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The Use of Acceptable Daily Exposures (ADEs) for Managing the Risk of Cross Contamination in Pharmaceutical Manufacturing

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This article presents a convincing justification for the use of Acceptable Daily Exposures (ADEs) to scientifically manage the risk of cross contamination in all types of bio/ pharmaceutical facilities.

Introduction

ISPE's Risk-MaPP Baseline Guide® has brought the term ADE to the forefront for the management of cross contamination in pharmaceutical manufacturing facilities. 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.[1] By this definition, the ADE is a conservative value and is protective of all populations (including infants, elderly, ill, etc.) by any route of administration.

Once an ADE has been established for a compound, this value can be used to set limits for cleaning validation (rinse and swab) limits and cross contamination limits. ADEs are established by qualified toxicologists who reference all safety data for the compound in question to set the various factors needed in the calculation of the ADE. The safety data can include data generated from clinical trials used to support drug applications, package inserts for commercial products, and various resources that provide information on drug safety such as PubMed.[2] For a more detailed understanding of how ADEs are established, refer to the Risk Identification section of the Risk-MaPP Baseline Guide®.

Although the term ADE[3] is fairly new, several companies have been using health-based limits for a while and many companies are now getting ADEs developed so that their cross contamination risk management program is based on scientific data linked to the protection of the patient. Note that one of the primary principles of quality risk management as stated in ICH Q9[4] is that the "evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient." Companies are realizing this principle by incorporating the ADE into the company's risk management program.

Cleaning and Cleaning Validation

Retention is where product residue is left behind on product contact parts of equipment. The potential carry-over of the retained residue to the next product can be a major source of cross contamination. The purpose of cleaning and cleaning validation is to minimize this source of potential cross contamination so that there will be no adverse effects to the patient.

Traditionally, cleaning validation limits have been based on either not more than 1/1000th of a therapeutic dose or 10 ppm of the previous product in the maximum daily dose of the subsequent product and typically firms will use the lower of the two values. While these methods were the best information at the time of their inception (early 90s), they do not take into account the potential harm to the patient.[5] The therapeutic dose by definition is an amount that provides an effect to the patient, not a safe level for anyone. Using a safety factor of 1000 has not been scientifically proven to equate to a no adverse effect level for all compounds. The 10 ppm limit is not correlated to the safety of the product at all. The 1/1000th of therapeutic dose or 10 ppm methods are not linked to patient safety and therefore are not scientific based methods for setting the cleaning limits.

As discussed previously, the ADE is based on scientific data analyzed by toxicologists to set safe levels for long term exposure without adverse effects. Using the ADE to set cleaning limits provides the scientific justification as the basis for the limits as required by the FDA.[6]

The use of ADE values to determine cleaning limits is gaining acceptance from the pharmaceutical industry and more importantly the regulatory bodies. For example, at the ISPE Risk-MaPP launch sessions in Brussels September 2010, the presentation by Catherine Lefebvre of Agence française de sécurité sanitaire des produits de santé (AFSSAPs) – the French Agency for the Safety of Health Products stated:

> *"Some MSs are considering that the approach with the ADI is an improvement for risk evaluation over the arbitrary appoach of 1/1000th of the lowest clinical dose or 10 ppm."*[7]

MSs refers to the member states of the European Medicines Agency (EMA) and Acceptable Daily Intake (ADI) is synonymous with ADE.

In October of 2011, the EMA Safety Working Party in response to a request from the EMA GMP/GDP Inspectors Working Group published their Concept Paper on "the development of toxicological guidance for use in risk identification in the manufacture of different medicinal products in shared facilities" where they state:

> *"Currently toxicological data are not always used in establishing limits for cross-contamination. In some cases arbitrary limits such as 1/1000th of the lowest clinical dose or 10ppm are used as limits for cleaning validation. These limits do not take account of the available pharmacological/ toxicological data and possible duration of exposure and may be too restrictive or not restrictive enough. A more scientific approach based on current available pharmacological and toxicological information is required to establish threshold values to be used as part of the overall quality risk management in shared facilities."*[8]

Selecting Cleaning Limits

In some cases, the acceptance limit calculated with the ADE may be significantly higher than the limit calculated with either the 1/1000th of therapeutic dose or 10 ppm. Many are tempted to set the cleaning limits based on the lowest value determined by using the ADE, 1/1000th of a therapeutic dose or 10 ppm methods because many feel lowering the limit makes the process more robust. But in actuality by artificially lowering the limit the process may be more prone to failures. First remember that the ADE is a very conservative value set on data that is used to approve the product, support labeling claims and is evaluated by toxicologists. This is a safe limit. Lowering the limit does not make the limit "safer," but it does tend to bring the limit down to the level of the data, hence a larger probability of failure. The best way to have a more robust process is to improve the process (clean better),

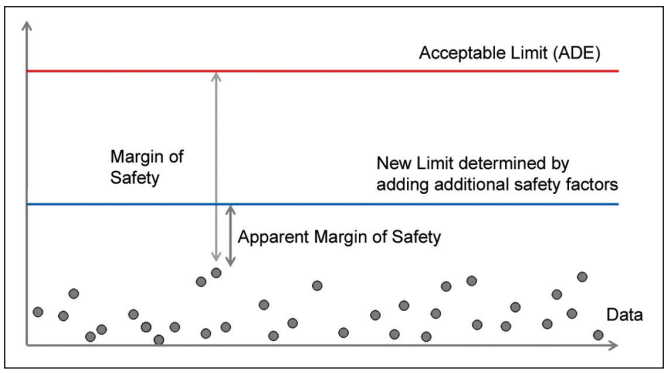

Figure 1.

not lower the limits. The margin of safety for the process is determined by the difference between the highest data point to the acceptance limit. As shown in Figure 1, the margin of safety is actually reduced when the limit is artificially lowered.

Some companies also may use the LD50 to set the cleaning limit by calculating an ADI based on modifying the LD50 by a safety factor to determine a No Observed Effect Level (NOEL). The LD50 represents the lethal dose of 50% of the test population. This method is described in the APIC's "Guide to Cleaning Validation in API Plants" and "Guidance on Aspects of Cleaning Validation in Active Pharmaceutical Ingredient Plants"[9] where the underlying document that is referenced for this approach clearly states that using the LD50 to determine the NOEL to calculate the ADI is an interim approach and is not a substitute for actual testing for the NOEL.[10] Clearly, there are adverse effects before death so the use of this value to set safe cleaning limits is not scientifically valid nor is it a safe value.

There may be situations where the limit calculated with the ADE is a large value that would not be acceptable as a carry over to another product even though it will be considered a safe amount. In these situations, visually clean would become the overriding acceptance value where the visual detection threshold is typically 4 mcg/cm^2 or less.[11] In these cases, using visual inspection as the method of detection can significantly save time and cost since analytical methods are not necessary because the visual threshold is more stringent than the calculated acceptance limit (safe limit).

Verification that equipment is clean to the required limit is necessary after each cleaning prior to using the equipment for the next product. It is important to note the distinction between cleaning validation which proves that a particular method will in fact clean to the necessary levels and cleaning verification which shows that the cleaning did in fact clean to the necessary levels. This distinction becomes much more necessary with manual systems. Automated systems should in fact perform as validated unless there is a failure that is usually noted by the equipment as an alarm condition. Manual systems are variable just by virtue of human nature. In manual situations, it is more important to verify the equipment is clean to the necessary limits each time. So it becomes advantageous to have limits that are above the visual threshold so that visual inspection can safely be

the verification method. When limits are below the visual threshold, other methods are necessary to prove the cleaning is meeting the requirements.

As more data are collected on the actual results of the cleanings, statistical analysis should be used to help determine the process control limit[12] where the process naturally works, alert limits where the process begins to veer out of the normal operating range, and action limits where the process is trending out of control, but still well within the overall acceptance limits. The advantage of this type of hierarchy of limits is that remediation can be implemented well before the process is out of control and far from the acceptance limit. This also minimizes the number of cleaning validation failures that require extensive root cause analysis and justification on acceptability of the product affected by the failure.

Cross Contamination

ADEs can be used to assess the risk of cross contamination by several methods. The true test is to analyze product for the presence of the previous product. This is not really an ideal situation as it is akin to testing quality into the product. Obviously, it is preferred to build quality into the system. Processes can be and should be challenged for their ability to minimize the risk of cross contamination through several testing scenarios that can then provide some scientific basis to predict the likelihood of the risk of cross contamination.

One test is similar to surrogate testing containment systems where a surrogate material is processed and testing is in place to determine the level of containment the system provides. To adapt this testing scenario for determining the risk of cross contamination, a placebo should be processed into final dosage form after the surrogate also has been processed into final dosage form with the required cleaning processes between the two "products" and then the placebo is analyzed for the presence of the surrogate.[13]For the test to be meaningful, a statistically relevant number of samples should be analyzed. A statistical analysis should be used to determine the process capability of the system. The system should then be routinely monitored against this process capability and similar to the cleaning systems outlined above, alert and alarm limits can be set and monitored where the actual acceptance limit based on the ADE is well above these limits.

Another testing scenario is to collect data relative to the potential for mechanical and airborne transfer in the facility. Care should be taken when obtaining data to support the potential occurrence of cross contamination due to mechanical and airborne transfer as merely determining the presence via air sampling or swab samples does not indicate that cross contamination by these routes is inevitable. Some companies are gathering and analyzing data to assist them in creating databases that are used to help predict the likelihood of mechanical or airborne transfer leading to an increased risk of cross contamination.

In addition, it is necessary to prove whatever systems are in place to manage the risk of cross contamination are working as intended and are indeed supporting the management of cross contamination. The FDA is citing firms for the lack of monitoring for cross contamination. Some firms assume this means testing the product for the presence of another product. This should be a last resort scenario. Firms should be monitoring the systems in place to manage the risk of cross contamination. For example, containment systems if used should be challenged to prove that they are containing to the levels needed. Pressure cascades are often used as a means to managing the risk of cross contamination and as such verification that the necessary cascades are in place is also needed as well as proving the pressure cascades are indeed managing the risk. These systems should be challenged at regular intervals as part of the ongoing monitoring requirements for the management of cross contamination. The key to success is to use science as the basis.

Conclusion

ADEs should be used as the basis for cross contamination limits as they are protective of patient health, are conservative and are scientifically derived. In many cases, the ADE derived limit provides a large margin of safety from actual results. In cleaning, the ADE derived limits also allows more compounds to have acceptable limits above the threshold for visual detection so that analytical methods are not necessary to determine if the equipment is adequately cleaned. In some cases, the limit may be significantly above the ADE so that visual inspection also may be considered for the validated method.[14]

It may be tempting to set cleaning validation limits based on the lowest of the following criterion:

- ADE based limit
- 1/1000th of therapeutic dose method
- 10 ppm in the rinse water
- LD50

This will not lead to safer, better cleaning, but actually to increased failures as the limits will start to approach the level of the data leaving no apparent safety margin. It has already been stated that the ADE is a very conservative number based on the adverse effects that could occur to a patient, so why is there a need to add additional conservatism to this limit? The best way to protect the patient from inadequate cleaning is to actually clean better.

In many cases, the ADE derived limit will actually be higher than the limits calculated using the 1/1000th of therapeutic dose or 10 ppm and in some cases, it will be much higher. In all cases where the ADE value is higher than the more traditional methods, the visual detection threshold will actually override and become the acceptance limit. Following this thought process based on documented visual threshold limits, the highest limit for cleaning would be 4 mcg/cm2.[15]

In addition, with release of the FDA's new Process Validation Guide, the use of statistical analysis to determine operating parameters is gaining more momentum. As data is collected on the performance of the cross contamination management program, they can be statistically analyzed to determine process control limits where the process typically

performs as well as alert and action limits where notification and remediation should occur if the performance veers to these limits.

By using the ADE as the basis for setting cleaning validation and cross contamination limits not only will patients be protected from the risk of cross contamination, there is opportunity to be more cost efficient especially in the cleaning and cleaning validation processes.

References

1. *ISPE Baseline® Pharmaceutical Engineering Guide, Volume 7 – Risk-Based Manufacture of Pharmaceutical Products (Risk-MaPP),* International Society for Pharmaceutical Engineering (ISPE), First Edition, September 2010, www.ispe.org.
2. PubMed.gov, US National Library of Medicine, National Institutes of Health.
3 Draft versions of the guide as well as presentations and some companies use the term ADI (acceptable daily intake) based on the ADI from the food industry, but the FDA during final review asked that a different term be used so that it was not assumed to be only for the oral route of administration.
4. International Conference on Harmonisation, November 2005.
5. Walsh, A., "Cleaning Validation for the 21st Century: Acceptance Limits for Active Pharmaceutical Ingredients (APIs) Part 1," *Pharmaceutical Engineering*, July/August 2011, Volume 32, No. 4, www.pharmaceuticalengineering.org.
6. FDA's Guide to Inspections Validation of Cleaning Processes, July 1993.
7. Status on Dedicated Facilities at the EMA GMP GDP Inspection Working Group as presented by Catherine Lefebvre, GMP Inspector AFSSAPS at the ISPE Brussels Conference September 2010.
8. EMA GMP GDP Inspectors Working Group concept paper on the development of toxicological guidance for use in risk identification in the manufacture of different medicinal products in shared facilities.
9. APIC "Guidance on Aspects of Cleaning Validation in Active Pharmaceutical Ingredient Plants," 2000 and APIC "Guide to Cleaning Validation in API Plants," 1999.
10. Layton, D. W., et. Al., "Deriving Allowable Daily Intakes for Systemic Toxicants Lacking Chronic Toxicity Data," *Regulatory Toxicology and Pharmacology,* 7 96-112 (1987).
11. Forsyth, R.J., Van Nostrand, V., and. Martin, G.,"Visible-Residue Limit for Cleaning Validation and its Potential Application in a Pharmaceutical Research Facility,"*Pharmaceutical Technology,* 28 (10), 58–72 (2004).
12. FDA Guidance for Industry, Process Validation: General Principles and Practices, January 2011.
13. Wilkins, J.,"A Quantitative Study in Cross Contamination," *Pharmaceutical Engineering*, January/February 2011, Volume 31, No. 1, www.pharmaceuticalengineering.org.
14. Forsyth, R., and Hartman J., "A Risk-Based Approach to Cleaning Validation using Visible Residue Limits," *Pharmaceutical Engineering,* May/June 2008, Volume 28, No. 3, www.pharmaceuticalengineering.org.
15. Fourman, G.L., and Mullen, M.V.,"Determining Cleaning Validation Acceptance Limits for Pharmaceutical Manufacturing Operations," *Pharmaceutical Technology,* 17 (4), 54-60 (1993).

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