Applying Health-Based Risk Assessments to Worker and Product Safety for Potent Pharmaceuticals in Contract Manufacturing Operations

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Abstract

In the manufacture of potent active pharmaceutical ingredients (APIs) and products, there is a need to conduct qualitative and/or quantitative health-based risk assessments for both occupational and product (patient) safety purposes. When performed from an occupational standpoint, qualitative health-based risk assessments involve the categorization ("banding") of the API based on toxicity and potency, which provides a measure of relative hazard. Each occupational health categorization is then linked to task-specific safe handling practices for worker protection purposes. Alternatively, quantitative occupational health-based risk assessments involve the development of Occupational Exposure Limits (OELs) and Acceptable Surface Limits (ASLs), ("safe" or acceptable concentrations of contaminants in the air or on work surfaces, respectively) which allow the contract manufacturing organization (CMO) and/or the drug innovator to quantitatively assess worker exposure potential through industrial hygiene air and surface monitoring. Without quantitative risk and exposure assessments, a determination of the acceptability of containment, controls and work practices cannot be fully made.

From a product safety perspective, multi-purpose plant manufacturing operations need to be able to adequately clean product contact surfaces to prevent cross-contamination of one product to the next. Previously adopted approaches had established safe or acceptable limits based on a percentage of the human therapeutic dose or on the lethal dose in laboratory animals. More scientifically supportable health-based risk assessment approaches are currently employed, which establish an Acceptable Daily Intake (ADI) for amount of material into next product. The ADI for product cross-contamination protection is then employed by the CMOs Quality Assurance department to determine a cleaning limit for the API in the process or specific piece of equipment and to establish quantitative targets for analytical methods.

OEL, ASL and ADI determinations are similar because they all require evaluation and interpretation of toxicological, pharmacological, and clinical data, selection of the appropriate critical studies/endpoints for assessing health risk to workers or patients, and extrapolation to acceptable levels from these studies. With potent compounds, health-based risk assessments are especially needed to be adequately protective for worker or patient safety because of their potentially serious toxicity profiles. The appropriate application of health-based risk assessments can assist both the drug innovator and the CMO to determine the adequacy of controls, work practices and procedures for worker and product safety at the CMO's facilities.

Introduction

In the past two decades, there has been an increasing use of CMOs paralleled by the development of more potent and toxic APIs. This article is intended to provide a brief introduction to methods for health-based risk assessments that are being implemented with increasing frequency in the pharmaceutical industry by drug innovators, CMOs and regulatory authorities. The ability of the CMO to appropriately conduct and document their health-based risk assessments should be determined by drug innovators as a matter of due diligence, in order to qualify the CMO to adequately manufacture potent APIs and products.

Occupational Health Categorization and Banding

In the pharmaceutical industry, because novel compounds are constantly being synthesized and developed, qualitative health-based approaches have been developed to assess and communicate the potential health hazards of these novel compounds to workers. This approach, called "categorization" or "banding," typically places compounds into one of several bands or categories depending on the anticipated potency and toxicity of the compound. A corresponding set of handling guidelines is "linked" to the category or band. This has been described as a "hand-in-glove" system where compound characteristics are matched to task-specific safe work environment descriptors. Without a qualitative health risk-based determination, acceptable handling practices as well as containment and control procedures cannot be established. Most companies, including many CMOs, employ these systems, which are typically 4- or 5- category or band systems for the handling of potent compounds.

The SafeBridge "Occupational Health Toxicity / Potency Categorization and Handling Practices" system (1, 2) is a four-category system that has proven useful for a number of drug innovators and CMOs over the past decade or more. The placing of a material into a category or band is not based on determination of the Occupational Exposure Limit (OEL) but is primarily based on the qualitative aspects of the toxicity and potency of the API. It is critical to understand that placing a compound into a category should be based on a health-based risk assessment of the data and professional judgment regarding the most important factors to consider. Criteria employed are listed in Table 1. It is common that only one or two criteria are used to place a compound into a category, and it is not expected that all the listed criteria will be relevant in all cases. To properly categorize a compound, a document should be developed that establishes the data that were reviewed and clearly states the basis and criteria used for determining the category or band.

Table 1. Criteria used to determine occupational health category or band of an API

Therapeutic Dose
Bioavailability
Pharmacological Mechanism of Action
Severity of Potential Clinical Effects
Target Organ Toxicity
Reproductive and Developmental Toxicity
Carcinogenicity
Mutagenicity/Genotoxicity
Sensitization Potential
Acute Toxicity
Other Elements – If insufficient data are available; If there is a sensitive subpopulation of concern

In general in the SafeBridge categorization system, Category 1 materials may have irritating qualities but limited or no systemic organ effects, and no permanent or "-genic" effects [["Genic" effects include mutagenicity, carcinogenicity, developmental toxicity (which may include teratogenicity) and reproductive system toxicity]. Category 2 includes a wide variety of pharmaceutical substances and can be characterized by materials that have organ system effects such as on the heart, liver, lung, etc., but limited or no "-genic" effects at doses expected to be encountered in the workplace. Category 3 materials are considered potent and/or toxic and include substances that can elicit health effects at low doses (i.e., potent) and may cause permanent and potentially severe effects such as "-genic" effects at doses expected to be encountered in the workplace (i.e., toxic). Category 4 is reserved for ultra-potent and/or ultra-toxic materials that have permanent and potentially severe effects at extremely low doses. Category 4 also includes materials that may have a severe effect at low doses on sensitive sub-populations of the workforce such as women of child bearing potential, and asthmatics. Category 3 (Potent/Toxic) is the default category in this system, as it is assumed that a compound may be toxic or potent if limited data to make a determination are available.

A general overview of handling recommendations and basic descriptors of safe work environments can be found in other references (1, 2). CMOs should have defensible documentation of the scientific rationale for assigning a category and apply a safe handling practice system to each API or novel chemical being manufactured. Most importantly, workers need to know the meaning of the categorization and handling practices associated with the category or band. However, categorization should only be used as an interim step in the risk and exposure assessment process for potent compounds, as it is primarily a qualitative risk assessment. Quantitative health-based risk assessments, as described in the following sections, together with exposure assessment and quantitative analytical determinations should ultimately be used assess the acceptability of worker safety approaches at the CMO and drug innovator.

Setting Acceptable Airborne Limits for APIs

The primary route by which workers are exposed to chemicals in the workplace, including drug substances, is by inhalation. For the most part, drugs are powders and any handling of powders may result in airborne dispersion. For highly potent compounds, very small amounts may pose a health concern, even at airborne concentrations that cannot be seen. One of the approaches that is commonly used to protect workers from inhalation exposure is to determine an acceptable or "safe" airborne concentration of these compounds. This value is generically called an Occupational Exposure Limit (OEL). US OSHA refers to these as Permissible Exposure Limits (PELs) and the American Conference of Governmental Industrial Hygienists (ACGIH), a non-governmental body of occupational health professionals, refers to these as Threshold Limit Values (TLVs®). OELs, PELs, and TLVs® are usually defined as:

> *"Airborne concentrations of substances under which it is believed that nearly all workers may be repeatedly exposed day after day without adverse health effects, usually for 8 hours per workday, 40 hours per week, over one's working lifetime."*(3)

ACGIH has been setting TLVs® since 1939 and this list of TLVs® is updated yearly. The Occupational Safety and Health Act was passed in 1970 and under the Act it adopted the TLVs® established as of 1968 as PELs. Since 1970, very few chemicals have been added to the list of enforceable limits under OSHA and very few limits have changed. Thus, even though the PELs and not the TLVs® are enforceable, many companies opt to comply with TLVs® when these values are more stringent than PELs.

When one looks at the list of TLVs® or PELs, very few pharmaceuticals are found. This is in part because ACGIH and OSHA are primarily interested in chemicals that might affect a large number of workers. Airborne exposure to pharmaceuticals tends to be relevant only to employees of specific drug innovator and their CMOs. Because of this, pharmaceutical companies have started developing their own OELs.

The traditional approach for determining an OEL is to identify a no-observed-effect level (NOEL) from animal or human studies and then to apply appropriate safety or uncertainty factors, based on the perceived robustness of the data (4-9). A typical equation used for determining an OEL by this approach is:

$$OEL = [(NOEL)] / [(SFn)\ (\alpha)\ (V)] \text{ (for doses in mg)}$$

Or

$$OEL = [(NOEL)\ (BW)] / [(SFn)\ (\alpha)\ (V)] \text{ (for doses in mg/kg)}$$

Where:

- NOEL = No-Observed-Effect Level for the endpoint of concern (sometimes called a NOAEL or No-Observed-Adverse-Effect Level);
- BW = Body weight of an adult worker, typically assumed by default to be 70 kg;
- α = Absorption factor – factor to account for differences in absorption by route of NOEL to absorption by inhalation which in the absence of quantitative data is assumed to be 100%
- SFn = A number of safety factors which consider uncertainties in the data (such as animal-to-human extrapolation, human-to-human variability in response, and severity of the endpoint being considered); and
- V= Volume of air inhaled during an 8-hour workday, typically assumed by default for a 70-kg adult worker to be 10 m3.

A modifying factor (MF) may also be added to the equation in cases where there is a potential for bioaccumulation or to account for lack of data.

If an appropriate NOEL cannot be identified, then an appropriate Lowest-Observed-Effect Level (LOEL) may be used. To extrapolate to a NOEL, the LOEL is typically adjusted by a safety factor of up to 10, depending on the severity of the adverse effect. For instance, if the LOEL is for minor liver toxicity, the safety factor used may be 3; if it is for a more serious effect (e.g., developmental toxicity), a safety factor of 10 or more may be used. Other issues including the quality of the available data are considered for the determination of the magnitude of this and the other safety factors.

OELs can be developed during R&D of the API, depending on the availability and robustness of the data. Customarily, at Phase IIb of development, the drug innovator has sufficient information to make this determination. CMOs can assist by encouraging this process be completed by or for the drug innovator, and should conduct quantitiative exposure assessments to assess compliance with the OEL.

Setting Acceptable Surface Limits for Worker Contact Surfaces

The other major route of occupational exposure is by dermal contact; dermatitis is the most common reported occupational disease. An API may exert a local effect or may be absorbed through the skin and cause the pharmacological or toxicological effects of the drug or drug product. When these materials are in the presence of permeation-enhancing solvents and adequate gloves are not worn, the probability of absorption increases.

Development of Acceptable Surface Limits (ASLs) is relatively new compared to airborne limits. This is because there is a paucity of data on dermal absorption of chemicals, including drugs, unless they are topically administered. While certain toxicity tests may be helpful in predicting whether a compound may cause a local effect, a compound's ability to cause a local skin effect in workers often is discovered after-the-fact. In such situations, the extent of skin exposure may not be readily known. For a compound to cause systemic effects, an understanding of the rate of absorption through the skin is needed. Skin absorption is dependent on many variables including: location of skin in contact with the compound, the extent of hydration of the skin, skin pH, skin integrity, physico-chemical properties of the compound, concentration or amount of the compound in contact with the skin, the length of time in contact with the skin, and metabolic transformations that might occur in skin cells. Thus, the amount of the compound that is absorbed is difficult to predict.

Even though it may be difficult to set ASLs, surface sampling can be helpful in a qualitative way, such as to determine whether: (1) housekeeping and cleaning measures are adequate, (2) engineering containment approaches are adequate, or (3) the chemical is present in areas of a facility where the chemical ought not to be present, such as lunch rooms or administrative offices. The detection of a chemical on surface samples in work areas where it should not be present or on the outside of final product packages or drums may help to identify how the chemical is getting to those places (e.g., as a result of ineffective containment, processing equipment, cleaning, and/or administrative controls).

There are several approaches for calculating an ASL due to the uncertainties discussed above. One is similar to the OEL calculation previously mentioned:

$$ASL = [(NOEL)] / [(SFn)\ (\alpha)\ (SA)] \text{ (for doses in mg)}$$

Or

$$ASL = [(NOEL)\ (BW)] / [(SFn)\ (\alpha)\ (SA] \text{ (for doses in mg/kg)}$$

Where:

- SA = Surface area potentially contacted, typically assumed to be 100 – 200 cm^2 for the average adult (approximately the surface of 1-2 palms).

Setting Acceptable Daily Intakes (ADIs) for Quality Assurance Purposes

There is an inherent risk in a multi-purpose pharmaceutical or chemical facility for material from one process, product or piece of equipment to "carry over" to the next process, product or piece of equipment. This may include the API itself, cleaning agent(s), decomposition products, intermediates, excipients, or other residues. To ascertain that the levels of these trace materials are acceptable or "safe," health-based risk assessment approaches have been employed which are more scientifically robust than arbitrary approaches based on a proportion of the therapeutic dose, such as 1/1000th of the therapeutic dose, especially for potent pharmaceuticals.

An ADI represents an estimate of a daily exposure to the potential patient population that is likely to be without an appreciable risk of deleterious effects during an average lifetime. The concept of ADI arose from regulatory action by the US Food and Drug Administration (FDA) to limit residues of potentially toxic or hazardous materials in food. Other terminology has similarly been employed for determining acceptable or "safe" limits for low concentrations of materials by other authoritative bodies. These terminologies include Reference Dose (RfD) and Reference Concentration (RfC) used by the US Environmental Protection Agency (EPA), Permissible Daily Exposure (PDE) used by the International Conference on Harmonization (ICH) Q3 Guidelines on Residual Solvents, and Minimum Risk Levels (MRL) of the US Agency for Toxic Substances and Disease Registry (ATSDR) (10). Like the OEL and ASL descriptions above, ADIs and the other terms just described have as a common element the determination of an acceptable daily amount of a material by selecting a NOEL and applying safety or uncertainty factors to establish a "safe" level. Other risk assessment approaches may be used on occasion, such as for carcinogens, where if the percent response rate is available from animal bioassays, it is possible to extrapolate from known responses at "benchmark doses" to acceptable levels of risk (e.g., 1:10,000 or 1:100,000). The typical approach for calculating an ADI is similar to the formulas previously described for OELs and ASLs, and is as follows (11):

$$ADI = NOEL\ (BW) / (SF)\ (MF)$$

The major differences between calculating an ADI and an OEL are that the ADI is for patient safety, is expressed as mg (or µg) per day, and may need to consider sensitive subgroups that may take the next drug (e.g., elderly and children), where as the OEL is for worker safety, is expressed as an airborne concentration ($\mu g/m^3$), and is applied to a healthy working population.

Once calculated, the ADI can then be used to establish cleaning limits for equipment and processes employed to make the API or drug product. The cleaning limit should account for the dose of the next drug, amount that can come off all surfaces that may come into contact with the drug (product contact surface area), and the batch size, to validate that no more than the ADI will end up as residue in the next product. CMOs should have defensible documentation of the scientific rationale for health-based ADIs to support their cleaning validation programs.

Appropriate Development of Health-Based Risk Values for Worker and Patient Safety

To appropriately develop health-based risk values such as ADIs, OELs and ASLs, an appropriate assessment of the available data is needed. Both animal (nonclinical) and human (clinical) studies, some of which are complex to interpret, and any of which may critically affect the health-based value should be evaluated. The individual performing the assessment may find that determination of the LOEL or NOEL of the drug is not a simple task. In addition, the uncertainties associated with the data must be understood including uncertainty in extrapolating from:

- Effects observed at high doses to predict the adverse health effects that may occur following exposure to the low levels that may occur occupationally or in patients;

- Variability between animal studies in homogeneous populations and a heterogeneous human population;
- Variability between humans; and
- Extrapolation from results of short-term studies to predict potential chronic effects.

Therefore, it is recommended that these assessments be performed by qualified health professionals and that the determinations be documented. Where applicable, calculation of each health-based value should be performed from multiple endpoints or "points of departure,", such as from both nonclinical toxicology and clinical data. Appropriate safety or uncertainty factors should be applied to each point of departure to arrive at the values. Then, each calculation should be evaluated for relevance to human (worker or patient) health to arrive at a supportable health-based value.

CMOs need to establish OELs, ASLs and ADIs for their most potent drugs, and to ensure that sufficient systems are available to use these values to protect their workers and patients. The principles of employing OELs and ASLs (to some degree) have been well-established for worker safety. An OEL established using a health-based approach can assess the adequacy of containment, controls and work practices through industrial hygiene air and surface sampling.

The International Society of Pharmaceutical Engineering (ISPE) is in the process of establishing the ADI as a risk-based tool to employ for safely manufacturing APIs and products in the Risk-Based Manufacturing of Pharmaceutical Products (Risk-MaPP) guideline initiative currently under review and to be issued in late 2009 or early 2010. By appropriately applying the ADI to cleaning limits for APIs in a multi-purpose plant, these facilities will be able to have greater confidence that residual levels will be below acceptable levels based on sound scientific judgment and application of risk-based approaches; this will result, hopefully, in further protecting the supply of high-quality APIs and drug products.

Summary and Conclusion

Approaches have been presented to determine and calculate OELs, ASLs, and ADIs for worker protection and patient safety. Significant interpretation and assessment of human and animal studies is needed to arrive at these values. CMOs and drug innovators need to determine these values, especially for potent compounds. The OEL, ASL and ADI determinations are similar because they all involve: interpreting toxicological, pharmacological, and clinical data; selection of the appropriate critical studies for assessing health risk to workers or patients; and extrapolation to acceptable levels from these studies. Health-based risk assessments are especially needed for adequately protecting against exposure to potent compounds because of their potentially serious toxicity and potency profiles. The appropriate application of health-based risk assessments will assist both the drug innovator and CMO to determine the adequacy of controls, work practices and procedures for worker safety and product safety at the CMO

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