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Identifying and assessing highly hazardous drugs within quality risk management programs

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ABSTRACT

Historically, pharmaceutical industry regulatory guidelines have assigned certain active pharmaceutical ingredients (APIs) to various categories of concern, such as “cytotoxic”, “hormones”, and “steroids”. These categories have been used to identify APIs requiring segregation or dedication in order to prevent cross-contamination and protect the quality and safety of drug products. Since these terms were never defined by regulatory authorities, and many novel pharmacological mechanisms challenge these categories, there is a recognized need to modify the historical use of these terms. The application of a risk-based approach using a health-based limit, such as an acceptable daily exposure (ADE), is more appropriate for the development of a Quality Risk Management Program (QRMP) than the use of categories of concern. The toxicological and pharmacological characteristics of these categories are discussed to help identify and prioritize compounds requiring special attention. Controlling airborne concentrations and the contamination of product contact surfaces in accordance with values derived from quantitative risk assessments can prevent adverse effects in workers and patients, regardless of specific categorical designations to which these APIs have been assigned. The authors acknowledge the movement away from placing compounds into categories and, while not yet universal, the importance of basing QRMPs on compound-specific ADEs and risk assessments. Based on the results of a risk assessment, segregation and dedication may also be required for some compounds to prevent cross contamination during manufacture of APIs.

1. Introduction

The use of health-based limits, such as the Acceptable Daily Exposure (ADE) or Permitted Daily Exposure (PDE), to guide pharmaceutical manufacturing is becoming a key component of Quality Risk Management Programs (QRMPs) (EMA, 2014; ISPE, 2010). However, drug regulatory agencies in some countries still require the segregation of certain categories of drug products in manufacturing facilities. Their primary concern is the potential for cross-contamination of one drug product with another substance that may be considered highly hazardous. However, control of contamination as well as occupational exposures must also be considered. In past years, regulatory authorities have identified “categories of concern” for potentially hazardous active pharmaceutical ingredients (APIs) to implement this mission (Sargent et al., 2016, this issue). This method allowed manufacturers to provide appropriate segregation, where necessary, according to current Good Manufacturing Practices (cGMP).

The following requirements have been applied to APIs in certain categories of concern, such as “cytotoxics”, “hormones”, “steroids”, or where a risk assessment and equipment cleaning could not adequately demonstrate the lack of potential risk of cross-contamination:

- DEDICATION (separate building, self-contained),
- SEGREGATION (same building, dedicated area), and

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- CAMPAIGN MANUFACTURING (temporal segregation, dedicated equipment).

As explicit regulatory or industry definitions for many of these categories are lacking, identification of those APIs requiring segregation has been subjective and inconsistent. If standardized definitions for these categories had been adopted, manufacturers and regulators could have used consistent criteria to evaluate APIs and determine when segregation and containment was appropriate.

The regulatory requirement for segregation was intended to provide a level of safety for patients, as it was believed that, for these categories of APIs no level of cross-contamination was considered acceptable. This was based on the premise that for non-threshold effects, such as carcinogenicity by direct acting agents that damage DNA, no exposure is without risk. Like *beta*-lactams, which may cause severe allergic reactions from cross-contamination at low levels in susceptible individuals, other categories of APIs considered for segregation may also cause undesirable effects at low doses. Drug innovators often receive questions from contract manufacturing organizations (CMOs) as to whether or not their drug falls into one of these categories because of internal requirements and the perception of specific regulatory expectations. The CMO must then determine whether manufacturing the API in question will compromise their ability to make other drug products in the same facility or equipment. Drug innovators are equally concerned that their API may be manufactured in facilities and equipment used previously by the CMO to manufacture a cytotoxic, genotoxic, steroid, or sensitizer and thus are questioning CMOs as to whether they have ever handled these types of compounds. This request creates a great deal of confusion because the innovator and CMO may have very different definitions of cytotoxicity (Olson et al., 2016, this issue). The problem with focusing on specific categories of drugs is that some compounds and/or therapeutic classes that can produce serious adverse effects at very low doses may not get the same scrutiny. For example, prostaglandins may be overlooked because they are not steroidal hormones, but can cause uterine contractions, miscarriage, and bronchoconstriction at microgram-range doses. The shift to reliance on health-based exposure limits (*e.g.*, ADEs and PDEs), which should be estimated or formally derived for all compounds, addresses this concern. A similar strategy has been used for potential mutagenic impurities in drug substances (EMA, 2006; ICH, 2014a; Müller et al., 2006; U.S. FDA, 2008). These documents have contributed thoughts and ideas towards the definition of genotoxic versus non-genotoxic and the "science of setting safe exposure limits".

In addition to overlooking compounds worthy of scrutiny, the use of these categories of concern can lead to the implementation of excessive requirements for API handling and disposal. By using appropriate quantitative risk assessments, safe levels of occupational exposure or cross-contamination can be determined on a compound-by-compound basis. For example, APIs developed as antineoplastic agents may not need segregation if an ADE can be established and facility cleaning standards can be achieved and validated to provide sufficient protection. As the science of setting safe exposure limits has evolved significantly over the past two decades, there is no longer a need to single out these compounds of concern.

Using a risk-based approach, as recommended in the ISPE Risk-MaPP Baseline Guide, a CMO can use a health-based limit (ADE) to develop an appropriate cleaning program, and an Occupational Exposure Limit (OEL) for engineering design and worker protection (Faria et al., 2016, this issue; Hayes et al., 2016, this issue; ISPE, 2010). Risk assessments based on ADEs can also be used to determine whether there is a sufficient margin of safety (MOS) for co-manufacturing in a shared facility. A transparent way to identify and assess highly hazardous drugs that may require segregation or dedication is still needed. The derivation of an ADE for each of these compounds, coupled with a risk assessment, allows a manufacturer to determine if co-manufacturing is possible or if dedication of an entire facility, equipment, or the dedication of specific parts (*e.g.*, filling heads and tubing) is required. Fig. 1 illustrates the concept of "degrees of segregation" that may be appropriate for different major classes of compounds.

Under this new paradigm, the purpose of assigning a drug substance to a specific category should now be to prioritize individual assessments of these compounds and focus attention on the most hazardous APIs. It should not be done solely to determine whether segregation or dedication is required.

2. Regulatory history

In the past, various cGMP guidelines [*e.g.*, those from Brazil, Canada, European Union (EU), Pharmaceutical Inspectors Cooperative Scheme (PIC/S), UK, US, and the World Health Organization (WHO)] identified the "most hazardous contaminants" to include (with minor variations): highly sensitizing materials (*e.g.*, penicillins), biological preparations containing live organisms, and certain hormones, certain cytotoxics, and other highly active compounds (Sargent et al., 2016, this issue). While not complete, the following provides a few examples of how regulators have approached the segregation of certain classes of compounds. The original language in a recently revised version of Chapter 5 of the EU GMP Guide (EMA, 2008) read as follows:

> "In order to minimise the risk of a serious medical hazard due to cross-contamination, dedicated and self-contained facilities must be available for the production of particular medicinal products, such as highly sensitizing materials (*e.g.*, penicillins) or biological preparations (*e.g.*, from live microorganisms). The production of **certain** additional products, such as **certain** antibiotics, **certain** hormones, **certain** cytotoxics, **certain** highly active drugs, and non-medicinal products should not be conducted in the same facilities. For those products, in exceptional cases, the principle of campaign working in the same facilities can be accepted provided that … "

The EU GMP/Good Distribution Practice (GDP) Inspectors Working Group issued a concept paper in February 2005, followed by updates in January 2008 and December 2009, to request

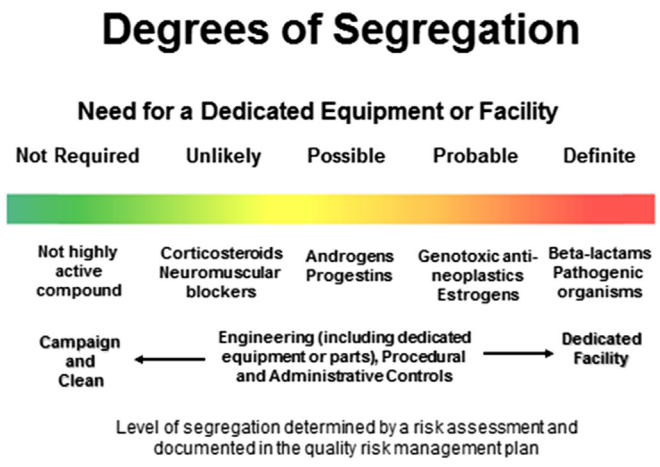

Fig. 1. Levels of segregation determined by a risk assessment.