). It aims to enhance the protection of human health and the environment through the better and earlier identification of the hazardous properties of chemical substances and better management of risks throughout their use. Although a European Regulation, it applies not only to European manufacturers but also to anyone importing chemicals into Europe, hence it has global implications. Failure to register a substance means that it cannot be manufactured, imported or used in the EU market.

REACH introduces a fundamental change in how chemicals are regulated. Prior to REACH, governments had to undertake the risk assessment and show that a chemical needed to be controlled or banned.
Under REACH, it is the manufacturer who is required to conduct the assessment, following a defined testing and assessment protocol. It is for the manufacturer to show that the material can be used safely. Raw materials used in the industry, including solvents and reagents, are covered by REACH and must pass through the extensive regulatory process of testing, assessment and evaluation. However, the principal responsibility rests with the manufacturer of the raw materials rather than the pharmaceutical company that uses them.

REACH contains an exemption from its principal requirements for substances used in human medicinal products. Hence APIs are not directly covered. However, issues arise for the pharmaceutical industry in respect of isolated intermediates. These are covered by REACH unless they are used under “strictly controlled conditions”, ie. the substance is rigorously contained by technical means during its whole lifecycle including manufacture, purification, cleaning and maintenance of equipment, sampling, analysis, loading and unloading of equipment or vessels, waste disposal or purification and storage. Occupational hygienists can assist here. By prior air monitoring and surrogate testing, the capability of process machinery can be detailed and close containment can be proven for the intermediates. It can sometimes be very difficult to demonstrate strictly controlled conditions, so some companies choose to register their intermediates instead.

GHS

The UN Globally Harmonised System for Classification and Labelling (GHS) is gradually being implemented around the world. National and regional transposing regulations vary somewhat in requirements, affecting labelling requirements for materials being transported. Pharmaceutical and cosmetic products in the finished state, intended for the final user, are generally considered to be excluded from the scope of the GHS as they are covered instead by the regulatory requirements for pharmaceutical labelling and information provision. APIs and intermediates could be affected though.

8.3.2 Hazard Communication

The process of hazard testing and assessment of APIs must be complemented by an integral programme of hazard communication. Hazard communication aims to provide employees with full information concerning the known hazards of materials to which they may be exposed.

Drugs, cosmetic, and medical or veterinary devices or products, are often exempt from the legal requirements for worker chemical hazard communication programmes. It is still important, however, to protect workers by adopting standards and processes for hazard communication equivalent to, and compatible with, those required for other chemicals.
A hazard communication programme should include:

- **Maintaining a list of all hazardous materials** used.
- **Obtaining Safety Data Sheets** (called Material Safety Data Sheets (“MSDSs”) in some countries) for all purchased chemicals. Suppliers should be asked to provide data sheets for process chemicals, catalysts, laboratory chemicals, maintenance chemicals and service chemicals. The information should be checked to make sure it is adequate and may need to be supplemented or re-formatted to make it suitable for in-house use.
- **Production of Safety Data Sheets for APIs and isolated intermediates.** Although the GHS is not formally required for pharmaceuticals it can nevertheless provide a good basis for standardisation of SDSs and labelling. Major pharmaceutical companies have developed in-house rules for classifying APIs by hazard (or potency) band, with notations for sensitisers, carcinogens, reproductive toxins etc.
- **Use of labels** on containers, pipelines, storage vessels etc. This is particularly important when materials are transported, when Dangerous Goods legislation may apply.
- **Arrangements and procedures** for communication of hazards, SDSs and labels. Large pharma companies tend to have online databases for SDSs which can be accessed by managers and employees.
- **Training of employees and independent contractors.** Employees should know how to interpret safety data sheets and labels. When introducing the concept of Potency Bands, it is key to spend a lot of effort on creating a high level of management understanding, ensuring managers can distinguish between hazards and risks. Employees who perform non-routine tasks will need a broad awareness of the health hazards which may be encountered and procedures for protecting against those hazards, including use of monitoring instruments, engineering controls, work practices, and personal protective equipment.
- **Keeping of health records** to identify situations where hazardous materials have caused harm. Evidence of ill health should trigger a review of data sheets and precautions.

Hazard communication programmes are often led by the occupational toxicology function but hygienists can contribute to both the development and delivery of the information and training. The hygienist can enhance the hazard communication programme by making clear the distinction between hazard and risk, and showing how risks can be managed. Easy access to the latest exposure data will assist in developing management awareness and commitment. The results of exposure monitoring and risk assessments should be provided to workers in an understandable format. As always with communication, keep it simple and to the point. Don’t just use formal occupational hygiene reports.
8.3.3 Exposure Assessment and Monitoring

Technical issues concerning exposure assessment and monitoring, such as the selection and use of sampling equipment, are discussed in Chapter 5.

Monitoring Strategy

All processes using APIs should be subject to a risk assessment which will usually include a baseline exposure assessment. It should identify whether routine monitoring of airborne exposures is needed to demonstrate compliance, detect poorly-controlled work environments or detect upward trends in exposures.

Priority for routine monitoring should be given to:

- operations likely to cause high exposures, e.g. where respirators are already required, or where there is considerable manual handling of APIs without containment.
- operations where health effects have been reported or alleged.
- operations involving highly potent compounds.

The scope of monitoring programmes should include exposure during maintenance and non-routine activities. Other airborne exposures such as Laboratory Animal Allergens may need to be included as well as APIs.

Establishing a monitoring programme is a sizeable undertaking with important resource implications. Thought should therefore be given in advance to:

- **Efficient design of the programme.** The use of Performance-based Exposure Assessment is becoming more common within the pharmaceutical industry. It offers resource efficiencies and improved assurance of outcomes.

- **Realistic frequency of measurements.** Frequency is likely to depend on the proximity of the exposure level to the Occupational Exposure Limit, the likelihood of failure of control measures, the severity of any health effects that may be produced and the time that would be needed for the plant to respond to adverse findings.

- **What training will be given** to the technical staff carrying out the work. It is very important that they can gather reliable observations and contextual information such as product and process details, room sizes, ventilation movements and working practices. They should also be aware that observation and monitoring influence the results – practices change (and often deteriorate) when the observers leave.

- **How the quality of results will be assured.** Choice of analytical laboratory will be a critical decision, taking into account not only the laboratory’s credentials and capabilities but also cost, location, transportation and storage issues, and communication barriers.
o How decisions will be made on what actions to take arising from the monitoring and who will be responsible for communicating and implementing them.

o Procedures for audit and review of the monitoring strategy. Risk assessments of unit operations should be reviewed if knowledge or circumstances change, and routinely every 2-5 years.

**Statistical Considerations**

Workers are first grouped into Similarly Exposed Groups (SEGs) which consist of workers whose job classifications, task or work areas represent similar exposures. These homogeneous groups may be selected on the basis of:

- Location
- Job Description
- Tasks conducted
- Chemicals handled
- Unit operations

However, the small scale, intermittent batch nature of many pharmaceutical operations often makes it difficult to identify SEGs of more than one or two operators. The resource requirement for monitoring is therefore very high.

To compensate for the difficulties of obtaining comprehensive monitoring data, the pharmaceutical industry makes use of exposure prediction techniques to estimate likely exposures. Some companies have established committees of experts to make predictions, while others have used exposure models such as the Advanced REACH Tool (ART). In either case, it is increasingly common in large companies to combine the predicted exposures with real data using Bayesian statistics to obtain the best possible exposure estimates. These then provide a framework for prioritising interventions and further monitoring.

Whichever approach is taken, it is critical to have knowledgeable personnel using and interpreting the data. Hygienists working in the industry are recommended to attend specialist courses on use of exposure modelling and Bayesian statistics. Very useful guidance is available from the American Industrial Hygiene Association and from the British and Dutch occupational hygiene societies.

There is a clear need to keep good records of exposure measurements. Some pharmaceutical companies use a centralised database but most use spreadsheets, perhaps with a standardised template. There are specialist database packages available and also business enterprise software with exposure assessment modules. The choice is usually a compromise here between site specific aims and corporate strategic ones. Ultimately, the effectiveness of a database system depends on the users (i.e. occupational hygienists and others) feeling that the value of the information obtained justifies the time
and effort to populate and administer the database. It is therefore important to involve stakeholders in the choice of system.

8.3.4 Health Surveillance

The term "health surveillance" is used to describe a variety of procedures to monitor the health status of individuals or groups of workers. It includes:

- collecting, maintaining and reviewing health records
- observation of early signs of disease
- biological measurements of hazardous substances in body fluids

The health of individuals directly influences their ability to work safely and effectively. Health surveillance can identify job-related, individual health risk factors and facilitate positive health interventions and alterations to the workplace which protect employees and maximise productivity. Health surveillance can also detect health effects from specific risks at an early and reversible stage. Analysis and investigation of these events enables corrective action to be taken promptly, thereby minimising the risks of recurrence.

Health surveillance programmes should be under the control of a qualified medical practitioner because the techniques used need to be sensitive, specific and minimally invasive. They can be useful at different stages of working life: at the outset of employment to screen people who may be susceptible to certain agents in the workplace; during employment to check on any work-related health effects; and post-employment for early detection of long-term illnesses and as a contribution to epidemiological studies. Records of individuals’ health surveillance need to be kept confidential and maintained for a number of years after that individual ceases to work.

Hygienists will need to analyse patterns in health surveillance data to identify any corrective actions required. It is important to recognise, though, that health surveillance is not a substitute for adequate assessment and control of exposures.

Linking exposure assessment with health surveillance is difficult. Many health surveillance techniques lack specificity and individuals will respond differently to exposure. However the techniques should be seen as complementary. For example, environmental exposure surveillance for sensitisers can detect failures of control measures but cannot determine which individuals are likely to have an adverse response.

Routine health surveillance is therefore commonly done for sensitisers such as penicillins and cephalosporins. It may also be appropriate for potent compounds where serious adverse effects can be caused by minor weaknesses in engineering or administrative control measures. This can apply not only to pharmaceutical company employees but also to healthcare workers who prepare, administer, or transport hazardous drugs or dispose of hazardous drug waste.
8.3.5 Control Measures
The international nature of many pharmaceutical businesses creates problems of consistency when different countries operate different legal requirements for control of exposure. Multinationals are often forced to define their own minimum requirements, with higher standards imposed where required by local legislation.

Respiratory Protection Factors
In the past, the pharmaceutical industry has often relied on Respiratory Protective Equipment as the first line of defence against over exposure to APIs. This is changing as the standard of engineering controls improves, and RPE now tends increasingly to be used only as a precaution against failure of controls. However, air supplied respirators and Powered Air Purified Respirators (PAPRs) are still commonplace, particularly in maintenance operations and development functions.

There are major differences between national standards for Assigned Protection Factors of RPE. For instance, in the United States of America, some models of PAPR currently (2019) have APF=1000 if a full RPE programme is in place while the same equipment in the UK has APF=40. This can lead to industrial relations problems when different standards are applied to the same operations in different countries. The issue remains a contentious one within the pharmaceuticals industry, with different companies taking different approaches.

The United States and European respirator classification schemes have similar approaches. Both systems classify the respirators by mode of operation and design which indicates the expected performance. The performance is indicated by an assigned number that identifies overall performance—a “protection factor.” Performance requirements differ between the two classification schemes resulting in similar looking devices having a different performance rating.

In early 2016, ISO published a Technical Specification on the classification of RPDs (ISO/TS 16973 2016). The respirator classes depart from the previous two classification schemes discussed in that classification is based on respirator performance rather than design. If adopted, the ISO specification could result in worldwide harmonization.


The scheme is contentious though. See, for example, Larry Jonsson in The Synergist, Feb 2015, https://synergist.aiha.org/two-views-on-iso-respirator-standards, accessed 26 Aug 2019. It is unlikely that the scheme will be incorporated into US or European Standards before 2022 at the earliest. In the
meantime, consideration should be given to asking suppliers / vendors to provide third party workplace simulation studies that demonstrate the claimed level of protection can be achieved.

**Maintenance of engineering controls**

Maintenance needs should be considered at the capital investment stage to create a design that minimises exposures occurring during maintenance. To reiterate some key points made in Chapter 6:

- Equipment should be designed for easy maintenance, with access from outside the containment. Filters usually need to be of a “safe-change” type that enables their removal and replacement without contaminating the operator or the workplace. Use of “clean-in-place” equipment may be appropriate for process plant such as tanks and pipework.
- Surfaces should be designed for cleaning using HEPA vacuum systems or wet mopping. Chemical decontamination may sometimes be necessary.
- Duct velocities should be calculated and ductwork layout should be designed to avoid particulate settling.

Factory and/or Site Acceptance Testing are generally required to validate the performance of new systems.

Large pharmaceutical companies tend to have well-managed preventive maintenance programmes. Occupational hygiene checks should be built into the programme, e.g.

- checking dampers on ventilation systems.
- testing alarms or performance indicators in accordance with manufacturers’ specifications.

Engineering controls including Local Exhaust Ventilation need to be:

- visually checked every week
- examined and tested at least annually

Building hygiene checks into the maintenance programmes may reduce the frequency of exposure measurements that is needed. Trends in maintenance failures (e.g. filter failures) should be monitored and analysed to identify the root cause.

### 8.3.6 Training of Employees

An occupational hygiene training programme is necessary to create awareness within the organisation and win over the hearts and minds of managers and employees. Some groups (such as engineers and technical staff) may also require specific training in skills or procedures.

The training should be made relevant to the audience by conducting a training needs analysis and creating a training matrix. Most groups will need an awareness of the organisation’s occupational hygiene hazard and risk assessment process, including OELs and the company’s OEL setting processes.
In general, training should be oriented towards practical actions rather than theory. It is often appropriate to use actual monitoring results to make the training more relevant. For these reasons, training is often best delivered by the occupational hygienist rather than by a generalist training person. However, hygienists must be careful to use plain language and not fall into use of technical jargon.

Training needs to be repeated quite frequently, perhaps annually. It can be more procedure-driven than in other industries because of the highly regulated pharmaceuticals’ environment.

**Key learning points:**

- Hygienists will need to be involved in, or lead, a number of technical programmes.
- It is likely that the hygienist will need to design and implement a programme of exposure assessment and monitoring for APIs. Such a programme ought to be statistically sound, employing techniques for exposure prediction as well as actual measurements to target priority exposures and optimise the efficiency of the programme.
- Toxicologists are likely to lead programmes for Hazard Assessment and Communication. The hygienist will need to understand and contribute to them.
- Qualified medical practitioners should lead the Health Surveillance programme but the hygienist should be informed of the outcomes and involved in investigative work.
- Maintenance engineers will lead preventive maintenance programmes but the hygienist should seek to incorporate beneficial occupational hygiene checks.
- Operational or Safety personnel are likely to deliver any Respiratory Protective Equipment programme but the hygienists should advise on appropriate equipment, fit testing and maintenance requirements.
- Occupational hygiene training programmes should be customised to the audience using a Training Needs Analysis.

### 8.4 Business Processes

The pharmaceuticals industry is very strongly oriented towards “process thinking” – analysing activities by the “process chain” rather than by the activities of individuals.

A business process is a structured collection of related activities or tasks that produce a specific service or product for a particular customer. It often can be visualized with a flowchart as a sequence of activities with interleaving decision points, or with a Process Matrix as a sequence of activities with relevant rules based on the data in the process. Business processes often operate across departments or functions, trying to break down silos.

Business Processes are designed to add value for the customer and should not include unnecessary activities. The outcome of a well-designed business process is increased effectiveness (value for the customer) and increased efficiency (lower costs for the company).
Hygiene managers will need to integrate into a range of business processes if they are to be effective in influencing standards of hygiene performance across the company. To do so, they will need to become proficient in the language and the tools used by the business, and to collaborate with a number of other support functions.

### 8.4.1 Operational Excellence

Most major pharmaceutical companies have a business improvement programme such as Operational Excellence (OE). The term used varies from company to company. OE has its roots in Japanese quality systems and the concept of Total Quality Management which was introduced in the 1950s and is usually credited to W. Edwards Deming. Forerunners and variants include Six Sigma, Lean Manufacturing, and Lean Sigma (which combines the other two).

OE aims to bring about a change of culture, introducing different ways of working and behaving, by using standardised processes, methods and tools to ensure reliable output. It is underpinned by several key principles:

- **Add value to the customer.** All activities should be directed towards adding value “in the eyes of the customer”. For some purposes, “customer” may be interpreted as an internal customer, rather than the final customer for the pharmaceutical product.

- **Use data.** Objective improvements are produced by a data driven approach. Processes are observed and measured, and statistical tools are used to analyse the data. OE projects typically begin by asking the customers what they want: the data from the “voice of the customer” then defines the project.

- **Continuous improvement.** Continual questioning of the *status quo* is encouraged with an aim to keep improving performance.

- **Eliminate waste at all levels.** Waste is interpreted broadly to include not just physical materials but unproductive activities and the waste of time.

- **Involve everybody.** OE is based on a skilled, trained workforce using all the education tools available. OE often uses visual displays in the workplace to communicate and reinforce messages.

- **Benchmark.** Compare the business with the best in class, across all industries.
Most major companies offer training in OE, either in-house or externally. Training normally leads to the award of a qualification:

- **Champion/Advocate**: for business leaders who need to plan, drive, facilitate and sustain a change initiative.
- **Green Belt**: for those who want to lead teams and improve processes in their immediate work areas.
- **Black Belt**: for practitioners who need a detailed understanding of the methodology and tools for data-driven problem-solving and process improvement.

Hygienists will be expected to use OE tools in the course of their daily work, and hygiene studies that do not follow OE principles may be criticised or denigrated. Hygiene functions can also expect to be periodically subject to “activity analysis” using OE tools to identify activities where waste can be eliminated. It is therefore strongly recommended that hygienists become trained in OE tools as early as possible, at least to Green Belt level. Some widely used tools that are simple to learn are listed below.

- **Plan-Do-Check-Act (PDCA) cycle.** A 4-step management process.
  - Plan: establish the objectives and processes
  - Do: Implement the plan
  - Check the actual results against the expected ones
  - Act (or Adjust) to correct deviations.

- **Situation-Target-Proposal (STP).** A problem solving technique, useful when writing project proposals.
  - Situation: Define the issue
  - Target: Define desired outcomes.
  - Proposal: How to get from the situation to the Target.

- **Brainstorming and affinitisation.** A technique for generating and categorising ideas.
  - Brainstorming: ideas are suggested and noted without any criticism. Building on ideas is allowed.
  - Affinitisation: related ideas are grouped together as a theme.

- **Input-Output (IPO) Diagram.** A visual representation (or “mapping”) of a process that shows the relationship between inputs and outputs. The figure shows a generic example. One effective use of an IPO is as a way of planning a meeting (the meeting becomes the “Process”).
○ **Fishbone diagram (Ishikawa Diagram).** A simple way to analyse a complex situation to identify root causes of an effect or problem. Starting from the standard diagram below, specific causes are added to the branches. Root causes can be found by asking “Why?” each proximate cause happened, adding subsidiary branches to the tree.

○ **Pareto diagrams.** A prioritisation tool based on the Pareto Principle (also known as the 80–20 rule, or the law of the vital few). The principle states that, for many events, roughly 80% of the effects come from 20% of the causes. The Pareto diagram is a bar chart of ranked data and is constructed with the most frequent or largest categories on the left. A cumulative curve can be added.
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- **DMAIC.** A process improvement methodology:
  Define - Measure - Analyse - Improve – Control

- **Activity and Customer Value Analysis (ACVA).** Looks at the importance and performance of a service from the customer’s perspective and plots the results on a chart to show prioritisation (see example in Figure).
8.4.2 Governance
Governance is the mechanism by which corporations monitor and account for their actions, policies and decisions. It ensures that corporations set and pursue their objectives in a way compatible with the social, regulatory and market environment, aligning internal interests with those of external stakeholders who may hold the company accountable.

A governance structure includes standards, rules and processes that:
- Ensure the highest standards of integrity
- Ensure operational and compliance risks are identified and escalated to appropriate levels of the business so that they are addressed and mitigated
- Establish and maintain open and honest (“transparent”) communications that encourage continuous improvement and in turn support and protect the company’s ability to innovate and operate
- Build and maintain stakeholder trust (see Corporate Responsibility, Section 8.5)

Governance may be codified in internal documents such as a code of practice. The Plan-Do-Check-Act model can provide a convenient framework to design or evaluate a governance system.

a. Planning
As a minimum, standards for occupational hygiene should require the organisation to:
- Identify, assess and mitigate health-related risks arising from work-related exposures and activities. These include risks from:
  - chemical and sensitising agents
  - radiation
  - biological agents
  - noise
  - workplace and task design
  
  Pharmaceutical companies often use formal “Risk Registers” or “Risk Maps” to visually model and communicate risk.
- Ensure adequate and competent specialist resources are available to identify and manage health risks and impacts. Resource needs may be benchmarked against industry leading companies.
- Set performance and improvement targets for critical risks. Examples of targets might be:
  - 80% of high-hazard chemical exposure situations are controlled without the use of respiratory protective equipment.
  - work-related ill-health performance is benchmarked in the first quartile of the industry
  - zero fines or penalties are incurred for legal non-compliance. Dependent on the regulatory regime, potential penalties might relate to dysfunctional control systems or non-compliance with internally set exposure limits.
b. Accountability
A designated senior executive should be accountable for the effectiveness of the occupational hygiene programme. He or she should:
- act as a champion for the programme
- ensure the programme is understood and supported by executives and employees
- arrange for periodic review of performance at executive level
- ensure that specialist resources are adequate
- obtain and respond to feedback about the programme

c. Monitoring, Reviews and Audits
Hygiene monitoring should make visible where and when performance falls short of standards. Bayesian statistics, Pareto charting, visual “dashboards” and “traffic light systems”, which colour code results as red, yellow or green, are widely used to communicate performance status.

Procedures should be in place for reporting deficiencies and escalating serious issues to the attention of senior management.

Regular reviews using Operational Excellence methodologies should be in place to ensure continued effectiveness and drive continuous improvement. Benchmarking with industry-leading pharmaceutical companies is common.

Internal auditing strengthens the feedback loop by providing a level of independent oversight to ensure that deficiencies are objectively identified and reported upwards. Occupational hygiene audits can take many different forms. For example:
- Audits may focus on individual facilities, product supply chains, or business processes. Supply chain auditing is increasingly common in the pharmaceutical industry. Such audits may be conducted in conjunction with the Procurement function and may address contract manufacturers and key suppliers of APIs, intermediates, raw materials or finished products. These external audits can raise difficult issues about which organisation carries the responsibilities and determination of potential liabilities. Legal advice will be needed and is likely to differ according to the legal code of the counsel.
- Audits may be combined with quality assurance, health and safety, or environmental audits. Broader audits can reduce the administrative burden on the operating facilities but may overlook important detail.
- Audits may be performed by a central audit group or by specialist hygiene staff. Having staff with more hygiene experience in the audit team will pick up more occupational hygiene issues. Some companies use hygienists from different sites to audit each other. Auditors need specific training in audit technique and in the protocols used, as well as good familiarity with GMP.
Audits may be scored or qualitative. Scored results are easier to summarise and compare but may conceal issues not reflected in the scoring system.

Prioritisation, frequency and depth of audits should always be decided on the basis of risk assessment. Some companies use a cascade of audits types at different levels depending on the risk and previous findings.

### 8.4.3 Capital Investment

Occupational hygienists should ensure that hygiene considerations are integrated into facility, engineering or process change projects. In the pharmaceutical industry this is usually done by a series of formal reviews and checks at key stages of the project. It is referred to here as the Capital Review process.

A Capital Review process should apply to a new facility, process or piece of equipment or a major modification to an existing facility, process or piece of equipment. The checks aim to ensure and then verify that the facility, process or equipment will function safely and reliably as intended (“Prevention through Design”).

A Capital Review process should involve a wide range of functions including production, quality, environment, safety, risk management and finance to ensure alignment of interests and support of top management. The hygienist will need to bring facts to support the arguments, including monitoring data and benchmarking. If the hygienist is making the investment proposal it is important to find out about budget timings to catch the planning window.

Projects vary in scale and complexity, but typically they will include design, development, construction, installation, validation, qualification and final hand-over. The detail and extent of occupational hygiene issues to be considered will depend on the nature of the project. Key questions to consider are:

- Are adequate control measures planned to prevent or minimise exposure of staff to harmful chemicals and substances?
- Have adequate facilities been planned to allow safe sampling and measuring for monitoring purposes?

Key steps in a typical Capital Review process are as follows:

- An initial **user specification** (scope) for the project, developed by the originator. The project scope is the foundation for the project and, along with consideration of project requirements, should provide an agreed basis for proceeding with design, costing and programming. Occupational Hygienists can provide input into the user specification by including specific targets to be accomplished, for example, target of < 1 ug/m3, or sound levels <60 dBA, or guarding, solvent
handling and human interaction with equipment can all be relevant to a user specification document.

- A **screening assessment** prior to project approval to provide an initial overview of the project and to determine whether a project is feasible and can proceed. It should identify any major occupational hygiene implications on operability or cost.

- A **preliminary assessment** at the start of the design phase when the project has been authorised. It will require inputs such as:
  - process description;
  - timing, duration and scale of the project;
  - process chemistry including any possible undesirable side reactions occurring during abnormal processing conditions;
  - chemical risk assessments;
  - inventory of materials introduced by the project;
  - Safety Data Sheets;
  - regulatory requirements;
  - briefs for any licences or permits.

- A **detailed assessment** once design work has been initiated. If adequate project information is available, the earlier that these assessments are undertaken the more the project will benefit and the less likely the project will have to be redesigned and result in an overspend. These **Fehler! Verweisquelle konnte nicht gefunden werden.** will often require the formation of separate study teams and rely on the use of detailed flow diagrams, line drawings and mass balances.

- A **commissioning review** (validation of performance and qualification to meet regulatory requirements) undertaken to ensure that all critical user requirements and aspects have been met. Incorporated into the review should be simulated operational tests using inert materials to ensure that the equipment is performing as designed.

- A **hand-over review** pre-start-up to provide assurance of safe operation. It covers technical and management issues such as equipment operability and construction specifications, training, normal operating, non-routine and emergency procedures, and changes to procedures.

- A **Close-out and final review** should check compliance with all recommendations and design standards. Areas of non-compliance should be identified and corrective actions agreed. Any learning points for improvements with future projects should be documented.

Knowledgeable technical personnel should conduct the reviews which may require a multi-disciplinary team. The number of people involved and the scope of the review should be related to the magnitude
of the change or of the equipment, plant or process. Guidelines should always be followed, though, even where the project is considered small.

8.4.4 Due Diligence

Acquisitions and divestitures require “due diligence” assessments on the part of the organisation. Examples include:

- Purchase of a company / business or formation of a new company
- Purchase / lease of property
- Sub-leasing a property (co-tenancy)
- In-licensing of product(s)
- Divestiture of land / lease

Occupational hygienists may be asked to identify risks and liabilities arising from the operations being acquired or divested. The following activities may be needed:

- Review all available data (regulatory history, permits, licences, leases, history of site, safety procedures, environmental documents, incident/accident records, waste disposal records, spill records).
- Conduct a Public Records search for information about the proposed business and its operations, excursions from regulatory standards, and general conduct of business practices.
- Conduct site visits, audits, and/or interviews with employees, neighbours to the business, and regulatory agencies.
- Determine potential for exposure of employees to hazardous materials and dangerous processes.
- Evaluate available data associated with existing or potential APIs in regards to their impact on the environment and potential for employee exposures. This may necessitate exposure modelling and/or Bayesian analysis.
- Ensure the availability of Safety Data Sheets about hazardous materials that employees may be handling.
- Inform affected employees about hazardous materials they may be handling in the future.
- Quantify liabilities to acquiring company as part of decision making process.
- Ensure the development of corporate reserves, as appropriate, to cover significant liabilities.
- Document all risks and liabilities for review with the key decision makers for consideration as part of the overall decision making and planning process.
- Obtain appropriate regulatory licenses and permit closures through proper authorities.
- Coordinate any facility clean-out/decommissioning/decontamination.
- Interface with consultants, contractors, regulatory authorities, agents, etc. during the decommissioning of the facility.
8.4.5 New Product Introduction

Developing new products is the lifeblood of the pharmaceutical research companies and as such receives a very high business priority. Each company has a business process designed to systematically identify and resolve the issues while speeding the new product into production.

Many new chemical leads are generated. Testing of newly designed substances is limited by the concern for balancing good stewardship of laboratory and animal resources with the possibility that in early stages of development a specific chemical may be created only once or in limited quantities. Testing therefore takes place in a phased manner as the candidate substance progresses closer to manufacture. Testing of intermediates is only triggered at the point the API in the process is moved into position for clinical Phase III trials and then takes about 3 - 6 months to complete. Figure 1 shows a schematic of a typical testing regime.
Figure 1: Typical hazard testing scheme for new product introduction (Source: GSK)
Timely hazard testing and interpretation is of paramount importance for occupational health. Occupational health input to the business process is often led by toxicology or hazard assessment professionals. Occupational hygienists need to engage with the process so that they are aware of issues likely to arise in R&D laboratories or production operations. Key stages for the hygienist are:

- **Early identification of issues and risks**: Preliminary health hazard assessment of API & process chemicals allow likely issues to be identified early.
- **Support for early clinical trials**: Health hazard assessment of isolated intermediates and process chemicals are needed to support pilot plant scale production. A Safety Data Sheet for the formulated product will be needed to support clinical trials.
- **Identification of manufacturing sourcing options**: OELs for high potency materials will be a factor in choosing where to source a new material. The manufacturer must have appropriate containment capability.
- **Preparation for manufacturing and launch**: All necessary information should be available for all materials, including Safety Data Sheets and OELs.
- **Supply chain and life cycle management**: OELs and data sheets may need to be updated as a result of post-launch adverse events.

Testing of substances may not be the only testing required in new product development. There may also be issues surrounding devices, returns of products, and dangerous goods transportation issues.

**8.4.6 Technology Transfers**

Existing products and processes may need to be transferred between companies or between manufacturing locations.

Products acquired from other pharmaceutical companies, either as existing products or as late stage development materials may not have been through a comprehensive hazard testing and evaluation process, which can cause problems when they are introduced to the receiving organisation. It is therefore important that such issues are identified as early as possible in the in-licensing business process and the knowledge gaps are quickly filled.

In-licensing of products, outsourcing and transfers between sites or departments should be subject to a Technology Transfer business process which requires a sign off by both the sending and receiving locations.
Important information that should form part of the transfer includes:

- Chemical Risk Assessments
- Material data safety sheets
- Documentation of hazard testing and evaluation
- Documentation of Occupational Exposure Limits and Occupational Hazard Categories
- Documentation of handling and containment methods
- Procedures for cleaning and maintenance
- Occupational hygiene air sampling data
- Personal protective equipment (PPE) requirements
- Validated Occupational hygiene analytical methods and procedures for sample collection
- Medical health surveillance methodologies and information of adverse health events experienced
- Training plan for training personnel involved in processing and handling
- Details of relevant laws, regulations and licenses

There is an ISPE Good Practice Guide to Technology Transfer.

### 8.4.7 Awards Programmes

An awards programme can provide a valuable incentive for others to improve their performance, as well as rewarding actual achievements. It is unlikely to be practicable to organise an award scheme just for occupational hygiene, so it may be necessary to link into a broader company schemes, such as a Human Resources’ or Chief Executive’s award programme. If no scheme is available, you could collaborate with related functions, such as EHS, to create one.

Awards could be used to recognise people or teams, for example:

- sites or departments who have achieved outstanding occupational hygiene performance
- teams that have brought important projects to a satisfactory conclusion
- leaders who have inspired others to improve occupational hygiene performance.

The recognition could take the form, as appropriate, of:

- public thanks and congratulations
- a small gift or memento
- a donation to an agreed charity.
Key learning points:

- Hygiene managers will need to integrate their teams into a wide range of business processes.
- Business processes are cross-functional activities designed to produce a specific service or product for a particular customer.
- Operational Excellence provides tools and techniques that hygienists will need to utilise.
- Key business processes include governance, capital investment, due diligence, new product introduction, technology transfer and awards processes.

8.5 Corporate Responsibility (CR)

8.5.1 The Importance of CR to Pharmaceuticals Industry

The high impact of life-saving and life-changing medicines on social and economic issues means that society has come to have high expectations of the pharmaceutical industry. However, a number of issues that have been much publicised in the media have severely affected public trust in the industry. There have been unforeseen side effects from marketed medicines, accusations of companies hiding adverse clinical trials data, arguments about prices and affordability, intellectual property disputes with developing countries, allegations of improper lobbying, cases of mis-selling, bribery and corruption, problems with manufacturing quality and concerns about pharmaceuticals in the environment. These ethical issues have led to litigation and prosecutions, massive fines, and increased regulation. Opinion surveys showed that public trust and confidence in the industry has fallen to a very low level.

The industry has been under intense scrutiny. Being a responsible company means more than complying with the letter of the law. Compliance is not enough. At the same time, research points towards a strong correlation of social and environmental performance with financial performance, offering a business rationale for companies to behave ethically. Transparency is now seen by the industry as key to re-building trust.

Most large pharmaceutical companies have a staff unit dealing with “corporate responsibility” (sometimes termed Corporate Social Responsibility and sometimes under the banner of Sustainability – see below). It is often positioned within the communications function and holds responsibility for reporting and public relations. Its scope commonly includes:

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Chapter 8: Management of Occupational Hygiene
Reputation and ethics
- Social issues for the industry such as access to medicines, publication of research data, animal testing
- Employee health as a human right
- Importance of exposure control to legal and ethical operation of the industry
- Health and performance
- Trust, transparency and ways of working

8.5.2 Occupational Hygiene as a Corporate Responsibility Issue

Occupational hygiene is itself a corporate responsibility issue for the industry. As the industry prides itself on improving health, it would be unacceptable for employees to have their health harmed by over-exposure to a company’s products. Hygienists, particularly at senior level, are therefore likely to have contact with Corporate Responsibility staff and to be asked to provide information about health impacts and how they are controlled. Such issues can have a massive impact on product sales as well as damaging reputation and trust, so they can escalate rapidly to senior levels of the organisation.

Involvement of hygienists may arise at an early stage in the emergence of an issue, when occupational health and hygiene data are still incomplete and when the need to act is still contentious. Table 1 illustrates how a social responsibility issue typically evolves. Reputational damage is already occurring at Stage 2, yet it can be difficult to prevent because consensus on causes and actions does not emerge until Stages 3-4. Occupational hygienists need to be aware that they may be asked for advice at an early stage when it is scientifically difficult to formulate clear answers. At such times, it must be remembered that the hygienist’s primary professional duty is to protect the employees. It is generally necessary to take a precautionary approach, even though that may involve higher costs for the employer and the hygienist will be challenged to justify the advice given. It is also important that the hygienist communicates the issues and advice in layman’s language so that they are clearly understood.
Table 1  Issue Maturity: Stages in Society

<table>
<thead>
<tr>
<th>Stage</th>
<th>Characteristics</th>
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| 1. Latent     | • Activist communities and NGOs (Non-Governmental Organisations) are aware of the issue.  
• There is weak scientific or other hard evidence.  
• The issue is largely ignored or dismissed by the business community. |
| 2. Emerging   | • There is political and media awareness of the societal issue.  
• There is an emerging body of research, but data are still weak.  
• Leading businesses experiment with approaches to dealing with the issues. |
| 3. Consolidating | • There is an emerging body of business practice around the societal issue.  
• Sector-wide and issue-based voluntary initiatives are established.  
• There is litigation and increasing view of the need for legislation.  
• Voluntary standards are developed and collective action occurs. |
| 4. Institutionalised | • Legislation or business norms are established.  
• The embedded practices become a normal part of a business excellence model. |

Corporate responsibility issues may also result in hygienists becoming involved with customers - for example, with medical professionals handling cytotoxic drugs in healthcare facilities – and with suppliers to ensure they protect the health of their own employees and to ensure the security of the supply chain.

8.5.3 Corporate Responsibility Reporting

Many countries, particularly in Europe, have legal requirements for businesses to report on non-financial issues relevant to their business within annual reports. One widely recognised standard for such reporting is the Global Reporting Initiative (GRI). GRI is a non-profit organization that promotes sustainability and provides a comprehensive reporting framework.

The pharmaceuticals industry has not developed sector guidance on the use of GRI, but many individual companies relate their reporting to GRI requirements. Hygiene typically fits under the Occupational Health and Safety guidelines, for which current standard reporting requirements are:

- Percentage of total workforce represented in formal joint management–worker health and safety committees that help monitor and advise on occupational health and safety programmes.
Rates of injury, occupational diseases, lost days, and absenteeism, and number of work-related fatalities by region.

Education, training, counselling, prevention, and risk-control programmes in place to assist workforce members, their families, or community members regarding serious diseases.

Health and safety topics covered in formal agreements with trade unions

Key learning points:

- Corporate (Social) Responsibility is an important concern for the ethical pharmaceutical industry.
- A wide range of issues have led to a decline in public trust, litigation and prosecutions.
- Occupational hygiene can rapidly become a CR issue if effects on employee health escalate to become issues of public concern.
- Hygiene managers will need to provide input to the corporate communications team.

8.6 Sustainability

“Sustainability” is the capability of an organisation to continue its activities indefinitely. It incorporates 3 dimensions – environmental, social and economic – so it encompasses the commercial sustainability of the business as well as the social and environmental aspects. The goal is to find a balance that allows the business to be commercially successful in the long term without causing social or environmental harm.

Some companies prefer to use the term “sustainability” instead of “corporate responsibility” since it embraces many of the same issues but is seen as more proactive by business.

In this section, we will focus mainly on the overlaps between environmental issues and occupational hygiene, but sometimes the social and economic aspects of sustainability are inextricable.
8.6.1 Environmental Issues for the Pharmaceuticals Industry

The high profile of the industry’s environmental issues reflects the public interest in the huge social and economic impacts of pharmaceuticals. Notable environmental concerns include:

- The impact of pharmaceuticals and consumer healthcare products entering the environment from excretion by patients and from unused medicines. Sewage treatment systems are not always able to remove these substances and the residues sometimes pass through treatment facilities and enter rivers, streams or lakes. Residues of some pharmaceuticals may persist in the environment. There are measurable impacts on aquatic life and potential impacts on human health as levels in the environment rise.

- The use of hazardous chemicals in manufacture and the potential for environmental releases from factories.

- Climate change, traditionally associated with energy consumption and, in pharmaceutical research and manufacturing, particularly through the use of Heating Ventilation and Air Conditioning (HVAC). Occupational hygiene controls such as Local Exhaust and General Ventilation can make a significant contribution. Improving containment at the source, might allow for a reduction of tertiary controls such as single pass air or the number of air changes. In the broader context of carbon footprinting, though, resource efficiency may be a much bigger issue for the industry.

- Resource efficiency, in the pharmaceutical context, is driven largely by the mass efficiency of chemical reactions. Conventional multi-step chemical synthesis routes typically have an overall mass efficiency of only 1-2% - simply put 98-99% of raw materials end up as waste. New green chemistry routes to synthesis and the introduction of synthetic biology are rapidly improving that.

- Impacts on biodiversity and conservation from exploitation of natural sources of pharmaceuticals. International rules are in place (the UN Convention on Biological Diversity, 1993).

- The release of genetically modified organisms. Even after sterilisation there are concerns about modification of DNA in bacteria leading to antibiotic resistance.

- Ozone depletion from chlorofluorocarbons in some inhaler treatments for asthma. The industry is progressively moving to alternative technologies such as dry powder inhalers and propellants with low Ozone Depleting Potential. Some of these, such as hydrofluorocarbons (HFAs) still have high Global Warming Potentials.
o Nanotechnology, which offers hope of improved treatments but raises concerns about unknown side effects.

o Water usage in parts of the world that are increasingly water stressed.

o Labelling and recycling of packaging materials.

o Supply chain management including a duty of care for contract manufacturing, distribution and sales.

The basic principles of environmental sustainability in the industry can therefore be summarized as:

o Maximise the efficiency of manufacturing processes to optimise resource utilisation.

o Understand and minimise the impacts of pharmaceuticals on the environment.

o Take responsibility for the fate of products in the environment.

o Avoid the use of hazardous chemicals wherever practicable.

o Minimise the use of non-renewable energy.

o Involve everyone in identifying and resolving sustainability issues.

o Consider sustainability issues as an element in routine business decisions.

o Encourage third party contractors to adopt similar standards.

8.6.2 Occupational Hygiene and Sustainability

Although sustainability is often regarded as an environmental programme, the heart of the pharmaceutical industry is making products that are designed to promote health and at the most basic level a business cannot be sustainable if employees suffer adverse health effects.

Sustainability issues have many characteristics that are familiar to occupational hygienists. They require risk assessment based on measurements and modelling, and an understanding of manufacturing processes to make improvements. So while the subject matter may be different, the skills developed in industrial hygiene are eminently transferable.

There is a strong relationship between protecting the health of workers and the environmental aspects of sustainability. For example, eliminating solvents and reducing waste protect both workers and the environment. Broadly, pursuing sustainability will lead to smaller quantities of less toxic materials being used, so environmental aims are congruent with preventing occupational hygiene exposures at source.
Sustainability addresses environmental, social and economic impacts over the entire lifecycle of a product. Decisions about the introduction of new products, the choice of manufacturing processes and the design of buildings provide opportunities to improve standards of occupational hygiene by, for instance:

- encouraging substitution
- reducing quantities of hazardous materials handled
- avoiding production of waste
- integrating hygiene into the business.

Sustainability can have a major impact on the way that occupational hygiene is managed. Decisions made in drug discovery have implications for the chemicals that have to be handled in manufacturing and the biodegradability of products. Packaging, logistics and facilities raise additional questions about occupational exposures. So there is a need to think beyond what happens locally in individual parts of the business and to join up the corporate strategy (see figure).

The business case for addressing sustainability in pharmaceuticals industry rests on the opportunities it creates to:
Build trust with stakeholders
Support innovation
Reduce waste and costs
Use resources efficiently
Generate competitive advantage

Good occupational hygiene practice reinforces this business case:

- it is core to respect for people and building trust
- it encourages innovation and simplification
- it benefits efficiency and product quality

Sustainability performance can be assessed and benchmarked through the Dow Jones Sustainability Group Index (DJSGI), which gives a systematic methodology for identifying leading sustainability-driven companies.

Becoming a more sustainable business is a complex, long-term challenge. Businesses that embrace sustainability are likely to be managed differently (see, for example, R. Barrett (1998) Liberating the Corporate Soul). Sustainability implies a culture shift that will progressively move the organisation from the traditional regulatory-driven, compliance-based approach, to a values-driven approach. Typically, steps are needed to:

- streamline the management of EHS
- release resources from low-value bureaucratic work
- stimulate self-regulation
- motivate and empower people to do their best work
- encourage diversity and innovation
- liberate the business to achieve higher levels of performance

These trends create opportunities to embed occupational hygiene in the business so that fundamental issues are owned by the business rather than driven by specialists. For example:

- Most professionals will be embedded in operations with only strategy development and targeted specialist support provided from above site level.
- Professionals will focus on transferring knowledge and skills into the businesses, increasing understanding and capability.
- Occupational hygiene will be embedded in management systems, business processes and governance systems, so that it becomes a consideration in decision making processes and a driver for competitive advantage.
- Hygiene will become recognised as a driver for innovation, to find more sustainable and cost effective approaches.
Hygiene will be embedded in internal engagement processes as a driver for openness and transparency to build trust and co-operation with internal and external stakeholders.

Hygienists are likely to become engaged in resilience programmes that enable individuals, teams and the whole organisation to maintain performance under conditions of constant challenge and change.

The introduction of “sustainability thinking” is therefore likely to have long term implications for the roles of occupational hygienists and related professionals in the industry. For the individual hygienist, it also offers opportunities to develop broader skills, gain better knowledge of the business and demonstrate leadership.

**Key learning points:**

- **Sustainability** is the capability of an organisation to continue its activities indefinitely. It has environmental, social and economic dimensions.

- Occupational hygiene has strong overlaps with environmental issues, which can arise at any point in the product lifecycle.

- Opportunities to improve standards of occupational hygiene include encouraging substitution, reducing quantities of hazardous materials handled, avoiding production of waste and integrating hygiene into the business.

- Embedding sustainability in business processes implies a culture shift from the traditional regulatory-driven, compliance-based approach to a values-driven approach. It brings implications and opportunities for the way occupational hygiene is managed.
Further Reading and Resources


**ROHSEI.** Further information is available online at URL: https://www.orchsestrategies.com/rohsei-page/ (accessed Sep 2019).


**Global Reporting Initiative.** Available at www.globalreporting.org (accessed Sep 2019)

Chapter 9: Safe Handling of Hazardous Drugs

9 END USER SAFE HANDLING OF HAZARDOUS DRUGS

9.1 Background
9.2 Hazardous Drug Handling in Healthcare
9.3 Exposure Assessment in the Healthcare Setting
9.4 Medical Surveillance of Healthcare Workers
9.5 Exposure Controls for Hazardous Drug Handlers
9.1 Background

A great deal of global and historical documentation exists regarding the potential risk of exposure and acute and chronic health effects of over 200 commonly used hazardous drugs for healthcare workers. For the purposes of this chapter, the term healthcare workers can include pharmacists, nurses, physicians, housekeepers, maintenance and material management workers. Most scholarly references on this topic indicate that millions of global healthcare workers are negatively impacted by improper handling of hazardous or potent drugs. Little is known about the potential number of patients and visitors that could also be impacted by exposures resulting from improper handling. Organizations such as the UK Health and Safety Executive (HSE), the National Institute of Occupational Safety and Health (NIOSH), the American Society of Health System Pharmacists (ASHP), and the United States Pharmacopeia (USP) have published over the past decade sound guidance for proper handling in receiving, transfer, preparation, administration and disposal of hazardous drugs. The USP has recently published a comprehensive guide for handling HDs, entitled “USP General Chapter <800> Hazardous Drugs – Handling in Healthcare Settings” that provides a framework for much of the content of this chapter in addition to several other globally-recognized health and safety organizations.

9.2 Hazardous Drug Handling in Healthcare

According to USP, the USP General Chapter <800> describes requirements including responsibilities of personnel handling hazardous drugs; facility and engineering controls; procedures for deactivating, decontaminating and cleaning; spill control; and documentation. These standards apply to all healthcare personnel who receive, prepare, administer, transport or otherwise come in contact with hazardous drugs and all the environments in which they are handled. Essentially, any healthcare worker that is part of the hospital medication chain is potentially at risk of exposure to hazardous drugs. To protect patients and healthcare workers from potential harm, USP’s General Chapters <800> Hazardous Drugs – Handling in Healthcare Settings, <797> Pharmaceutical Compounding – Sterile Preparations, and <795> Pharmaceutical Compounding – Nonsterile Preparations were developed to provide an aligned and complete set of standards for all healthcare workers to help ensure the safe handling of hazardous drugs throughout the healthcare system, including in the practice of compounding.

USP 800 requires entities to have a comprehensive health and safety management system for hazardous drugs (HDs) that includes the following elements at a minimum:

- A list of HDs
- Facility and engineering controls
- Competent personnel
- Safe work practices and training
Proper use of appropriate Personal Protective Equipment (PPE), and Policies for HD waste segregation and disposal.

The focus of this course will be on the following occupational hygiene elements –

- Facility and engineering controls,
- Safe work practices, and
- Proper use of appropriate PPE.

### 9.3 Exposure Assessment in Healthcare Settings

One of the most effective and typical approaches in healthcare settings for determining worker exposure potential to hazardous drugs is surface exposure assessment via wipe sampling, as opposed to the more conventional air sampling. The migration of HDs through air and surface contact from the receipt, transfer, preparation, administration, storage and disposal of hazardous/potent drugs makes surface wipe sampling a good way to profile the potential for exposure within a facility.

Once the hazardous drugs for a facility have been identified and a Hazardous Drug Written Program has been developed, an exposure assessment should be completed by identifying the path that the hazardous drugs follow from the point where they enter the facility to where they leave as patient waste, contaminated laundry, IV bags, contaminated medical equipment etc. This includes materials receiving, transportation within the facility, storage (including refrigerators and freezers), drug preparation and administration, operating rooms, as well as laundry and waste handling. All potential sources of exposure should be identified. It is also important to identify all individuals who have the potential to come into contact with hazardous drugs.

There is reasonable likelihood that most areas where hazardous drugs are used, handled, stored, or disposed are likely contaminated with those drugs. Because only 6-8 drugs are commonly used as “markers” of exposure, this approach can only estimate the overall exposure from the dozens of drugs that may be in use.

**Environmental monitoring**

Environmental monitoring via surface wipe sampling allows the evaluation and measurement of chemical contamination by hazardous drugs and the results therefore indicate increased exposure potential due to dermal contacts. Wipe sampling kits should be verified before use to ensure the method and reagent used have been evaluated to recover a specific percentage of known marker drugs from various surface types found in the sampled area. Common marker hazardous drugs that can be
assayed include cyclophosphamide, ifosfamide, methotrexate, fluorouracil, and platinum-containing drugs. As such, there is a need for more studies demonstrating the effectiveness of a specific number or size of wipe samples in determining levels of hazardous drug contamination and validation of methods for sampling and analysis.

The level of hazardous drug contamination on work surfaces should be measured at least every 6 month or more frequently if any major change is made in controls used, personnel, placement of furniture, aseptic processes, or cleaning and disinfecting practices. If any measurable contamination is found, the hospital must identify, document, and contain the cause of contamination. Such action may include re-evaluating work practices, re-training personnel, performing thorough deactivation, decontamination, cleaning, and improving engineering controls.

Surface wipe sampling strategies should be developed based on activities in the work area, focused on high touch areas including, but not limited to:
- Interior of the containment primary engineering control (C-PEC) and equipment contained in it,
- Pass-through chambers,
- Surfaces in staging or work areas near the C-PEC,
- Areas adjacent to C-PECs (e.g., floors directly under C-PEC, staging, and dispensing area),
- Areas immediately outside the buffer room or the containment segregated compounding area (C-SCA),
- Patient administration areas,
- Receiving areas,
- Storage areas,
- Waste handling and storage areas,
- Transport containers and carts, and
- Restrooms in patient treatment areas.

When possible, a baseline assessment should precede any changes in preventive measures and monitoring should be repeated after implementation of such measures, to determine their effectiveness. Sampling strategy and frequency can be adjusted based on survey results and follow-up.

The goal of the surface sampling strategy is to complete the following:

1) identify potential contamination,
2) ensure systems or controls are implemented to reduce contamination and
3) to re-sample and confirm that implemented systems and controls are effective.
9.4 Medical Surveillance of Healthcare Workers

There is no standard approach regarding medical surveillance of healthcare workers exposed to hazardous drugs. Although some agencies guidance exists indicated the criteria for a medical surveillance program, limited literature is currently available which has evaluated the efficacy and usefulness of such monitoring. It also bears mentioning that medical monitoring cannot differentiate between problems (e.g. miscarriages, malformations, leukemias) related to occupational exposure and those which are not. Note that medical surveillance, if adopted, should be part of a comprehensive exposure control program which also includes engineering controls, safe work processes, and use of PPE.

Healthcare workers who handle hazardous drugs as a regular part of their job assignment should be enrolled in a medical surveillance program. The general purpose of surveillance is to minimize adverse health effects in personnel potentially exposed to hazardous drugs. Medical surveillance programs involve assessment and documentation of symptoms, physical findings, and biological exposure indices (such as a blood count) to determine whether there is a deviation from the expected norms.

Medical surveillance can also be viewed as a secondary prevention tool that may provide a means of early detection if a health problem develops. Tracking personnel through medical surveillance allows the comparison of health variables over time in individual workers, which may facilitate early detection of a change in a laboratory value or health condition. Medical surveillance programs also look for trends in populations of workers. Examining grouped data compared with data from unexposed workers may reveal a small alteration or increase in the frequency of a health effect that would be obscured if individual workers' results alone were considered.

Medical surveillance evaluates the protection afforded by engineering controls, administrative controls (such as safe work processes and worker education about the hazards of the materials they work with in the course of their duties), and PPE. The data-gathering elements of a medical surveillance program are used to establish a baseline of workers' health and then to monitor their future health for any changes that may result from exposure to hazardous drugs.

Elements of a medical surveillance program should be consistent with the organization’s Human Resource policies and should minimally include:
- Development of an organized approach to identify workers who are potentially exposed to hazardous drugs on the basis of their job duties
- Initial baseline assessment (pre-placement) of a worker's health status and medical history.
- Periodic assessments
- Termination exams
Data elements collected include a medical (including reproductive) history and work history to assess exposure to hazardous drugs, physical examination, and laboratory testing. Methods used to assess exposure history include a review of:

- Records of hazardous drugs handled, with quantities and dosage forms
- Duration and frequency of handling hazardous drugs
- A physical assessment and biological monitoring samples linked to target organs of commonly used hazardous drugs, such as a baseline complete blood count. Biological monitoring to determine blood or urine levels of specific hazardous drugs is not currently recommended in surveillance protocols, but may have a role in the follow-up of acute spills with a specific agent. Medical monitoring can also be performed through the biological monitoring of genotoxicity (genes-chromosomes-DNA). However, there remains a great deal of uncertainty regarding individual variability and the causal relationship between biomarker variation and the environment or the likelihood of developing pathology.
- Medical records of surveillance should be maintained according to local, state and Federal regularly requirements concerning access to employee exposure and medical records
- Development of a follow-up plan for workers who have shown health changes suggesting toxicity or who have experienced an acute exposure. This follow-up should include evaluation of current controls used to ensure that they are adequate (see Follow-Up Plan)
- Completion of an exit examination when a worker's employment at a facility ends, to document the information on the employee's medical, reproductive, and exposure histories. Examination and biological monitoring should be guided by the individual's exposure history and follow the outline of the periodic evaluation.
9.5 Exposure Controls for Hazardous Drug Handlers

According to USP 800, hazardous drugs must be handled under conditions that promote patient safety, worker safety, and environmental protection. Signs designating the hazard must be prominently displayed before the entrance to the HD handling areas. Access to areas where hazardous drugs are handled must be restricted to authorized personnel to protect persons not involved in HD handling. HD handling areas must be located away from breakrooms and refreshment areas for personnel, patients, or visitors to reduce risk of exposure.

Designated areas must be available for:

- Receipt and unpacking
- Storage of hazardous drugs
- Nonsterile HD compounding
- Sterile HD compounding

Certain areas are required to have negative pressure from surrounding areas to contain hazardous drugs and minimize risk of exposure. Consideration should be given to uninterrupted power sources (UPS) for the ventilation systems to maintain negative pressure in the event of power loss.

Compounding (general)

Engineering controls are required to protect the preparation from cross-contamination and microbial contamination (if preparation is intended to be sterile) during all phases of the compounding process. Engineering controls for containment are divided into three categories representing primary, secondary, and supplementary levels of control. A containment primary engineering control (C-PEC)* is a ventilated device designed to minimize worker and environmental HD exposure when directly handling hazardous drugs. The containment secondary engineering control (C-SEC) is the room in which the C-PEC is placed. Supplemental engineering controls [e.g., closed-system drug-transfer device (CSTD)] are adjunct controls to offer additional levels of protection.

Sterile and nonsterile hazardous drugs must be compounded within a C-PEC located in a C-SEC. The C-SEC used for sterile and nonsterile compounding must:

- Be externally vented
- Be physically separated (i.e., a different room from other preparation areas)
- Have an appropriate number of air changes per hour (ACPH)
- Have a negative pressure between 0.01 and 0.03 inches of water column relative to all adjacent areas

The C-PEC must operate continuously if it supplies some or all of the negative pressure in the C-SEC or if it is used for sterile compounding. If there is any loss of power to the C-PEC, or if repair or moving...
occurs, all activities occurring in the C-PEC must be suspended immediately. If necessary, protect the unit by covering it appropriately per the manufacturer's recommendations. Once the C-PEC can be powered on, decontaminate, clean, and disinfect (if used for sterile compounding) all surfaces and wait the manufacturer-specified recovery time before resuming compounding.

A sink must be available for hand washing. An eyewash station and/or other emergency or safety precautions that meet applicable laws and regulations must be readily available. Care must be taken to locate water sources and drains in areas where their presence will not interfere with required ISO classifications. Water sources and drains must be located at least 1 meter away from the C-PEC.

For entities that compound both nonsterile and sterile hazardous drugs, the respective C-PECs must be placed in separate rooms, unless those C-PECs used for nonsterile compounding are sufficiently effective that the room can continuously maintain ISO 7 classification throughout the nonsterile compounding activity. If the C-PECs used for sterile and nonsterile compounding are placed in the same room, they must be placed at least 1 meter apart and particle-generating activity must not be performed when sterile compounding is in process.

A. Non-sterile compounding

The C-PECs used for manipulation of nonsterile hazardous drugs must be either externally vented (preferred) or have redundant–HEPA filters in series. Nonsterile HD compounding must be performed in a C-PEC that provides personnel and environmental protection, such as a Class I Biological Safety Cabinet (BSC) or Containment Ventilated Enclosure (CVE). A Class II BSC or a compounding aseptic containment isolator (CACI) may also be used. For occasional nonsterile HD compounding, a C-PEC used for sterile compounding (e.g., Class II BSC or CACI) may be used but must be decontaminated, cleaned, and disinfected before resuming sterile compounding in that C-PEC. A C-PEC used only for nonsterile compounding does not require unidirectional airflow because the critical environment does not need to be ISO classified.

Note: A C-PEC is not required if manipulations are limited to handling of final dosage forms (e.g., counting or repackaging of tablets and capsules) that do not produce particles, aerosols, or gases. This is not the case if they are manipulated or crushed in a way that generates particles, aerosols or gases.

Due to the difficulty of eliminating HD contamination, surfaces of ceilings, walls, floors, fixtures, shelving, counters, and cabinets in the nonsterile compounding area, these surfaces must be smooth, impervious, free from cracks and crevices, and non-shedding per International Pharmaceutical Engineering Society guidelines for pharmaceutical containment.
B. Sterile Compounding

According to USP 800, all C-PECs used for manipulation of sterile hazardous drugs must be externally vented. Sterile HD compounding must be performed in a C-PEC that provides an ISO Class 5 or better air quality, such as a Class II or III BSC or CACI. Class II BSC types A2, B1, or B2 are acceptable. For most known hazardous drugs, type A2 cabinets offer a simple and reliable integration with the ventilation and pressurization requirements of the C-SEC. Class II type B2 BSCs are typically reserved for use with volatile components.

A laminar airflow workbench (LAFW) or compounding aseptic isolator (CAI) must not be used for the compounding of an antineoplastic HD. A BSC or CACI used for the preparation of hazardous drugs must not be used for the preparation of a non-HD unless the non-HD preparation is placed into a protective outer wrapper during removal from the C-PEC and is labeled to require PPE handling precautions.

The C-PEC must be located in a C-SEC, which may either be an ISO Class 7 buffer room with an ISO Class 7 ante-room (preferred) or an unclassified containment segregated compounding area (C-SCA). The table below summarizes the engineering controls required for sterile HD compounding.

<table>
<thead>
<tr>
<th>Configuration</th>
<th>C-PEC</th>
<th>C-SEC</th>
</tr>
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<tbody>
<tr>
<td>ISO Class 7 buffer room with an ISO</td>
<td>• Externally vented</td>
<td>• Externally vented</td>
</tr>
<tr>
<td>Class 7 ante-room</td>
<td>• Examples: Class II BSC or CACI</td>
<td>• 30 ACPH</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Negative pressure between 0.01 and 0.03 inches of water column</td>
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<tr>
<td></td>
<td></td>
<td>relative to adjacent areas</td>
</tr>
<tr>
<td>Unclassified C-SCA</td>
<td>• Externally vented</td>
<td>• Externally vented</td>
</tr>
<tr>
<td></td>
<td>• Examples: Class II BSC or CACI</td>
<td>• 12 ACPH</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Negative pressure between 0.01 and 0.03 inches of water column</td>
</tr>
<tr>
<td></td>
<td></td>
<td>relative to adjacent areas</td>
</tr>
</tbody>
</table>

ISO Class 7 buffer room with an ISO class 7 ante-room: The C-PEC is placed in an ISO Class 7 buffer room that has fixed walls, HEPA-filtered supply air, a negative pressure between 0.01 and 0.03 inches of water column relative to all adjacent areas and a minimum of 30 ACPH.
The buffer room must be externally vented. Because the room through which entry into the HD buffer room (e.g., ante-room or non-HD buffer room) plays an important role in terms of total contamination control, the following is required:

- Minimum of 30 ACPH of HEPA-filtered supply air
- Maintain a positive pressure of at least 0.02 inches of water column relative to all adjacent unclassified areas
- Maintain an air quality of ISO Class 7 or better

An ISO Class 7 ante-room with fixed walls is necessary to provide inward air migration of equal cleanliness classified air into the negative pressure buffer room to contain any airborne HD. A hand-washing sink must be placed in the ante-room at least 1 meter from the entrance to the HD buffer room to avoid contamination migration into the negative pressure HD buffer room.

Although not a recommended facility design, if the negative-pressure HD buffer room is entered through the positive-pressure non-HD buffer room, the following is also required:

- A line of demarcation must be defined within the negative-pressure buffer room for donning and doffing PPE
- A method to transport hazardous drugs, HD CSPs, and HD waste into and out of the negative pressure buffer room to minimize the spread of HD contamination. This may be accomplished by use of a pass-through chamber between the negative-pressure buffer area and adjacent space. The pass-through chamber must be included in the facility's certification to ensure that particles are not compromising the air quality of the negative-pressure buffer room. A refrigerator pass-through must not be used. Other methods of containment (such as sealed containers) may be used.

*Containment segregated compounding area (C-SCA):* The C-PEC is placed in an unclassified C-SCA that has fixed walls, a negative pressure between 0.01 and 0.03 inches of water column relative to all adjacent areas, and a minimum of 12 ACPH.

The C-SCA must be externally vented. A hand-washing sink must be placed at least 1 meter from C-PEC and may be either inside the C-SCA or directly outside the C-SCA.

**Containment Supplemental Engineering Controls**

Containment supplemental engineering controls, such as CSTDs, provide adjunct controls to offer an additional level of protection during compounding or administration. Some CSTDs have been shown to limit the potential of generating aerosols during compounding. However, there is no certainty that all CSTDs will perform adequately. Until a published universal performance standard for evaluation of CSTD containment is available, users should carefully evaluate the performance claims associated with
available CSTDs based on independent, peer-reviewed studies and demonstrated containment reduction.

A CSTD must not be used as a substitute for a C-PEC when compounding. CSTDs should be used when compounding hazardous drugs when the dosage form allows. CSTDs must be used when administering antineoplastic hazardous drugs when the dosage form allows. CSTDs known to be physically or chemically incompatible with a specific HD must not be used for that HD.

Sterile Preparation Cabinets per the Canadian ASSTSAS

According to the Canadian Joint Sector-based Association for Health and Occupational Safety for the Social Sector (ASSTSAS) publication for Handling Hazardous Drugs, class II type B2 biological safety cabinets with protective glass (also called vertical laminar flow hoods) should be used. Class II B1 cabinets can be used in institutions where hazardous drugs are rarely prepared or as a back-up preparation cabinet. The B1 cabinets exhaust all of the air to the outdoors if the work is performed at the back of the cabinet, near the rear grille. However, this practice may be contraindicated from an ergonomic standpoint. Class III cabinets are now becoming available; these closed cabinets may limit (at least, theoretically) outside contamination of the sterile preparation room related to handling. Further investigation regarding the efficacy and ergonomics of these cabinets should be carried out before a general recommendation is made in this regard.

Generally speaking, closed-circuit preparation systems (PhaSeal®, Tevadaptor®) are not a substitute for Class II B2 or B1 preparation cabinets.

The biological safety cabinets should remain in operation 24 hours a day, 7 days a week, as recommended by the manufacturers. To conserve energy, the glass panel can be lowered completely when the cabinets are not in use. To shut down the cabinets outside working hours to conserve energy, use a timer to make sure they are restarted 30 minutes before resuming work and stopped 30 minutes after finishing work; the ventilation in the sterile preparation room should always be adjusted accordingly. Clean the cabinet (i.e., floor, side walls, including the glass wall) after completing and before resuming work.

In the event of a stoppage (e.g. breakdown), decontaminate the cabinet and allow it to operate for at least 30 minutes before resuming preparation work.

A Class II A2 cabinet may be used in the sterile preparation room for non-hazardous drugs intended for oncology patients.

The cabinets may be positioned side by side, with a space of at least 0.3 metres between them (see Figure 11). Rolling carts may be used next to a cabinet to support the preparation activities. Smoke
pattern tests may be performed at the time of certification to confirm that the layout does not interfere with the laminar flow inside the cabinet.

**Non-Sterile Preparation Cabinets**

Regarding non-sterile preparation cabinets, ASSTSAS recommends that Class I biological safety cabinets exhausted to the outdoors may be used; when available, and Class II B2 or B1 cabinets may also be used.

At the very least, a work area should be dedicated. Physical monitoring must be performed on a regular basis. The aim is to monitor whether the BSC is performing to specification. A series of physical tests must be carried out upon installation, whenever changes are made to the installation (for example replacement of a HEPA filter), and on a regular basis as a preventative measure. Physical tests include checking the integrity of the HEPA filters (DOP test), checking the airflow velocity, checking the air circulation (smoke test), checking the airflow retention (KI [Potassium Iodide] disk test), checking the pressure, checking particulate contamination, checking temperature and humidity, and also a noise test.

The frequency with which these tests should be conducted varies according to the test. The leak test (BSC Class III and Isolators only) and the smoke test should be performed monthly. Air velocity and particulate count tests should be done every three months, and the DOP test every 6–12 months. These tests are discussed more thoroughly below.

C-PECs must be maintained in accordance with the manufacturer’s recommendations but certified according to the testing standards detailed in the Controlled Environment Testing Association (CETA) application guides CAG-003, CAG-005 and CAG-002-2006 (current versions).

On its own, sterile 70% isopropyl alcohol cannot be used to decontaminate hazardous drugs and may in fact spread any chemical contamination that is present to other surfaces. Therefore, for daily activities such as disinfecting the inside of a C-PEC, a surface decontamination step using an appropriate agent must precede the usual disinfection step with sterile 70% isopropyl alcohol.