Regulatory Toxicology and Pharmacology 79 (2016) S39–S47

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

A harmonization effort for acceptable daily exposure application to pharmaceutical manufacturing – Operational considerations

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ARTICLE INFO

Article history:
Received 19 May 2016
Accepted 1 June 2016
Available online 3 June 2016

Keywords:
Acceptable Daily Exposure (ADE)
Permitted Daily Exposure (PDE)
Active Pharmaceutical Ingredient (API)
Maximum Daily Dose (MDD)
Maximum allowable carryover (MAC) or maximum safe carryover (MSC)
Dedicated/segregated facilities
Starting materials (SM)
Process intermediates (PI)
Threshold of Toxicological Concern (TTC)
International Society of Pharmaceutical Engineers (ISPE)
Cross-contamination

ABSTRACT

A European Union (EU) regulatory guideline came into effect for all new pharmaceutical products on June 1st, 2015, and for all existing pharmaceutical products on December 1st, 2015. This guideline centers around the use of the Acceptable Daily Exposure (ADE) [synonymous with the Permitted Daily Exposure (PDE)] and operational considerations associated with implementation are outlined here. The EU guidance states that all active pharmaceutical ingredients (API) require an ADE; however, other substances such as starting materials, process intermediates, and cleaning agents may benefit from an ADE. Problems in setting ADEs for these additional substances typically relate to toxicological data limitations precluding the ability to establish a formal ADE. Established methodologies such as occupational exposure limits or bands (OELs or OEBs) and the threshold of toxicological concern (TTC) can be used or adjusted for use as interim ADEs when only limited data are available and until a more formal ADE can be established. Once formal ADEs are derived, it is important that the documents are routinely updated and that these updates are communicated to appropriate stakeholders. Another key operational consideration related to data-poor substances includes the use of maximum daily dose (MDD) in setting cross-contamination limits. The MDD is an important part of the maximum allowable/safe concentration (MAC/MSC) calculation and there are important considerations for its use and definition. Finally, other considerations discussed include operational aspects of setting ADEs for pediatrics, considerations for large molecules, and risk management in shared facilities.

1. Introduction: establishing ADE values

This manuscript focuses on the decisions and processes used by pharmaceutical companies to support the development of health-based assessments, such as acceptable daily exposure (ADE[1]) values, in support of internal and external manufacturing activities, including control of potential cross-contamination in shared

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[1] An ADE or acceptable daily exposure is defined as the dose of an API which is unlikely to cause adverse effects if an individual is exposed, by any route, at or below this dose every day over a lifetime (ISPE, 2010; EMA, 2014). It is considered synonymous with the term Permitted Daily Exposure or PDE.

http://dx.doi.org/10.1016/j.yrtph.2016.06.001
0273-2300/

multiproduct pharmaceutical facilities and cleaning validation efforts. To address this issue, regulators, industry, and other stakeholders (ISPE, 2010; EMA, 2014) have recommended the use of human health risk assessment principles to set health-based exposure limits for all active pharmaceutical ingredients (APIs). The use of health-based assessments replaces the more traditionally used methods (termed default methods here) such as 10 ppm or 1/1000th of the minimum clinical dose. The overall goal of integrating ADE-based cleaning limits into effective quality manufacturing systems [*e.g.*, ICH Q7 to Q10, FDA's cGMP for the 21st Century, FDA Process Validation Guideline, FDA Guidance for Industry (US FDA, 2005)] will more effectively and appropriately safeguard both product quality and patient safety.

The health-based ADEs can be used to calculate cleaning limits (or safe carryover values) and to decide if dedicated facilities or equipment are required for a particular API if the safe carryover value is below the facility cleaning capabilities. The European Medicines Agency (EMA) guideline, which became effective June 1, 2015, established aggressive timelines for implementation of ADEs for both new and existing products (EMA, 2014). In order to comply with these timelines, companies leveraged or built-up existing internal programs to establish ADEs. However, developing and implementing ADEs for all APIs in a pharmaceutical manufacturing environment in the allowed timeframe represents a significant challenge for many manufacturers; whether they are the innovator, a generic, or a contract manufacturer. Any of these manufacturers, particularly generics and contract manufacturers, may have hundreds of existing APIs for which ADEs are now required. Because of the number of affected APIs and the fact that the entirety of the API's dataset is reviewed when setting an ADE, the process can be time and resource intensive.

In addition to the challenges associated with creating large numbers of ADEs, once created, the ADEs then are translated to cleaning limits, compared to existing cleaning limits, and new cleaning procedures implemented, as needed. As with any new paradigm, a variety of concerns may be identified and require management. For example, if the new ADE-based cleaning limit is lower than the previously used limit, new cleaning procedures may need to be devised and validated which could impact manufacturing timelines, supply, and delivery. This may involve changing cleaning validation techniques, as well as developing new analytical methods to quantify residues at lower levels. Other risk-based decisions for this situation may be needed, such as addressing the usability of the currently available clinical supply previously manufactured using outdated processes. Conversely, business and technical decisions are also needed if the new ADE is higher than the previously used limit, *e.g.*, making a choice to continue using the more conservative, default limit which may be costlier than using a higher ADE-based cleaning limit.

Overall, there are a number of operational issues associated with the implementation of the ADE process. The purpose of this paper is to address how to meet the operational challenges associated with ADE development and implementation. Specifically, this paper will describe: (1) the impact of ADE implementation on cleaning operations; (2) which substances may need ADEs; (3) prioritization schemes for ADE development; (4) the value of interim ADEs; (5) ADE document management, revision, and communication; (6) maximum daily dose (MDD) for use in carryover limits; (7) application of the ADE to pediatric formulations; (8) differences in approaches for large molecules; and finally, (9) segregated or dedicated facilities in the ADE environment.

2. Impact of ADE implementation on cleaning operations

Historically, pharmaceutical and biotech companies have used 'default' approaches, such as 1/1000th of the therapeutic dose or 10 ppm as targets for limiting cleaning agent cross-contamination in pharmaceutical manufacturing (Fourman and Mullen, 1993; Faria et al., 2016, this issue). The historical application of these default approaches has resulted in many companies arbitrarily adjusting the 1/1000th of the therapeutic dose or 10 ppm limits to other default levels such as 1/100th (PDA, 2012) or 100 ppm (ECA Academy, 2007), without doing a risk analysis. A significant consequence of using arbitrary values without risk characterization by a toxicologist is the lack of scientific justification on the protectiveness of these values. The use of these arbitrary limits has potential impacts on analytical methods for cleaning and the potential need for dedicated equipment (Walsh, 2011a). For example, when it is unknown if default limits are protective, companies may have to manage operational issues to avoid cross-contamination, such as scheduling of manufacturing to avoid certain products following other products in the same equipment.

The advent of the ADE has brought a measure of scientific rigor to the derivation of safe levels of exposure for a patient to a drug or any other compound (ISPE, 2010) as a potential residual in an API. With the increased number of highly potent or hazardous compounds being manufactured, default limits might not be low enough. While 1/1000th of the therapeutic dose is typically expected to scale with a compound's potency (meaning automatically lower limits for more potent compounds), 10 ppm (a concentration) does not scale and so may not be protective for new highly potent compounds. However, when compared to risk-based approaches, in most cases the 1/1000th or 10 ppm limits resulted in a more conservative limit (Faria et al., 2016, this issue). Setting carryover limits on the basis of an ADE ensures the carryover limit is set to protective levels based on science and avoids this uncertainty associated with the traditional default methods.

Mitigation of toxicological impacts following unintended exposure to an API is one aspect of successful a cleaning validation program. Another aspect is the statistical evaluation of the data collected during validation (Walsh, 2015). These statistical boundaries are used for statistical process control techniques, and the comparison of the boundaries with the ADE-based limits provides a measure of risk. This is similar to a margin of safety (MOS) approach[2] as currently used in risk assessment to ensure an adequate (safe) buffer between exposures and the safe exposure level. Thus, health-based and statistics-based approaches that utilize the ADE are currently being implemented by pharmaceutical manufacturers to safeguard patient safety and strengthen product quality.

3. Which substances may need ADE(s)?

APIs now require ADEs according to the updated European Union (EU) Good Manufacturing Practice (GMP) guidelines (EMA, 2014). Some pharmaceutical manufacturers may choose to develop ADEs for other compounds such as starting materials (SMs), process intermediates (PIs), or cleaning agents. This section will discuss the operational aspects for deriving ADEs for each of these compounds. While the guidelines are specific on the need for ADEs for APIs, they are less clear on the need for SMs, PIs, or cleaning agents. Additionally, for these compounds there are a

[2] In a risk assessment context, the MOS is defined as the margin between the safe dose and the estimated or actual exposure dose. However, in a pharmaceutical development context, MOS is typically synonymous with the therapeutic index, which is typically the ratio of the therapeutic dose to the toxic dose. This paper uses the term MOS in the risk assessment context to reference an ADE compared with a carryover limit in order to assess the safe margin between the two values.