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The regulatory framework for preventing cross-contamination of pharmaceutical products: History and considerations for the future

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ABSTRACT

Cross-contamination in multi-product pharmaceutical manufacturing facilities can impact both product safety and quality. This issue has been recognized by regulators and industry for some time, leading to publication of a number of continually evolving guidelines. This manuscript provides a historical overview of the regulatory framework for managing cross-contamination in multi-product facilities to provide context for current approaches. Early guidelines focused on the types of pharmaceuticals for which dedicated facilities and control systems were needed, and stated the requirements for cleaning validation. More recent guidelines have promoted the idea of using Acceptable Daily Exposures (ADEs) to establish cleaning limits for actives and other potentially hazardous substances. The ADE approach is considered superior to previous methods for setting cleaning limits such as using a predetermined general limit (*e.g.*, 10 ppm or a fraction of the median lethal dose (LD_{50}) or therapeutic dose). The ADEs can be used to drive the cleaning process and as part of the overall assessment of whether dedicated production facilities are required. While great strides have been made in using the ADE approach, work remains to update good manufacturing practices (GMPs) to ensure that the approaches are clear, consistent with the state-of-the-science, and broadly applicable yet flexible enough for adaptation to unique products and situations.

1. Introduction

Pharmaceutical companies, regulators, and other stakeholders such as public health advocacy groups maintain a partnership in their concern for product quality and occupational safety during the manufacture of pharmaceutical products. While principles of risk management are considered integral to all aspects of pharmaceutical business, risk management principles and quality systems approaches have not been consistently utilized or applied in pharmaceutical manufacturing (ISPE, 2010). In recent years, cross-contamination of medicinal products in shared facilities has come under increased regulatory scrutiny. Global regulations and guidelines for preventing cross-contamination have been published and have increasingly taken a risk-based approach. To evaluate and discuss a consistent approach for assessing health hazards of drug substances (DS) and intermediates (IM) and derivation of health-based exposure limits, representatives of pharmaceutical companies and consultants joined efforts in an expert workshop (Weideman et al., 2015). The purpose of this manuscript is to review how Good Manufacturing Practice (GMP) regulations have evolved with respect to cross-contamination issues in multi-product facilities, the influences that led to this evolution, and finally identification of areas of future dialogue between private partners and regulatory authorities. This dialogue would ensure that the interests of all parties in achieving practical, consistent, science-based, and health-protective strategies for preventing

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cross-contamination can be achieved. Table 1 lists a summary of available guidelines for use in pharmaceutical manufacturing and safety. It also lists additional resources for using risk-based approaches to set safe exposure limits for environmental and workplace chemical exposures that can also provide useful information for pharmaceutical risk assessments.

2. Historical review of regulatory approaches for GMPs as they pertain to cross-contamination in multi-product facilities

In 1978, the US Food and Drug Administration (US FDA) issued regulations pertaining to "minimum current GMP" for preparation of drug products for administration to humans or animals (US FDA, 1978). Subpart C of 21 CFR 211.42 broadly outlined requirements for the prevention of cross-contamination. It states "Operations shall be performed within specifically defined areas of adequate size. There shall be separate or defined areas or such other control systems for the firm's operations as are necessary to prevent contamination or mix-ups during the course of the following procedures …" (US FDA, 1978). Other drug regulatory bodies including the European Medicines Agency (EMA), the World Health Organization (WHO), and the Ministry of Health, Labour, and Welfare (MHLW) in Japan followed with similarly broad requirements. The lack of specificity as to the scope of guidance, different interpretations as to the classification of compounds, and the lack of agreement as to the acceptable level of controls required for the manufacture of highly hazardous compounds led to concerns about manufacturing pharmaceutical products in multi-product facilities.

The Pharmaceutical Inspection Convention (PIC) and Pharmaceutical Inspection Co-operation Scheme (PIC Scheme) are two international instruments involving countries and pharmaceutical inspection authorities to improve cooperation in GMP. The PIC was founded in October 1970 by ten initial member countries of the European Free Trade Association (EFTA), under the title of "The Convention for the Mutual Recognition of Inspections in Respect of the Manufacture of Pharmaceutical Products". PIC has currently grown to 18 members. The PIC Scheme was formed in 1995 to allow new member countries to join PIC, and is an informal agreement between health authorities instead of a formal treaty between countries. PIC and PIC Scheme, which operate together in parallel, are jointly referred to as PIC/S. The PIC/S goal is "to lead the international development, implementation, and maintenance of harmonized GMP standards and quality systems of inspectorates in the field of medicinal products" (Rosa, 2014). At the PIC/S Conference in Canberra in 1996, consensus was reached to prepare an international GMP, with the draft document prepared during 1997 and 1998. The International Conference on Harmonization (ICH), in its Q7 document, assumed the work of PIC/S in mid-1998 to enable industry from US, European countries not already members of PIC/S, and Japan to become involved (ICH, 2001). There are now 50 member countries and organizations including the US FDA and WHO. The ICH Q7 GMP Guide (found in Table 1) was finalized in November 2000 after extensive public consultation. Most countries adopted the ICH Q7 document as a GMP requirement for active pharmaceutical ingredients (APIs) by April 1st, 2001 (in less than one year following finalization), and this ICH document became Part II of PIC/S GMP Guide in 2007 (Rosa, 2014). The PIC/S Guide to Good Manufacturing Practice for Medicinal Products has undergone 11 revisions since 2000 with the last being March 1st, 2014 (PIC/S, 2014).

ICH Q7 provides guidance "regarding GMP for the manufacturing of APIs under an appropriate system for managing quality" (ICH, 2001). ICH Q7 provided greater detail on when and how pharmaceuticals could be manufactured in multi-product facilities. In terms of requirements for containment, it states "dedicated production areas should be employed in the production of highly sensitizing materials such as penicillin or cephalosporin" and further that dedicated production areas "should also be considered when material of an infectious nature or high pharmacological activity or toxicity is involved (*e.g.*, certain steroids or cytotoxic anti-cancer agents) unless validated inactivation and/or cleaning procedures are established and maintained" (ICH, 2001). For more information on defining these terms, see Sussman et al. (2016a, this issue). ICH Q7 also provides further guidance on cleaning validation of multi-product facilities and equipment in that a representative intermediate or API can be used for cleaning validation for multiple products as long as the representative has similar potency, toxicity, and stability, among others. This guidance also states that validated analytical methods with sufficient sensitivity should be used that have adequate detection limits. The guidance further states "limits can be established based on the minimum known pharmacological, toxicological, or physiological activity of the API or its most deleterious component" (ICH, 2001).

ICH Q7 was adopted by many countries including the United States (US), European Union (EU), Canada, and Japan. In 2003, the EU issued GMP Guidelines in which the EudraLex modified the language in ICH Q7 for Chapters 3 and 5 of Volume 4 (EU, 2008) (found in Table 1). In Chapter 3, the EU GMPs stated "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 micro-organisms). 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. The manufacture of technical poisons, such as pesticides and herbicides, should not be allowed in premises used for the manufacture of medicinal products" (EU, 2008). In Chapter 5, the EU GMPs also modified the ICH Q7 language for equipment cleaning in multi-product facilities. It states "Contamination of a starting material or of a product by another material or product must be avoided. Amongst the most hazardous contaminants are highly sensitizing materials, biological preparations containing living organisms, certain hormones, cytotoxics, and other highly active materials. Products in which contamination is likely to be most significant are those administered by injection and those given in large doses and/or over a long time" (EU, 2008). This guidance suggests avoidance of cross-contamination by technical or organizational measures, such as segregated areas or separation in time with adequate cleaning measures (EU, 2008).

In February 2005, EMA issued a concept paper noting that there is "a lack of clarity in the existing GMP guide with respect to when a medicinal product should be manufactured in dedicated and self-contained facilities" and that no guidance is given to clarify what is meant by "*certain*" and "*exceptional cases*". EMA further proposed "that any guidance in this field should take into account the principles and concepts of quality risk management advocated in the forthcoming ICH Q9 document". In November 2005, ICH Q9 was issued which broadly "defines use of quality risk management for identification of dedicated or segregated facilities/equipment and mitigation of risk via quality procedures" (ICH, 2005a). ICH Q9 has been adopted by many countries, including the US, EU, and Japan (found in Table 1).

In June 2005 and January 2006, industry meetings were held at which the US FDA presented considerations for requiring manufacturing segregation (similar to penicillin) for potent or hazardous compounds. Further discussions on approaches to setting acceptable daily exposure (ADE) limits, cleaning, and