A Publication of Affygility Solutions

Potent Compound Safety

HANDBOOK

A guide to working with potent compounds

TABLE OF CONTENTS

CHAPTER ONE

WHAT IS A POTENT COMPOUND?

What is a Potent Compound?

While there may be many definitions of a potent compound, the definition that we at Affygility Solutions like to use is as follows:

"A Potent Compound is defined as a pharmacologically active ingredient or intermediate with biological activity at 150 ug/kg of body weight or below in adults (therapeutic dose at or below 10 milligrams); an active pharmaceutical ingredient or intermediate with an occupational exposure limit (OEL) at or below 10 ug/m^3 of air as an 8-hour time weighted average; a pharmacologically active ingredient or intermediate with high selectivity (i.e. ability to bind to specific receptors or inhibit specific enzymes) and/or the potential to cause cancer, mutations, developmental effects, or reproductive toxicity at low doses (at or near the therapeutic dose or lower); or a novel compound of unknown potency and toxicity."

However, it is important to remember that this definition is not in any regulatory text and that the definition may vary from company to company.

CHAPTER TWO

Eight steps to getting your potent compound safety program started

Eight steps to getting your potent compound safety program started.

1. **Identify the business value.** Determine both the cost-reduction and revenue-generating strategies that you plan to follow. Understand how you will "sell" your business case to executive management. See this article for additional information.
2. **Obtain executive management support.** This is critical. Implementing a potent compound safety program is a team effort and will require both monetary resources and time. Charging full-steam ahead without first obtaining executive management support is setting your program up for failure.
3. **Prepare an inventory of all active pharmaceutical ingredients that are in your company's product pipeline or current market portfolio.** Visit your company's website and determine what products are already approved and marketed, and what products are in late stage development (Phase II or III). These are your high-priority items.
4. **Determine the occupational hazard categories for these compounds.** At this stage, it really doesn't matter whether you use a four- or five-control band system. The main focus should be to get just enough information be able to conduct a risk assessment. OEL Fastrac monographs make this step easy.
5. **Perform baseline risk assessments of all unit operations and activities.** This is a critical step. Using a risk assessment tool such as Affytrac can greatly streamline the process.
6. **Implement and validate additional controls where the risks are unacceptable.** Additional controls can include engineering controls, administrative controls, and personal protective equipment.
7. **Perform industrial hygiene monitoring to determine the effectiveness of the additional controls. Implement additional controls as necessary.** At this point, based on your industrial hygiene results, you will begin refining your control banding system and will begin determining whether a four- or five-control band system works best for your company.
8. **Communicate results and perform periodic audits.**

CHAPTER THREE

What determines the category?

Understanding Occupational Health Categorizations (OHC) vs. Control Bands

When determining the occupational health categorization (OHC) of an active pharmaceutical ingredient (API), it's important to understand that the OHC of a specific active pharmaceutical ingredient is determined by reviewing the entire toxicological profile of the API. Therefore, the OHC is based solely on the toxicology of the compound and the OHC doesn't change based on scale or whether it's in a solution.

When determining the OHC, there is at least 16 factors that should be considered. These factors can include acute toxicity, warning properties, chronic toxicity, severity of effects, reproductive and developmental effects, and many others.

It's also important to remember, that while we would like to think that there is a 1:1 relationship between the OHC vs. the Control Band, it may not always be the case. For example, you may have a compound with a fairly large numerical OEL, but have a concern over skin irritation. In that case, you might assign it to a higher control band to further prevent skin exposure.

CHAPTER FOUR

10 MYTHS REGARDING PDEs, ADEs, AND OELs

10 Myths regarding PDEs, ADEs and OELs.

Here at Affygility Solutions, we frequently engage in conversations with pharmaceutical professionals from all over the world regarding dedicated facilities and the underlying concepts of permissible daily exposures (PDEs), acceptable daily exposures (ADEs), and occupational exposure limits (OELs) for active pharmaceutical ingredients. Often, we field questions that are similar in nature and unfortunately are just unsupported information, which I will call myths. These myths are as follows:

1. **Isn't there some magical database or computer program available on the Internet that will provide both the OEL and ADE for free?** Sorry there isn't, so you can stop wasting your time searching for one **right now.** There's several reason why this "free database" doesn't exist. These reasons are as follows: i) two groups of professionals establish OELs and ADEs, either toxicology professionals internal to a pharmaceutical company or expert consultants. **Neither have the time or desire to work for free** and most get paid extremely well. Researching and preparing the necessary documentation to support an OEL/ADE takes time and effort. **Don't be naive and discount the value of an informational product or service just because it's not a hard tangible item (like a tablet press)**; and ii) the number of potential employees exposed to APIs in relatively small when compared to the number of employees exposed to general industrial chemicals (methanol, xylene, etc.). Governmental agencies, such as OSHA and UK's HSE, tend to focus their efforts on programs that will have the largest impact. Occupational exposures to APIs won't get much attention from governmental agencies unless it impacts the health of a large number of employees. (cont.)

In addition, OSHA doesn't even have the resources or political clout to even update their existing permissible exposure limits. Now, with the advent of the ADE/PDE requirements for multi-product pharmaceutical manufacturing facilities, these values have the potential to impact patient populations (which will be a much larger population than a worker population), so ADE and PDEs will get attention from the applicable regulatory agencies, but there are just too many API compounds for governmental agencies to devote resources to deriving the ADE and PDE for you. Even if they did, you wouldn't agree with their numbers anyway. Finally, you should also remember that the PDE, ADE, or OEL has the potential to impact multi-million dollar (or rupee) decision. Who you want to base that decision on some unsupported, "free" number that you found on the Internet? Get your numbers from credible sources.

2. **If you have two OELs or ADEs for the same compound, the lower number must be correct or a better number.** Wrong. A lower number might be right – or it might be wrong. You would have to critically review the OEL/ADE monograph documentation to make that determination (this is why having just a "number" is a worthless and dangerous practice). Lower OEL/ADE numbers might exist because someone selected a difference point of departure, or more commonly, the person calculating the OEL or ADE was not confident in their own technical abilities so they overcompensated by using larger uncertainty factors than what is necessary. It could also occur because an OEL/ADE for the compound was established when the compound was early in development and uncertainty was high. Remember, unnecessarily low OELs or ADEs cost a pharmaceutical company money, in terms of unnecessary engineering controls, elaborate work practices, or elaborate cleaning practices. The documentation for an OEL or ADE must present a reasonable scientific argument to support the number.

3. **Once an OEL or ADE is established for a compound, it will never change.** Nope, not true. As a compound moves through the pharmaceutical development process, I would expect the OEL/ADE to change. In addition, sometimes adverse health effects appear that did not show up in clinical trials. Therefore, the OEL and ADE must be revised.

4. **OELs and ADEs are a bright line between safe and unsafe.** OELs and ADEs are NOT precise numbers. They are protective, but not precise. OELs and ADEs are an extrapolation of a known dose (NOAEL, NOEL, lowest daily dose, etc.) to an unknown dose that is believe to be protective. (cont.)

over a long period of exposure. The more uncertainty factors you use, the greater the extrapolation, and the fatter the pencil will be. A difference between an OEL of 200 vs. 233 ug/m3 is a meaningless rounding difference. Don't overthink things and try to argue this point, you're wasting your time. Unfortunately, regulatory agencies don't help us out much here with their foolish practices of saying that if you're just barely over an OEL, you're in violation.

5. **The equations for both OELs and ADEs look pretty simply, I can do these calculations myself.** You can try, but unless you're an expert with the advanced education, training and experience, you will have a tough time defending yourself to regulators or an attorney when you get it wrong. In addition, the EMA is requiring a CV summary of the person preparing the PDE. Good luck defending your number if you don't have the relevant training, education, and experience on your CV.

6. **An OEL that is presented on a material safety data sheet is always correct.** Nope. Many are wrong. Some are really wrong. In addition, the SDS may be a legacy version and never get revised with a new number once new data is available. Furthermore, here at Affygility Solutions, we have seen the practice of one company copying incorrect information from one SDS to the next SDS, resulting in dozens of safety data sheets for APIs with incorrect information. Vet out your sources!

7. **OELs and ADEs must be certified**. Nope, no requirement to be certified. We hear this often from companies in the developing world, "We need certification." Certification in what? In addition, certifications of any kind by private companies are meaningless. Only certifications by independent accreditation organizations based on a consensus based standard have any worth.

8. **All I need is the OEL and ADE number. Give me the number for free.** A number without documentation and cited references is not credible or the approach is not verifiable and won't survive the rigor of a regulatory inspection. You won't get an OEL or ADE monograph for free.

9. **I've taken a webinar, seminar, workshop, or bootcamp on potent compound safety and OEL/ADE setting, doesn't that make me qualified to do this work myself?** Not going to happen. There are NO overnight experts in any field. Taking webinars, seminars, workshops and bootcamps are all good things, but all they do is provide you with an awareness level of understanding, so you know the right questions to ask. (cont.)

10. If the SDS says that the OEL is "not available", or that it is "not listed" by OSHA, ACGIH, or AIHA, then it must be "non-hazardous." Repeat after me, "not available" does not equal "non-hazardous." We have seen many SDSs that have the OEL listed as "not available" and these were for highly potent compounds.

So, there are my top 10 myths regarding PDEs, ADEs, and OELs. If you need a credible OEL or ADE for an active pharmaceutical ingredient, please check out our OEL Fastrac with ADE catalog. If your compound is not listed, please contact us about creating one for you.

CHAPTER FIVE

The future of OELs

Occupational Health and Exposure Limits for APIs – The Future

BY DEAN CALHOUN // SEPTEMBER 17, 2012

Many Drugs in need of Occupational Exposure Limits (OELs)

Like many occupational health professionals, I read a lot of material. Early today I was reading a 1961 Time magazine article titled, "Medicine: Too Many Drugs." In this article, Dr. Walter Modell of Cornell University Medical College, one of America's foremost drug experts, was quoted as saying. "No fewer than 150,000 preparations are now in use, of which 90% did not exist 25 years ago, and 75% did not exist ten years ago." Just think, that was over 50 years ago. Based on that quote, I decided to explore a little deeper and find out how many drugs are today actually on the market. I went to the FDA's National Drug Code (NDC) Directory and downloaded their spreadsheet of all approved drugs in the United States. Based on this spreadsheet there are 55,782 drugs listed. While certainly there is some duplication of active pharmaceutical ingredients due to different formulations, the number of active pharmaceutical ingredients is still easily in the tens of thousands. In addition, it is my understanding, that the NDC directory does not include vaccines, biologics, animal therapeutics, and pharmaceuticals that are approved outside to the United States.

OELs: A Significant Challenge for Occupational Health Professionals in the Pharmaceutical Industry

As many occupational health professionals in the pharmaceutical industry know, this many drugs on the market presents a significant challenge to the profession in preventing occupational exposures. While establishment of a potent compound safety program and placement or categorization of APIs in an appropriate exposure control banding strategy is an important first step, ultimately, if the drug is successful in the marketplace, in order to ensure that occupational exposure are prevented, you will need to develop an occupational exposure limit for the active pharmaceutical ingredient.

Internal Occupational Health Resources are Stretched Thin

For the larger pharmaceutical companies, they typically have access to internal occupational health resources to have occupational exposure limits developed for their later stage compounds. But even then, with many compounds being looked at everyday, their resources are stretched thin. This leaves as the only option, to use external resources to perform the (cont.)

review and the preparation of the occupational exposure limit monograph. Unfortunately, this takes qualified occupational health professionals, with advanced degrees and years of industry experience. In addition, the number of college graduates with advanced degrees in the toxicology field is not keeping pace with those toxicology professionals that are retiring.

Development of Occupational Exposure Limits is not a Trivial Activity

Development of a robust occupational exposure limit and preparation of the supporting documentation is not a trivial activity. It requires reviewing a significant amount of pre-clinical and clinical data, as well as external sources of information. All of this information can be very challenging to read and should be left up to occupational health professionals with advance degrees and experience. Here at Affygility Solutions, we have seen very talented EHS professionals make attempts at developing their own OELs. Unfortunately, more often than not, the Dunning-Kruger effect takes a strong-hold, and people tend to overestimate their own level of skill in this area. In addition, many of OELs that are developed by pseudo-toxicologists lack internal review. This presents several problems for the organization's potent compound safety program:

1. If the OEL is too conservative, significant amounts of money are spent on engineering controls that are not necessary or productivity is lost; or
2. The potential for employees to experience an occupational exposure to a potent compound exists; or
3. Valuable drug development time is lost while they are trying to figure it all out

Taking a cookie-cutter approach to development of occupational exposure limits for active pharmaceutical ingredients is not an adequate approach in any potent compound safety program.

Solving the Occupational Exposure Limit Challenge

So, what can be done to solve the occupational exposure limit challenge in the pharmaceutical industry? Several steps can be taken:

- Encourage young people to pursue advanced degrees in occupational toxicology or related fields.
- Mentor the undergraduates: Offer internships, speak at student chapters, etc. (cont.)

- Ensure that you have a robust potent compound safety program in place.
- Use technology to make OELs affordable to smaller pharmaceutical manufacturers.

Here at Affygility Solutions, in order to make high-quality occupational exposure limit monographs affordable to smaller companies, we have developed OEL Fastrac. OEL Fastrac is a convenient way to obtain OEL monographs for common active pharmaceutical ingredients. These OEL monographs have been prepared by expert occupational health professionals with advanced degrees, professional certifications, and decades of industry experience. Each of these monographs are available for instant download. To search for an OEL monograph for your compound, go to the OEL Fastrac.

Occupational exposure to active pharmaceutical ingredients can be prevented, but it does require a good understanding of potent compound safety, control banding principles and ultimately the development of occupational exposure limits.

'Once the OEL is determined, the occupational toxicologist will then use the OEL and other information to assign an OHC to the compound. Therefore, the OEL and OHC is based solely on the toxicology of the compound."

- D. Calhoun, CIH