18 April 2017

Dear valuable customer,

As a valuable OEL Fastrac customer you are provided with this revised OEL Fastrac guidance document.

The amendments/revision to this guidance document include the following:

Q29: Question regarding ADE/PDE route of exposure

If you would like to subscribe to the update email list for this document, please go here: https://sowl.co/QJ5ca and enter your name and business email. In order not to clutter your email inbox, we typically only distribute updates on a quarterly basis.

If you have any questions of general nature that you would like us to add to this guidance document, please e-mail me at dcalhoun@affygility.com

Best regards,

Affygility Solutions, LLC

Dean M. Calhoun, CIH
President and CEO

OEL Fastrac Guidance Document

Version 5 (rev. 22 March 2017)

DO's and DON'Ts of OELs and ADEs

- **DO** understand that OELs and ADEs are just one part of a risk assessment toolbox. Lowering an OEL number or ADE value does nothing to reduce employee exposure or reduce cross-product contamination. Reducing the probability of exposure or the probability of cross-contamination through improving controls and procedures actually plays a bigger role than the OEL or ADE in reducing risk.
- **DO** understand that OELs and ADEs are not precise numbers. I know this makes the quality groups cringe, but it's the truth. OEL and ADEs are an extrapolation from a "known dose" (such as a NOAEL or a therapeutic dose) to an "unknown dose" that is believed to be protective over a long period of time for a daily exposure scenario. As such, there are many assumptions that are entered into the basic OEL and ADE equations.
- **DO** understand that OELs and ADEs are not "bright lines" between safe and unsafe. In most cases, OELs and ADEs are protective over a wide range.
- **DO** understand that the goal is to reduce uncertainty factors, not increase them. The more you increase the composite uncertainty factor, the more you are indicating that you really don't know much about the compound. With more toxicological and human relevant data you can reduce uncertainty.
- **DO** understand that OELs and ADE values can change over time. As new information from either clinical data or market experience becomes available, this new information must be reviewed and considered if it is relevant enough to modify or revise the OEL and ADE. In addition, the "default" uncertainty factors used by the toxicology community may change or new regulatory guidance may be published.
- **DO** understand that the vast majority of OELs **are not** based on actual worker exposures. In fact, only a handful of OELs actually incorporate any data from actual worker exposures.
- **DO** understand that it is not always necessary to use PK factors in the calculation of the OEL or ADE. If the point-of-departure is based upon a repeat dose and steady state has been achieved, then the PK factors were considered in the setting of the repeat dose. Therefore, in most cases, it would be incorrect to reapply those factors.
- **DO** understand that departmental biases' may enter into the discussions when selecting OEL and ADEs. Typically, the manufacturing groups want "higher numbers" because they believe they can make anything and don't like the expense, hassle, and CMO limitations of additional engineering controls. On the other hand, the quality groups typically want "low numbers" just to be certain. Usually, the correct answer is somewhere in between.

- **DO** understand that setting OELs or ADEs unreasonably low can result in unnecessary costs in the form of additional engineering controls, loss of productivity, ergonomic hazards, project delays, elaborate analytical methods, and even the requirement for dedicated equipment or facilities.
- **DO** understand that an OEL number or ADE value without the underlying documentation is worthless.
- **DO** understand that when an SDS for an active pharmaceutical ingredient says that the OEL is "not available", or that it is "not-listed" by OSHA, ACGIH, or AIHA that it doesn't mean that it is "non-hazardous."
- **DO** perform containment validation and industrial hygiene monitoring to understand site-specific exposure levels.
- **DON'T** get into the practice of "OEL/ADE shopping" to support whatever cause you are supporting. Review the OEL/ADE documentation and understand if it makes logical sense.
- **DON'T** get into the practice of comparing OELs and ADEs values without having the underlying documentation to review. OELs and ADEs amongst different consulting firms will vary, **sometimes quite significantly**. In one case, for a single compound, there were nine different numbers ranging from 100 $\mu g/m^3$ to 5,000 $\mu g/m^3$. Without having the underlying documentation to review, you cannot say one number is correct and the others are wrong. In fact, they all may be correct.
- **DON'T** assume that a lower OEL or ADE is a better or more accurate number. Again, review the underlying documentation to see how the number was derived and did they follow current practices.
- **DON'T** keep piling uncertainty factors on top of each other. When reviewing the data set for a specific compound, there are at least 18 different factors we are evaluating. However, just because there are 18 factors, doesn't mean that you will use all of them in the final calculations. You must consider what is important and what has been adequately addressed by other uncertainty factors. As an example, if there are 18 uncertainty factors and you assigned a default of 3 to each factor, you would end up with a composite uncertainty factor of over 387 million (3^{18}). The U.S. Environmental Protection Agency has stated that if your composite uncertainty factor is 10,000 or more, you shouldn't use the uncertainty method because you don't have much real information.
- **DON'T** believe that the ADE = 10 times the OEL. That was a "rule of thumb" that someone mentioned in a presentation once, it ended up on the Internet, and now everyone is accepting it an absolute truth - it is not. The OEL is for a worker exposure scenario, which means employees ranging from approximately 18-65 years of age, of generally good health, and with exposures that are typically 8-10 hours/day, 5 days per week. On the other hand, ADEs are for the entire population, ranging from pediatrics to the elderly, those with compromised health, and those individuals that may be on daily medication for their entire lifetime. In addition, the more current

regulatory guidance for ADEs uses slightly different “defaults” for the uncertainty factors than those that have been traditionally used for OELs.

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FREQUENTLY ASKED QUESTIONS

Q1. The equations for both the OEL and ADE seem pretty simple. Can't I do the literature searches and calculations myself?

While both the OEL and ADE equations are simply in appearance, the selection of the appropriate point-of-departure (POD), uncertainty factors, and pharmacokinetic (PK) factors can be quite complex, requiring advance knowledge in toxicology and pharmacology. In addition, the EMA's *"Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities"* states that an "expert review" is required (ref. 6, p. 9, sec 6.0). Unless you have an advanced degree (M.Sc. or Ph.D.) in a toxicology related field, approximately 10+ years of professional toxicology experience, and have published peer-reviewed journal articles in toxicology-related publications, it's fairly risky to defend yourself as an "expert" in the field.

Q2. I have an occupational exposure limit (OEL) from another source, such as a safety data sheet (SDS), that is different than the one on the OEL Fastrac document. Which one is correct?

The difference can be due to many factors, but the most common reasons are different uncertainty and safety factors were used, or the toxicological point of departure (POD) selected is different. Often, occupational exposure limits were established early in the drug development process and due to data gaps, large uncertainty factors were used, thus resulting in a low occupational exposure limit. In addition, the dose that was used to initially establish an OEL may have changed. Unfortunately, the OEL on the SDS may never get revised once more current information becomes available, or that legacy SDSs are still out in circulation. Just because one number is simply lower than the other number does not mean that the lower one is more correct. In addition, many companies have different internally policies on setting OELs and different number rounding practices. Finally, just because an OEL is published on a publically available SDS does not mean that the OEL is based on current information or that the number was correctly calculated. In the toxicology profession, if two OELs are the same compound are within a factor of 10, they are considered in good agreement.

Q3. How does Affygility Solutions determine the OEL?

The occupational toxicology professionals at Affygility Solutions calculate the OEL by using the uncertainty and modifying factor method, which is the most commonly used method for determining OELs in the pharmaceutical industry. We begin this process by collecting available information from both public sources and proprietary databases. After a thorough review of the available data, we select a toxicological point of departure (POD) based on numerous factors such as relevance to human occupational exposure, data quality, study duration, etc. In total, there are

at least sixteen factors we consider, prior to selecting the POD. Once we have determined the POD, we then determine the uncertainty factors and modifying factors to be used and the OEL is then calculated. The specific uncertainty factors and modifying factors used depend upon the completeness of the data set, whether we are considering animal or human data, whether the data is acute or chronic, and many other factors. If available, absorption and bioavailability information is also considered.

Q4. Are engineering controls and handling practices included in the OEL monograph?

No. Each OEL monograph contains a control band classification for both the Affygility Solutions' 5-band system and the traditional 4-band system. The specific engineering controls and handling practices for each band are unique to the individual company. These controls and practices depend on the unit operation being performed, existing engineering controls, the physical form and amount of material, and previous industrial hygiene or surrogate monitoring results. Through the use of Affytrac, Affygility Solutions can assist in performing qualitative exposure assessment to determine if the existing engineering, administrative, and personal protective equipment is adequate.

Q5. By listing the industrial hygiene method information, does that mean that Affygility Solutions developed that method and can do the industrial hygiene monitoring on site at our facility?

No. Affygility Solutions does not directly provide laboratory analytical services or method development. However, we work with key vendors that do provide this service. Affygility Solutions can do the on-site air monitoring and swipe sampling portion, but we would use an outside laboratory to perform the sample analysis.

Q6. Once we purchase an OEL Fastrac monograph, is there additional support from Affygility Solutions if needed?

Affygility Solutions is a full service occupational health and safety service provider and we are available for consulting on an ongoing basis. In order to make the OEL Fastrac monographs as affordable as possible, the online price does not include any additional built-in consulting time. Any follow-up or additional questions on potent compounds will be billed at standard current rates, which are available upon request. However, for purchasers of OEL Fastrac monographs, Affygility Solutions does provide limited online support to answer any questions that may arise about the specific monograph that was purchased.

Q7. We have an early stage compound; can we get an OEL Fastrac monograph developed for the compound?

While Affygility Solutions can develop an OEL Fastrac monograph for almost any active pharmaceutical ingredient (API). For early stage APIs, development of a robust occupational exposure limit is not always practical. This is because what is unknown about the API overwhelms what is known. Thus the uncertainty factors become large and the resulting OEL is unreasonably low. In these cases, Affygility Solutions recommends that a simple control banding classification report (without a numerical OEL) be prepared. Here at Affygility Solutions, we call these reports an Occupational Hazard Classification (OHC) report. Because data on the specific API may be extremely limited, the occupational toxicology experts at Affygility Solutions may have to use structure activity relationship information, as well as any early study information that you may have in your possession.

The occupational toxicology experts at Affygility Solutions are available to perform this initial assessment for your early stage compounds.

Q8. We need an OEL for a proprietary compound that will never be listed in your catalog. Can Affygility Solutions prepare one?

Affygility Solutions can prepare a custom OEL monograph. These documents are $5,700 USD, net of any country taxes or fees. In most cases, turnaround times for these documents are ten (10) business days or less for each document.

Q9. Can an OEL from an OEL Fastrac document be used in enforcement action against my company?

Occupational exposure limits on OEL Fastrac documents are not legal limits and Affygility Solutions does not support their use in enforcement actions. In addition, the U.S. Occupational Safety and Health Administration (OSHA) has stated in several of their letters of interpretation that exceeding a recommended OEL would not be the basis of their enforcement action, but a general duty clause citation would have to be issued on the basis of failing to mitigate a recognized hazard. OSHA has indicated that in over a two-year period, only five general duty clause violations referencing OEL have been issued.

Q10. Can't I get all this information for free from the safety data sheet?

Not necessarily. Currently, *there is no regulatory requirement* to state internal occupational exposure limits (OELs), control banding categorizations, or ADEs on a SDS. Manufacturers or importers of active pharmaceutical ingredients (APIs) are only require to state published legal exposure limits, such as OSHA permissible exposure limits (PELs), or widely-recognized professional association exposure limits, such as ACGIH Threshold Limit Values (TLVs) or AIHA WEELs, on their material safety data sheets. There are approximately 500 PELs and a similar number of TLVs, with very few of them being APIs.

To make matters worse, there are deficiencies in those exposure limit-setting processes. These deficiencies include:

- During the establishment of an OSHA PEL, both economic and technical feasibility considerations are involved in the process. This may result in the setting of an exposure standard that is not protective of employee health. For example, occupational health professionals in the pharmaceutical industry have long-recognized that the OSHA PEL for warfarin sodium does not provide adequate protection.
- OSHA PELs are updated or revised very infrequently.
- Both OSHA and ACGIH have limited resources, therefore they have to prioritize the number of compounds for which they choose to establish exposure limits. It would only make sense that the compounds that are either used in a wide number of industries or by a large number of employees would see a higher priority.
- The "default" exposure limit for dusts is the "particles not otherwise regulated (PNOR)" exposure limit. Unfortunately, the author of the SDS may not fully understand that the PNOR exposure limit is for "inert" and relatively non-toxic materials, and may state the PNOR exposure limit as the appropriate limit for the API. This can be misleading to the reader and they may believe that the API is relatively harmless.

In addition, manufacturers or importers of APIs may lack the internal expertise and experience to properly establish an internal OEL, or the manufacturer may choose, for a variety of legal reasons, not to indicate the internal OEL on the SDS.
In order to protect the health and safety of your employees, and to properly place a compound into a control-banding category, you need to understand all the important details regarding the API. OEL Fastrac documents explain these details in a concise manner. For more information about exposure limits on material safety data sheets, please view our YouTube video on this subject.

Q11. I see that the compound of interest is listed as the basic or acidic molecule, rather than the salt form. Does this make any difference in the calculation of the OEL/ADE?

A large majority of all drug molecules used in medicinal therapy are administered as salts. Often, a drug substance has certain suboptimal physicochemical or biopharmaceutical properties that can be overcome by pairing a basic or acidic drug molecule with a counterion to create a salt version of the drug. Creating a salt version of the drug can improve solubility, stability, taste, manufacturability, and other key properties. In all but a few rare cases, the toxicology of the basic or acidic drug and the salt form are the same.

Here at Affygility Solutions, when we are reviewing the scientific literature for a drug compound, we are mindful of any differences. Unless otherwise indicated, the

OEL/ADE for the basic or acidic drug molecule and the salt version of the drug would be the same.

Q12. In reviewing the OEL and ADE equations, I see that the lowest therapeutic dose was used as the point of departure rather than the NOEL (no observed effect level) or NOAEL (no observed adverse effect level) that is indicated in the EMA's *Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities.* **Can you explain your justification? Note: This is the most frequently asked question.**

While the equation in EMA's guidance document would lead you to believe that the NOAEL should always be used as the point-of-departure (POD), the EMA has indicated in stakeholder meetings that was not their intent (1, 2). NOAELs are generally based on animal data, and the preference is always for good quality human data. This is explained in Section 4.2 of the EMA's guidance document. In addition, the PDE approach used in the EMA guidance was originally developed for residual solvents or elemental impurities with little human data (2, 3). As you may know, solvents are rarely tested on humans. OEL Fastrac monographs are for active pharmaceutical ingredients that have been on the market for a significant period of time; therefore, a vast amount of good quality human data exists and should be preferred. In addition, when compared to human data, often, the use of PODs derived from animal model data will result in unnecessarily large uncertainty factors. The selection of the POD should be the data point that is most relevant to humans and results in the lowest dose with the least amount of composite uncertainty. The expert toxicologist performing the uncertainty factor analysis decides the POD. This approach is supported in the EMA guidance as follows:

> If the most critical effect identified to determine a health-based exposure limit is based on pharmacological and/or toxicological effects observed in humans rather than animals, the use of the PDE formula may be inappropriate and a substance-specific assessment of the clinical data may be used for this purpose.

Q13. When you are extrapolating from the LOEL to a NOEL, you are using the lowest therapeutic dose as the LOEL. From a pure definition standpoint the LOEL and the lowest therapeutic dose aren't the same. Please explain your justification.

Often, it is difficult to obtain a reliable "LOEL" value from the readily available scientific information; therefore, the lowest therapeutic dose is used as a substitute for the LOEL. This approach is supported in scientific publications (5).

Q14. When you extrapolate from the LOEL to a NOEL, you typically use an uncertainty factor of 3 instead of 10. Please explain your justification.

The uncertainty factor of 10 for LOEL to NOEL extrapolation originated from the residual solvent guidance document (3). As previously indicated in Q12, solvents are rarely tested on humans; therefore, an uncertainty factor of 10 may be necessary when setting a PDE for a residual solvent. Prior to performing the LOEL to NOEL extrapolation, the toxicology experts at Affygility Solutions consider the entire data set to determine the appropriate uncertainty factor. One of these considerations is dose response and the potential severity of the effect. Unless severe effects are indicated, a default value of 3 is used for LOEL to NOEL extrapolation. This approach is supported in several scientific publications (4, 5).

Q15. In the OEL and ADE equations, it appears that you didn't use a weight factor of 50-70 kg.

If you are using a NOEL, NOAEL, or LOEL as the POD, and that dose is expressed in units of mg/kg, then you must use a weight adjustment of 50-70 kg to convert from a mg/kg dose to a mg/day dose. However, if the POD used is the lowest daily therapeutic dose, the body weight has already been considered in the dosage, therefore the use of a body weight factor is not required. In addition, for some types of drugs (i.e. chemotherapeutic, skin ointments, inhalable therapeutics), the dosing schedules can be quite complication and it requires an expert toxicologist to convert these an equivalent daily dose. Here at Affygility Solutions, we use 50 kg as the average body weight because it is slightly more conservative.

Q16. If I use the ADE in my maximum amount of safe carryover (MSC) equation, I come up with a number that is significantly higher than the visual acuity limit, is your ADE value incorrect?

No. One of the basic concepts for cleaning is that <u>you always must clean to below visual detection</u>. If you see contamination, you must remove it from the equipment. Just because the ADE is a generous number, does not mean that visual contamination is allowed.

Q17. What is our rationale for the selection of critical endpoints?

The toxicology experts at Affygility Solutions examine a variety of toxicological endpoints. These endpoints could include the NOEL, the NOAEL, LOEL, and the lowest daily therapeutic dose. Once the data is collected, the toxicology experts then evaluate all of the endpoints using the following criteria:

a) The credibility of the information. Peer-reviewed, published information (such as information found in scientific journal articles or government databases) is given preference over non-peer reviewed information (such

as information contained on a manufacturer's safety data sheet without reference to the source of the information).

b) Human data is given preference over animal data.
c) Relevance to human exposure.
d) Relevance to sensitive sub-populations (infants or elderly).
e) Severity of the effect.
f) Long-term studies are given preference over shorter duration studies.
g) More current data is given preference over older data.

In all cases, the toxicology experts will calculate the OEL and ADE using the various endpoints. The endpoint selected and presented in the OEL Fastrac monograph is typically the endpoint that results in the lowest exposure value, with the least amount of uncertainty.

Q18. Can you provide the curriculum vitae (CV) of the experts preparing the OEL Fastrac monographs?

Absolutely. Our CVs can be downloaded here: http://bit.ly/1PHHc18

Q19. As required by the EMA *"Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities,"* what is Affygility Solutions' search strategy?

The Affygility Solutions' expert toxicologists perform an extensive scientific database search. Utilizing both the chemical name and CAS RN as the search parameter, at a minimum, ten governmental and proprietary databases are searched. These databases include: Drugs.com, Toxnet, Hazardous Substance Data Bank, ChemIDplus, DrugDex Evaluations, Reprotox, Martindale – The Complete Drug Reference, National Toxicology Program (NTP), International Agency for Research on Cancer (IARC), and Chemical Carcinogenesis Research Information System (CCRIS).

Since OEL Fastrac monographs with ADEs are for generic, off-patent compounds that have a well-established market history, searching and reviewing compound-specific primary literature sources is generally not necessary. However, if there is data lacking or not good agreement amongst the data, then the toxicologist will search PubMed for additional data references. In addition, the FDA and EMA websites are searched for compound-related information such as safety alerts.

Finally, as a last resort, the SDS (safety data sheet) from the innovator company is reviewed. However, since the SDS does not present the sources of their information, extreme caution is used to evaluate the credibility of the information.

The goal of the search strategy is to identify relevant critical endpoints, results of genotoxic assays, results of carcinogenic, developmental and reproductive studies,

and reported adverse health effects. In addition, understanding the mechanism of action is also desirable.

Q20. Does the OEL Fastrac monograph tell me if the drug is "cytotoxic?"

No. Toxicologists do not like to use the term "cytotoxic." This is because the term lacks precise regulatory definition. The commonly used definition of cytotoxic means "toxic to cells, cell-killing" and typically means highly potent, direct-acting chemotherapeutic drugs such as "cisplatin, doxorubicin, or topotecan." However, there are many modern day oncology products that have very specific mechanisms of action that really are not that potent. This point of view is consistent with ISPE's Risk-MaPP (9):

> Pharmacological and toxicological descriptions (dose-response, No-Observed-Adverse-Effect Level (NOAEL), and ADE) should be used to assess the hazards of compounds. Terms such as potent, cytotoxic, cytostatic, and other product class definitions tend to induce an emotional response that may imply that without exception these compounds are always difficult to handle and require the highest level of control.

Q21. Does the U.S. Food and Drug Administration, the European Medicines Agency, and other regulatory agencies accept OEL Fastrac monographs with ADEs?

OEL Fastrac monographs have been sold in over 34 different countries. In one case we had a regulatory agency question why we used the lowest daily therapeutic dose instead of the NOAEL when calculating the ADE (see Q12). Unfortunately, this was due to the agency's lack of toxicology knowledge. Once, we explained the rationale, the agency accepted our approach. At Affygility Solutions, we survey our customers to get feedback on the monographs. Recently, one client had the Medicines and Healthcare Products Regulatory Agency (MHRA) request to examine one of the monographs. The client stated, "The MHRA reviewed one our your monographs recently and the statement was 'that is what I was looking for'." As you know, regulatory agencies are prohibited from endorsing any private companies approach.

Q22. In the equation for the derivation of PDEs that depicted on page 4 of the EMA's *"Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities"* they uses a series of "F" adjustment factors to account for various uncertainties. In the OEL Fastrac with ADE monographs the term uncertainty factors (UF) is used. Is this acceptable to the EMA?

In their stakeholder meetings, this discussion arose and the EMA agreed that both the "F" adjustment factors methodology and the uncertainty factors (UF) methodology are analogous and any difference is purely a matter of semantics. Therefore, PDEs and ADEs are effectively synonymous and the EMA will and has accepted ADEs. This is indicated in the EMA's *"Guideline on setting health based*

exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities," but, unfortunately, it doesn't standout real well and is buried in footnote 4 on page 10 of the guideline.

Q23. Does Affygility Solutions stand behind their OEL Fastrac with ADE monographs?

Absolutely. Affygility Solutions offers a 100% customer satisfaction guarantee. If, within 6 months of purchase, either a typographical or technical error is brought to our attention, we will revise and provide the revised monograph at no additional costs.

Q24: Can you add a short-term exposure limit (STEL) or ceiling limit to the monograph?

Unfortunately, in most cases the answer is "no." In general, establishing compound-specific ceiling limits or STELs for active pharmaceutical ingredients (API) is not necessary or not practical, since the underlying toxicology data for the API is lacking the high-dose, short-term data. There are exceptions to this statement for compounds that have highly irritating, narcosis, or other acute effects.

As indicated in the *Introduction to TLV/BEI Guidelines* by the American Conference of Governmental Industrial Hygienists (ACGIH, 2015), STELs are described as follows:

> *"A 15-minute TWA exposure that should not be exceeded at any time during a workday, even if the 8-hour TWA is within the TLV–TWA. The TLV–STEL is the concentration to which it is believed that workers can be exposed continuously for a short period of time without suffering from 1) irritation, 2) chronic or irreversible tissue damage, 3) dose-rate-dependent toxic effects, or 4) narcosis of sufficient degree to increase the likelihood of accidental injury, impaired self-rescue, or materially reduced work efficiency. The TLV–STEL will not necessarily protect against these effects if the daily TLV–TWA is exceeded. The TLV–STEL usually supplements the TLV–TWA where there are recognized acute effects from a substance whose toxic effects are primarily of a chronic nature; however, the TLV–STEL may be a separate, independent exposure guideline. Exposures above the TLV–TWA up to the TLV–STEL should be less than 15 minutes, should occur less than four times per day, and there should be at least 60 minutes between successive exposures in this range. An averaging period other than 15 minutes may be recommended when this is warranted by observed biological effects."*

Additionally, in the ACGIH guide, ceiling limits are described as:

> *"The concentration that should not be exceeded during any part of the working exposure."*

The key point in the both above descriptions is that both STELs and ceiling limits are applicable when the compound has an acute health effect, not a chronic effect. The vast majority of OELs for active pharmaceutical ingredients are based on repeat-dose, chronic exposures and on an eight-hour exposure period.

So, an alternate approach, in the case where a compound-specific STEL or ceiling limit does not exist, is to follow the "excursion limit" concept (also called "the 3 by 5 rule"), as presented ACGIH guidebook. Excursion limits are described as:

> "Excursion Limits. For many substances with a TLV–TWA, there is no TLV–STEL. Nevertheless, excursions above the TLV–TWA should be controlled, even where the 8-hour TLV–TWA is within recommended limits. Excursion limits apply to those TLV–TWAs that do not have TLV–STELs.
>
> ***Excursions in worker exposure levels may exceed 3 times the TLV–TWA for no more than a total of 30 minutes during a workday, and under no circumstances should they exceed 5 times the TLV–TWA, provided that the TLV–TWA is not exceeded.***
>
> The approach here is that the maximum recommended excursion should be related to the variability generally observed in actual industrial processes."

The approach above is that no more than 3 times the OEL for a total of 30 minutes during a workday, and under no circumstances should exposures exceed 5 times the OEL.

Q25: Why are the units for the OEL (occupational exposure limit) and the ADE (acceptable daily exposure) different?

OEL's are for airborne "occupational exposures" in terms of mass/volume of air. Occupational exposures are for the worker population that generally meet the following characteristics:

- 18 to 65 years of age;
- Working on average 8 hours/day, 40 hours/week; and
- Generally healthy individuals.

OELs are expressed in units of $\mu g/m^3$ (sometimes expressed as mcg/m^3 because the author of the document couldn't figure out how to use the advance Greek symbol set in Microsoft Word) or mg/m^3 or ppm (typically used for gases and vapors).

Additionally, an OEL needs to indicate the period of time for which they were created, for example:

- 8-hour time-weighted average; or
- 15-minute short-term exposure limit; or
- Ceiling limit.

ADEs or PDEs are for unintended patient exposures due to cross-product contamination by any route of entry (injection, ingestion, inhalation, dermal, etc.), therefore are expressed in mass/body-weight/day. Patient exposures are a much broader population that may include the following sensitive sub-populations:

- Newborns;
- Pregnant patients;
- Individuals with compromised immune systems due to disease or illness;
- Individuals that may be on a medication for their entire life; and
- Elderly individuals.

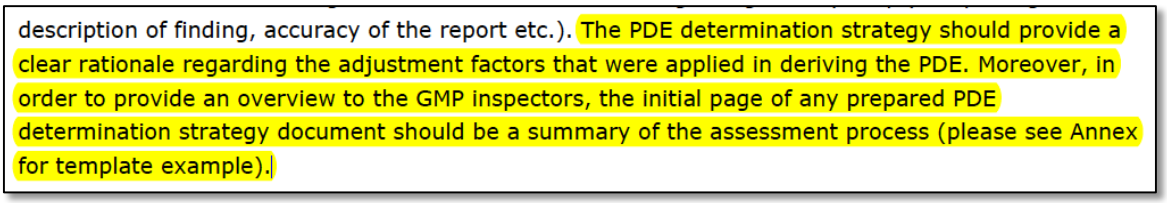
ADEs or PDEs are expressed in mass/day, such as mg/day or µg/day.

Q26: Are PDEs and ADEs different or the same?

As indicated in Q22, in their stakeholder meetings, this discussion arose and the EMA agreed that PDEs and ADEs are effectively synonymous and the EMA will and has accepted ADEs. This is indicated in the EMA's *"Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities,"* but, unfortunately, it doesn't standout real well and is buried in footnote 4 on page 10 of the guideline.

Q27: In the OEL Fastrac monograph, I noticed that it did not contain the PDE Determination Strategy that is contained the Annex to the EMA Guideline. Does this make the OEL Fastrac monographs "non-compliant?"

No. OEL Fastrac monographs with ADEs are compliant with the EMA Guideline. As indicated by the "should" in the excerpt from the EMA Guideline, the use of the template shown in the Annex is not mandatory and is unnecessary. Our search strategy is provided in Q19 and a link to our CVs is provided in Q18. Additionally, to date, it has been our client's experience that no inspectors have requested to see a summary sheet.


description of finding, accuracy of the report etc.). The PDE determination strategy should provide a clear rationale regarding the adjustment factors that were applied in deriving the PDE. Moreover, in order to provide an overview to the GMP inspectors, the initial page of any prepared PDE determination strategy document should be a summary of the assessment process (please see Annex for template example).

Q28: Does the ADE/PDE change if there is a change in the vendor that supplies the API?

No. The ADE/PDE is based solely on the toxicology of the specific molecule, not which vendor supplies it.

Q29: Does the ADE change if the route of administration changes?

This is an interesting question. If you review the definition of an ADE contained in ISPE's Risk-MaPP document, "ADE refers to an acceptable daily exposure which is defined as a daily dose of a substance below which no adverse effects are expected by any route, even if exposure occurs for a lifetime." As indicated in this definition, an ADE is by "any route." Therefore, when selecting a point of departure for an ADE, the toxicology experts at Affygility Solutions typically choose a PoD for the ADE that is either intravenous (i.v.) route or we account for that route by using additional factors. Thus, if you protect for the i.v. route, you are protecting all other routes. Note: There are some rare exceptions to this concept when you have unique compounds that are respiratory sensitizers.

References

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Definitions

ADC
Antibody Drug Conjugates (ADCs) are monoclonal antibodies (mAbs) attached to biologically active drugs by chemical linkers with labile bonds. By combining the unique targeting of mAbs with the cancer-killing ability of cytotoxic drug**s**, ADCs allow sensitive discrimination between healthy and diseased tissue.

Alkylating Agent
This is a term that describes any substance that introduces an alkyl radical into a compound in place of a hydrogen atom.

Biological Half-life
The term, which is used for the time, required for the amount of a particular substance in a biological system to be reduced to one-half of its value by biological processes when the rate of removal is approximately exponential. Substances with a long biological half-life will tend to accumulate in the body and are, therefore, particularly to be avoided. Substances with a short biological half-life may accumulate if some becomes tightly bound, even if most is cleared from the body rapidly.

Endpoint
In clinical trials, a parameter used to compare the results in different arms of the trial. End-points may be directly related to the condition (such as progression of the disease) or may be measurements of surrogate markers.

Enzyme
A protein that acts as a catalyst, affecting the rate at which chemical reactions occur in cells.

Generic Drug
Drug product sold under a branded drug's chemical name, following the expiration of the pertinent patents to the branded drug. Drug patents are issued for 20 years from time of filing. The active ingredients in the branded and generic products are the same. Both the branded and the generic versions must have the same potency, be available in the same dosage forms (i.e. tablet, liquid, injectable), be demonstrated safe and effective, and be manufactured under government-approved GMPs.

NOAEL
No-observed adverse effect level. Greatest concentration or amount of a substance, found by experiment or observation, which causes no detectable adverse alteration of morphology, functional capacity, growth, development, or life span of the target organism under defined conditions of exposure.

Occupational Exposure Limit
A generic term used to represent a pair of numbers (1) the agent concentration or intensity that is allowable (based on health-effects data); and (2) the time period over which one averages workplace concentrations to evaluate whether the minimized concentrations are less than the allowable limit.

Peptide
A molecule consisting of between two and twenty amino acids connected by peptide bonds; a short segment of a larger protein or a completely functional molecule.

Pharmacokinetics (PK)
The movements of drugs within biological systems, as affected by uptake, distribution, elimination and biotransformation. See also ADME/T.

Point of Departure
The dose-response point that marks the beginning of a low-dose extrapolation. This point can be the lower bound on dose for an estimated incidence or a change in response level from a dose-response model (BMD), or a NOAEL or LOAEL for an observed incidence, or change in level of response.

Preclinical studies
Studies that test a drug on animals and in other non-human test systems. Safety information from such studies is used to support an Investigational New Drug (IND) application.

Receptor
A protein or group of associated proteins in a cell or on its surface that selectively binds a specific substance (called a ligand). Upon binding its ligand, the receptor triggers a specific response in the cell.

Structure-Activity Relationship (SAR)
The relationship between chemical structure and pharmacological activity for a series of compounds.

Comparison of Different Occupational Health Category Schemes[1]

OHC Scheme	1 (Low)	2 (Moderate)	3 (High)	4 (Very High)	5 (Extremely High)
Affygility Solutions	> 100 µg/m³	100 – 20 µg/m³	20 – 5 µg/m³	5 – 0.5 µg/m³	< 0.5 µg/m³
Roche	> 100 µg/m³	100 – 10 µg/m³		Cat 3a: 10 – 1 µg/m³	Cat 3b: 1-0.05 µg/m³ / Cat 4 < 0.05 µg/m³
Catalent	> 100 µg/m³	100 – 10 µg/m³		10 – 1 µg/m³	< 1 µg/m³
GSK	> 1,000 µg/m³	1,000 – 100 µg/m³	100 – 10 µg/m³	10 – 1 µg/m³	< 1 µg/m³
J&J	> 100 µg/m³	100 – 20 µg/m³	20 – 5 µg/m³	5 – 0.5 µg/m³	< 0.5 µg/m³
Merck	> 100 µg/m³	100-10 µg/m³		10 – 1 µg/m³ (3)	1-0.1 µg/m³ (3+) / <0.1 µg/m³
Pfizer	> 1,000 µg/m³	1,000 – 100 µg/m³	100 – 10 µg/m³	10 – 1 µg/m³	< 1 µg/m³
Standard 4-band system	> 500 µg/m³	500 – 10 µg/m³		10 – 0.03 µg/m³	< 0.03 µg/m³
Confidential client A	5,000 – 1,000 µg/m³	1,000 – 100 µg/m³	100 – 10 µg/m³	10 - 1 µg/m³	< 1 µg/m³

[1] Currently, there are over 18 different control-banding schemes in use. The number of bands and their respective OEL cutoffs depend upon the number of control technologies available to a specific company and their effectiveness.