Regulatory Toxicology and Pharmacology 79 (2016) S19–S27

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

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

Issues and approaches for ensuring effective communication on acceptable daily exposure (ADE) values applied to pharmaceutical cleaning

Michael J. Olson [a, *], Ellen C. Faria [b], Eileen P. Hayes [c], Robert A. Jolly [d], Ester Lovsin Barle [e], Lance R. Molnar [f], Bruce D. Naumann [g], Alison M. Pecquet [h], Bryan K. Shipp [i], Robert G. Sussman [a], Patricia A. Weideman [j]

[a] SafeBridge Consultants, Inc., USA
[b] Janssen Pharmaceutical Company, An Affiliate of Johnson & Johnson, USA
[c] EPHayes Toxicology Services, USA
[d] Eli Lilly and Company, USA
[e] Novartis, Switzerland
[f] Mylan, USA
[g] Merck & Co., Inc., USA
[h] University of Cincinnati, USA
[i] Pfizer Inc., USA
[j] Genentech, Inc., USA

ARTICLE INFO

Article history:
Received 9 May 2016
Accepted 19 May 2016
Available online 24 May 2016

Keywords:
Acceptable Daily Exposure (ADE)
Permitted Daily Exposure (PDE)
Stakeholder
Contract manufacturer
Regulatory agencies
Pharmaceutical manufacturing
Monograph
Communication

ABSTRACT

This manuscript centers on communication with key stakeholders of the concepts and program goals involved in the application of health-based pharmaceutical cleaning limits. Implementation of health-based cleaning limits, as distinct from other standards such as 1/1000th of the lowest clinical dose, is a concept recently introduced into regulatory domains. While there is a great deal of technical detail in the written framework underpinning the use of Acceptable Daily Exposures (ADEs) in cleaning (for example ISPE, 2010; Sargent et al., 2013), little is available to explain how to practically create a program which meets regulatory needs while also fulfilling good manufacturing practice (GMP) and other expectations. The lack of a harmonized approach for program implementation and communication across stakeholders can ultimately foster inappropriate application of these concepts. Thus, this period in time (2014–2017) could be considered transitional with respect to influencing best practice related to establishing health-based cleaning limits. Suggestions offered in this manuscript are intended to encourage full and accurate communication regarding both scientific and administrative elements of health-based ADE values used in pharmaceutical cleaning practice. This is a large and complex effort that requires: 1) clearly explaining key terms and definitions, 2) identification of stakeholders, 3) assessment of stakeholders' subject matter knowledge, 4) formulation of key messages fit to stakeholder needs, 5) identification of effective and timely means for communication, and 6) allocation of time, energy, and motivation for initiating and carrying through with communications.

* Corresponding author. SafeBridge Consultants, Inc./Trinity Consultants, One Copley Parkway, Suite 310, Morrisville, NC 27560, USA.
E-mail address: michael.olson@safebridge.com (M.J. Olson).

http://dx.doi.org/10.1016/j.yrtph.2016.05.024
0273-2300/

1. Introduction: ADE values and communication goals

This manuscript focuses on communication regarding Acceptable Daily Exposures (ADEs) and Permitted Daily Exposures[1] (PDEs) applied to pharmaceutical cleaning with internal and external stakeholders. It is intended to be read in conjunction with the related paper on company-internal operations related to ADE programs (Hayes et al., 2016, this issue). While there is a great deal of technical detail in the written framework underpinning the use of ADEs in cleaning (for example, ISPE, 2010; Sargent et al., 2013), little is available to explain how to practically create a program which meets regulatory needs while also fulfilling good manufacturing practice (GMP) and other expectations. The lack of a harmonized approach for program implementation and communication across stakeholders can ultimately foster inappropriate application of these concepts.

An example of how lack of harmonization in stakeholder communication can impede appropriate application of ADEs is in the writing style of the ADE document itself. Most ADE documents are written by scientists and as such are not always understandable or accessible to non-scientific stakeholders. This can have several consequences, including lack of confidence in the ADE derived, reduced support in implementing the ADE, or inappropriate implementation. Harmonization efforts on how to succinctly and consistently communicate key information in the ADE document (such as the rationale for the limit derived, any areas of uncertainty or assumptions made, and the applicability domain of the limit derived) to scientists and non-scientific audiences alike will help to ensure that these documents are widely understood, and that true collaborative partnerships between those who write ADEs and those who consume them can take place.

Another example of how lack of harmonization can adversely impact communication is inconsistency in the use and definitions of key technical terms used in ADE preparation and implementation. The terms ADE and PDE are essentially synonymous; yet different groups have historically preferred the use of one term over the other, leading to confusion. Clearly defining and consistently using these terms will assist in more effective and more efficient conversations between stakeholders (see Sussman et al., 2016a, this issue). Thus, the period in time for the initial growth of ADE implementation (2014–2017) could be considered transitional with respect to establishing best practices related to ADEs, including creation of communication mechanisms that clearly articulate ADE program structure within a company and across companies, and regulatory expectations resulting from implemented practice.

There is no universally identified stakeholder group in the ADE process, especially when considering stakeholders external to an individual business enterprise. Certainly, regulatory bodies charged with the oversight of pharmaceutical safety and efficacy and individual inspectors representing regulatory bodies are key stakeholder groups. Outside of the regulatory community, the inventory of enterprise partners performing contract or toll manufacture have a need to understand and correctly apply ADE concepts and specific values. Understanding key regulatory arenas is critical to tailoring ADE documentation and communication plans for the end-stakeholder uses and for their regulatory needs.

[1] For this discussion the terms Acceptable Daily Exposure (ADE) and Permitted Daily Exposure (PDE) are treated as synonymous, but with recognition that specific terms have been chosen by different regulatory bodies (ISPE, 2010; Sargent et al., 2013; EMA, 2014a). In this paper, use of the term ADE implies application to PDE derivation as well. In general, these terms describe calculated values intended to safeguard human (patient) health from unintended exposure to pharmaceutical substances.

Effective stakeholder communication and ultimately stakeholder engagement regarding ADE programs requires careful planning and acceptance by all stakeholders; internal and external to a company. This is a large and complex effort that requires: 1) clearly explaining key terms and definitions, 2) identification of stakeholders, 3) assessment of stakeholders' subject matter knowledge, 4) formulation of key messages fit to stakeholder needs, 5) identification of effective and timely means and venues for communication, and 6) allocation of time, energy, and positive motivation for initiating and completing communications. Ultimately, sharing suggestions for best practices to initiate and sustain a program supporting product quality activities could help guide companies and regulators to engage in a dialog that will lead to a more complete understanding of the merits and complexities of the ADE paradigm.

1.1. Identification of key terms and definitions

A communication strategy for actively engaging stakeholders begins with clarity about what is implied by ADE values, as well as why the concept of health-based risk assessment is an important addition to existing methods supporting product contact surface cleaning. As defined by the International Society for Pharmaceutical Engineering (ISPE), an ADE is “a dose that is unlikely to cause an adverse effect in an individual if exposed, by any route, at or below this dose every day for a lifetime” (ISPE, 2010). ISPE further expands this definition to incorporate qualifiers regarding the scope of application of an ADE value – “By definition the ADE is protective of all populations by all routes of administration”. The European Medicines Agency (EMA) defines the PDE as “a substance-specific dose that is unlikely to cause an adverse effect if an individual is exposed at or below this dose every day for a lifetime” (EMA, 2014a). Recent updates to the European Union (EU) guidance on GMP Chapters 3 and 5 indicate that risk assessment for the control of cross-contamination and cleaning should rely on a toxicological evaluation to yield threshold, or ADE values (EMA, 2014b,c; EU, 2008).

Risk assessors use many specific technical terms when developing ADEs, but there has been lack of consistency in the use of terms, as well as a lack of clarity as to what these terms mean (Bercu et al., 2016; Faria et al., 2016; Gould et al., 2016; Hayes et al., 2016; Reichard et al., 2016; Sargent et al., 2016; Sussman et al., 2016a, 2016b; all in this issue). An important first step in harmonizing ADEs is to ensure that these often used terms are defined unambiguously, precisely and in a manner that is easily understood by all parties. Table 1 reports definitions of several of these key terms used in ADE derivation and implementation, including multiple definitions for the same term when they are not aligned. It is hoped that use of these definitions will improve communication, increase consistency across ADE documents and ultimately facilitate sharing of information.

2. ADEs and program management

ADE values are derived through an organized program led by technical experts who have a thorough understanding of the product portfolio and access to applicable datasets. While different assessment programs may follow similar underlying principles, specific methodologies and conventions will vary from program to program and consequently result in some differences in the final assessments (discussed below). This is considered acceptable because it has been established that different programs can produce varying values that are equally scientifically sound while using slightly different methodologies, defensible, and protective of human health. In addition, the flexibility to use program specific