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IN-DEPTH REVIEW

Occupational toxicology and the control of exposure to pharmaceutical agents at work

S. P. Binks

Background	The pharmaceutical industry employs >350 000 people worldwide in operations including research and development (R&D), manufacturing, sales and marketing. Workers employed in R&D and manufacturing sectors are potentially exposed to drug substances in the workplace that are designed to modify physiology and also to chemical precursors that are potentially hazardous to health. Pharmaceutical workers are at risk from adverse health effects, including occupational asthma, pharmacological effects, adverse reproductive outcomes and dermatitis.
Aim	This study aimed to describe the approaches taken by pharmaceutical companies for identifying and communicating potential adverse health effects that may result from workplace exposures and in setting 'in-house' exposure control limits and to highlight the challenges in controlling workplace exposures to increasingly potent compounds.
Method	The literature was reviewed by searching the Medline and HSELine databases.
Results	The findings are presented in five sections, covering: test methods and approaches to occupational toxicology; hazard communication; approaches to setting health-based occupational exposure limits for pharmaceutically active agents; recent approaches to risk control; and occupational hygiene and exposure controls.
Conclusion	Significant efforts have been directed at predicting and evaluating potential occupational health hazards in the pharmaceutical industry. The pharmaceutical industry has provided leadership in controlling exposure to hazardous substances. Much of this work has been driven by a real need to control occupational exposures to substances that can have profound adverse health effects in exposed employees and that are becoming increasingly more potent.
Key words	Occupational exposure limit; occupational exposure to pharmaceuticals; occupational hygiene; occupational toxicology.
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Introduction

Pharmaceutical companies have long recognized that the development and manufacture of pharmacologically active agents can lead to undesired pharmacological or other adverse health effects if exposure in the workplace is not adequately controlled [1]. A review of the health effects related to occupational exposure to active pharmaceutical ingredients is presented in a related article in this in-depth review [2]. Reports of adverse health effects resulting from occupational exposure to chemical intermediates handled during the manufacture of the active pharmaceutical ingredient are rare [3,4]. However, some later-stage intermediates may possess pharmacological activity, whilst many have the potential to exhibit classic toxicological effects more typical of industrial chemicals. In addition to isolated intermediates, manu-

GlaxoSmithKline Corporate Environment, Health & Safety, Ware, Hertfordshire, UK.

Correspondence to: Dr Stephen Binks, Corporate Environment, Health & Safety, GlaxoSmithKline, Park Road, Ware, Hertfordshire SG12 ODP, UK.
e-mail: sb17854@gsk.com

facture of pharmaceuticals also involves chemicals such as solvents, catalysts, acids and bases.

It is clear that methods for predicting hazardous properties, ensuring that any known health hazards are adequately communicated to the workforce, and the evaluation and control of potential occupational exposures are required to avoid potential adverse health effects.

In this review, the methodology used to predict potential health effects resulting from occupational exposures to pharmaceutical agents and chemical intermediates, and approaches to setting health-based occupational exposure limits (OELs) and generic control bands are reported. In addition, some approaches taken to control exposure to dusts in pharmaceutical manufacturing are described.

Method

To inform the review, an electronic search of the MEDLINE (1966–October 2002) and HSELINE (1995–October 2002) databases was conducted using subject heading and key word search terms for pharmaceutical industry, hazard evaluation, occupational exposure standards, hazard communication, COSHH, exposure controls, containment, personal protective equipment and occupational hygiene. All of the abstracts were reviewed and relevant articles retrieved. The bibliographies of retrieved papers and reviews were checked for further relevant material. The findings are presented in five sections, covering: test methods and approaches to occupational toxicology; hazard communication; approaches to setting health-based OELs for pharmaceutically active agents; recent approaches to risk control; and occupational hygiene and exposure controls.

Findings

Test methods and approaches to occupational toxicology

The focus of the occupational toxicologist in the pharmaceutical industry is to identify potential adverse effects that are a result of occupational exposure to drug substances (and chemicals required to manufacture the pharmacologically active agent) that may be handled during research and development (R&D) and manufacturing activities. One of the challenges is to define what represents an adverse effect for an agent that is designed to modify biological function. 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. The discipline of occupational toxicology has gained momentum in the pharmaceutical industry over the last few years, with many of the global companies implementing programmes. Several reviews have been published outlining the basis of test methods employed and approaches to occupational toxicology [5,6] and a general review of toxicology testing recommended for worker safety has also been published by ECETOC, the European Centre for Ecotoxicology and Toxicology of Chemicals [7].

Toxicological studies are an important part of the pre-clinical safety evaluation of potential new drug substances, as they are used to determine whether it is safe to administer the compound to humans clinically. This pre-clinical safety evaluation of pharmaceuticals is tightly regulated by national agencies such as the US Federal Food and Drug Administration (FDA), and many data, such as acute and repeat dose toxicity by clinically relevant routes, reproductive toxicity, genotoxicity, carcinogenicity and metabolism, are generated in a variety of animal species. These data, 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 as a result of occupational exposure to pharmaceuticals. Additional hazards that are of concern for occupational exposure are often distinct from the primary pharmacological effects. This is illustrated by the case of penicillins and cephalosporins that are designed for antimicrobial activity, but which are also known to induce allergic contact dermatitis and asthma in occupationally exposed individuals [1]. Therefore, the pre-clinical and clinical studies undertaken on pharmaceuticals to establish patient safety must be supplemented with additional toxicology studies to identify such effects as eye and skin irritation and sensitization. Isolated chemical intermediates and other chemical process materials used for pharmaceutical manufacture are not investigated in pre-clinical or clinical testing programmes; therefore, a distinct occupational testing schedule needs to be established for this class of materials. Additionally, these materials may also be subject to the requirements of the Notification of New Substances (NONS) regulations [8] and toxicological (as well as physico-chemical, and environmental fate and effects) data may need to be generated to support this regulatory requirement.

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 and very few new drug candidates 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 [9]. 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) [10,11]; physico-chemical characterization (e.g. pH, octanol–water partition co-efficient); automated high-throughput bacterial mutagenicity tests, e.g. SOS/*umu* assay [12]; and *in vitro* cytotoxicity tests to predict acute toxicity potential [13]. Since these tests can be conducted relatively quickly, they may be undertaken prior to any early small-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 [14] and eye irritation [15] 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* [16], skin sensitization using the local lymph node assay [17], skin and eye irritation using rabbit models [18,19] and an evaluation of acute toxicity [20]. 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) [21] and repeat-dose studies to establish target organs [22], may be conducted. Figure 1 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 programmes.

Hazard communication

Regulatory agencies throughout the world are increasingly enacting legislation requiring employers to implement hazard communication programmes to inform their workforce, customers and the public about the known hazards of the chemicals to which they may be exposed. In the UK, the current regulatory tools governing aspects of hazard communication are the Chemicals (Hazard Information and Packaging for Supply) Regulations 1994 as amended (the 'CHIP' regulations) [23], the Health and Safety at Work Act [24] and the Control of Substances Hazardous to Health Regulations (COSHH) [25]. Safety data sheets should conform to the requirements of the EU Safety Data Sheets Directive

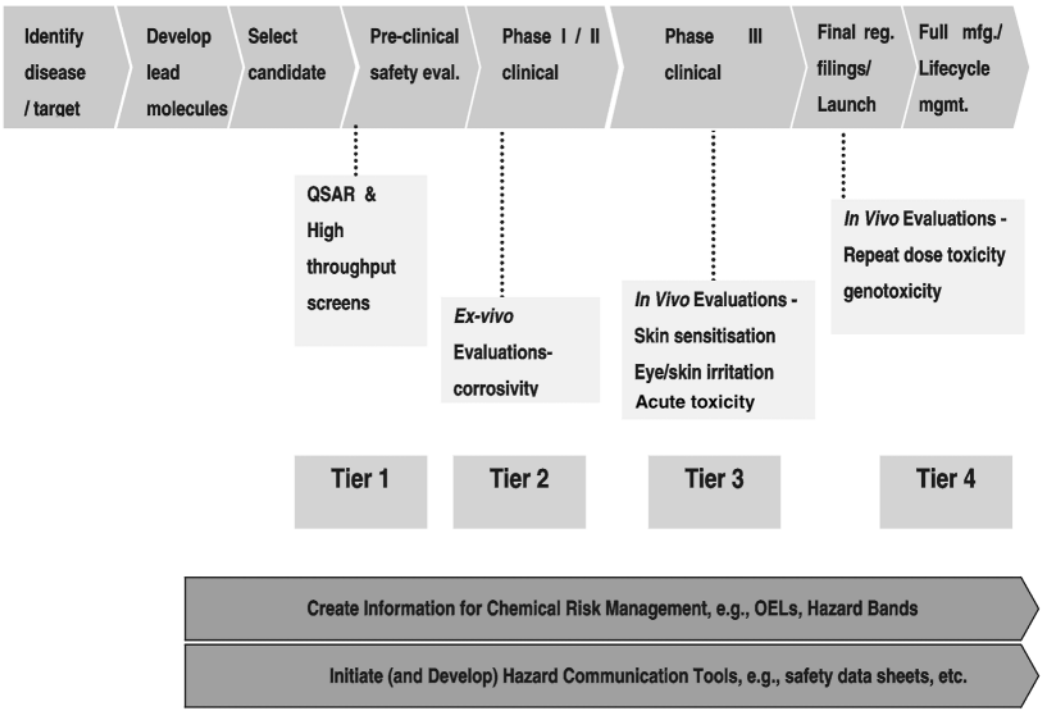

Figure 1. Alignment of occupational toxicology testing and pharmaceutical product development.

(91/155/EEC, as amended by Directive 2001/58/EC) [26], which specifies the content and layout of data sheets and the conditions that mandate the provision of a data sheet from a supplier to a customer. Since the introduction of these regulations in the UK, the presentation and content of safety data sheets have undoubtedly improved. However, a review undertaken by the Health & Safety Executive (HSE) in 1999 indicated that there is still a problem in getting accurate and understandable safe handling information to employees [27]. This finding has been replicated in countries having similar requirements for safety data sheets, such as the USA [28]. Various organizations in the UK, such as the Chemical Industries Association, have published guidance on the compilation of safety data sheets [29] to improve the quality of these documents, since it was recognized that they are fundamental to hazard communication and chemical control programmes, such as the COSHH Essentials scheme [30].

In the UK, while safety data sheets and labelling requirements are mandated by the requirements of CHIP, human or veterinary medicinal products, in their finished state, intended for the final user, are exempt from these requirements. However, many pharmaceutical companies realize that pharmacies, hospitals and physicians often require hazard information on formulated pharmaceutical products to fulfil their COSHH obligations and therefore produce safety data sheets and other documentation to meet customer demand and fulfil their product stewardship responsibilities.

One of the challenges in implementing hazard communication programmes in companies having a global manufacturing base is that many countries have their own specific regulatory requirements. For example, in the EU, a substance having an acute oral LD_{50} of 250 mg/kg would be described as 'harmful', whereas in the USA it would be 'toxic'. Companies must therefore prepare safety data sheets and labels specific to the country in which the substance is to be handled. Alternatively, they must try to develop 'harmonized' hazard communication tools that meet the spirit, if not the letter of the law, in as many countries as possible, in an effort to simplify the message and reduce the workload [31]. Harmonization of classification and hazard communication schemes is therefore desirable and may be accomplished in the future if jurisdictions adopt and implement the so-called 'Global Harmonisation Scheme' (GHS) [32], that aims to standardize hazard assessment, classification and communication practices throughout the world.

Approaches to setting health-based OELs for pharmaceutically active agents

The establishment of OELs as tools to prevent adverse health effects resulting from exposure to pharmaceuticals has largely been the result of in-house risk assessment efforts undertaken by pharmaceutical companies. In the UK, relatively few regulatory OELs have been established for pharmaceutical actives, with only aspirin, paracetamol and propranolol being listed in EH40 [33]. Procedures used to establish in-house OELs for pharmaceuticals have been described previously by several authors [34–38]. The Association of the British Pharmaceutical Industry (ABPI) has also issued guidance [39]. Methodologies employed to set in-house limits are typically based on the traditional 'uncertainty' or 'safety' factor approach and are established on the basis of the available scientific data and not the feasibility or economic cost of controlling exposures in manufacturing facilities. As described previously, when setting OELs for new pharmaceutical actives, the entire pre-clinical and clinical data package developed to support the drug registration is reviewed. Any supplemental studies, such as irritation or skin sensitization, specifically designed to evaluate effects of occupational exposures are also evaluated and an endpoint that is the most sensitive adverse effect considered to be relevant to human occupational exposure is identified. This 'lead effect' is often an endpoint related to the pharmacological action of the drug substance. The dose response for this 'lead effect' is then examined so that a 'no observable adverse effect level' (NOAEL) can be identified. This is then corrected for body weight (BW) and divided by the volume of air (V) breathed by a worker in 8 h (typically, 10 m^3 is used as a default) and an appropriate uncertainty factor (UF) is selected. The OEL may also be adjusted to account for differences in bioavailability (α) between the inhaled route and the clinical route from which the NOAEL was derived, and for steady-state (S) plasma concentrations if they are higher due to accumulation following repeated exposures [35]. Therefore the OEL can be described as:

$$\mathrm{OEL} = \frac{\mathrm{NOAEL\ (mg/kg)} \times \mathrm{BW\ (kg)}}{\mathrm{UF} \times \mathrm{V\ (m^3)} \times \alpha \times \mathrm{S}}$$

Traditionally, 100-fold uncertainty factors with a value of 10 each to account for inter-individual variability and interspecies extrapolation have been employed. However, greater efforts have been made recently to derive more scientific uncertainty factors based upon quantifying inter-individual variations in kinetics and dynamics on a compound-specific basis from human clinical trial data [40–42]. This methodology typically allows for reduction in the size of the uncertainty factor for drugs that are well tolerated at a wide range of dosages and eliminated rapidly and gives risk managers important information to help them make decisions regarding adequate, cost-effective exposure control strategies.

Most companies have realized the importance of

preparing a written monograph summarizing the rationale for setting the limit. This is necessary to ensure that other stakeholders, such as occupational hygienists, physicians, engineers and line management, are engaged in the limit-setting process. This monograph 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.

Recent approaches to risk control

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 [43,44]. This generic control approach, sometimes known as 'exposure banding' or 'performance-based exposure control', uses available toxicological or pharmacological properties to assign the substance to one of four or five discreet occupational hazard bands. These bands correspond to a strategy known to provide the necessary degree of workplace exposure control to protect employees. These controls range from conventional open handling for low hazard materials to those involving closed systems, or robotics for extremely potent or hazardous substances. While assignment of active pharmaceuticals to an appropriate hazard band is typically undertaken with some knowledge of likely pharmacological potency and mechanism of action, the scheme is easily genericized and adapted to a ranking based upon toxicological hazard. For example, one could use the risk phases assigned to substances as described in Annex I of the EC Dangerous Substances Directive or by suppliers under the CHIP Regulations [45–47] to make appropriate assignments. This information is readily available in safety data sheets and on supply labels and thus is accessible to small or medium-sized companies who may not have access to the specialist toxicological or medical knowledge necessary to set an OEL. It is for this reason that occupational hazard banding based upon risk phrases has become the technical basis for selection of appropriate control strategies as described in the HSE COSHH Essentials guide [30].

Occupational hygiene and exposure controls

Examination of the few OELs for pharmaceutical agents cited in EH40 might lead to the conclusion that control of exposure would not be a great challenge for this class of substance. However, with a better understanding of disease mechanisms, pharmaceuticals are now being developed that are more targeted to specific receptors or that inhibit specific enzymes. Typically, this increasing specificity has lead to increased potency, resulting in lower occupational exposure limits and more stringent workplace control requirements. Therefore, whereas the OELs for substances such as aspirin or paracetamol are in the mg/m^3 range, the majority of newer pharmaceuticals require exposure controls that reduce workplace exposure to levels <100 μg/m^3, with some in the sub-μg/m^3 range. These extremely low control limits not only present a significant challenge for bulk pharmaceutical manufacturing operations in controlling dust during solids handling, but also present significant challenges to the occupational hygienist when developing appropriately sensitive personal air sampling and analytical methods [48]. In the primary manufacture of the active pharmaceutical ingredient, operations such as drum charging, unloading reaction vessels, sampling, drying and milling can lead to short-term personal exposures in excess of 10 mg/m^3 in the absence of appropriate controls. Due to the complexity of dosage forms produced, formulation of the drug product ('secondary manufacture') can involve a variety of operations including sieving, compressing, granulating, filling and packing, with dispensing of the drug active required for formulation producing the greatest potential for high exposures. However, the active drug substance is typically diluted with other less hazardous materials such as excipients to produce the product, resulting in lower exposure than encountered in primary manufacture.

The challenges represented by the development of potent new compounds and the potential for dusty operations in both primary and secondary manufacturing has led to the development of high containment techniques. This has resulted in the use of novel engineering control methods such as ventilated enclosures, glove boxes, contained transfer couplings and use of continuous liners or bags [49,50]. In practice, successful control of exposures sometimes requires a combination of engineering containment and personal protective equipment (PPE) such as gloves and respirators. However, it should be recognized that both powered respirators and air-supplied air suits can significantly under-perform compared to their design specifications due to inappropriate use, poor user training or poor fit [51]. Guidance on the selection, use and maintenance of respiratory protective equipment has been issued by the ABPI [52].

Occupational exposure to airborne active pharmaceutical ingredients is usually assessed by personal air sampling of the inhalable dust fraction in the breathing zone of the operator. There is no ideal, universally accepted sampling device for pharmaceutical dust, although the IOM inhalable dust sampler using 25 mm filters is the most scientifically well-characterized and popular personal sampler available. In dealing with potent compounds possessing low OELs, background contamination of filters and poor sample stability can be a significant problem and the re-use of sample holders is not recommended [48]. Another problem with measurement of airborne levels of potent compounds is sample analysis. Suitably validated analytical methods need to be developed specifically for the purpose of the occupational hygienist [53] and frequently require the use of specialized analytical methods such as gas chromatography/mass spectroscopy (GC/MS) [54] or high performance liquid chromatography (HPLC) with fluorescence detection [55] to achieve the sensitivity required. It is therefore not surprising that routine substance-specific airborne monitoring is not a widespread practice and that more reliance is now placed on validating performance-based exposure controls [44].

Conclusions

The most obvious occupational heath hazards in the pharmaceutical industry are related to exposure to the biologically active compounds that are being developed and manufactured as pharmaceuticals. Although the literature carries reports of adverse health events in workers exposed to these substances, significant efforts have been directed at predicting and evaluating potential occupational health hazards and effectively communicating them to the workforce so that appropriate work and containment practices can be designed and implemented.

The pharmaceutical industry has provided leadership in a number of key areas, including: the adoption of tiered approaches to occupational toxicology testing that utilize non-animal predictive methods; the methodology for setting in-house exposure control limits; the design and promotion of the use of performance-based control approaches now being promoted in COSHH Essentials as an aid for controlling exposures in small and medium-sized businesses; and the implementation of novel engineering solutions. Clearly, much of this work has been driven by a real need to control occupational exposures to substances that can have profound adverse health effects in exposed employees and that are becoming increasingly more potent.

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