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Formalized Risk Assessment for Excipients

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Foreword

Joint Initiative between IPEC Federation and PDA

In March 2018, the IPEC Federation and PDA announced their first joint initiative. Both associations signed a memorandum of understanding to collaborate on the development of a joint technical report on excipient good manufacturing practices risk assessment in response to input from their respective memberships. Prior to the collaboration announcement, however, both parties were active on the topic of quality risk management. PDA published the *PDA Technical Report No. 54* series. In March 2016, IPEC Europe published the *How-To Document – A Guide to Support Manufacturing Authorization Holders (MAH) in their Compliance with the European Commission Guidelines on Risk Assessment for Excipients (2015/C 95/02)*. Subsequently, in May 2017, IPEC-Americas and IPEC Europe jointly published the *Risk Assessment Guide for Excipient Makers, Users, and Distributors*.

Both PDA and IPEC Federation believe that presenting a common approach to the legal, regulatory, and related issues concerning excipients is best done as "one voice." Both collaborators see significant potential benefit in leveraging the two organizations' expertise on excipients and drug product manufacture. This technical report will serve as a practical guidance intended for use with existing regulatory and industry standards. The authors expect that the document will enable Manufacturing Authorization Holders of drug product to either set up or benchmark their quality systems and further establish or continue to collaborate with parties in their excipient supply chain.

This joint PDA-IPEC technical report extends the *PDA Technical Report No. 54* series and provides guidance on risk assessments for excipients by presenting a model risk assessment, guidance on key elements, and a collection of actual examples from excipient users in the pharmaceutical industry.

About Parenteral Drug Association (PDA)

The Parenteral Drug Association (PDA) is the leading global provider of science, technology, and regulatory information and education for the pharmaceutical and biopharmaceutical community. Founded in 1946 as a nonprofit organization, PDA is committed to developing scientifically sound, practical technical information and resources to advance manufacturing science and regulation. Through the expertise of more than 10,000 members worldwide, PDA promotes the exchange of rapidly evolving information on science, technology, and regulations concerning high-quality pharmaceutical production to better serve patients.

About IPEC Federation

The IPEC Federation (IPEC) is a global organization that promotes quality in pharmaceutical excipients. The IPEC Federation represents five regional International Pharmaceutical Excipient Councils (IPECs) — IPEC-Americas, IPEC Europe, IPEC Japan, IPEC China, and IPEC India — and provides a unified voice to promote the best use of excipients in medicines as a means of improving patient treatment and safety. IPEC's objectives are to contribute to the development and harmonization of international excipient standards, the introduction of useful new excipients to the marketplace, and the development of good manufacturing and good distribution practices for excipients.

1.0 Introduction

Excipients are integrated into the drug product formulation for various reasons: to aid the drug product formulation, to serve as functional or nonfunctional ingredients, or to enable the drug to be released from the drug product in a particular, desired manner. The rationale for their use extends beyond the point of medical use to include maintenance of the safety or function of the drug product, even during storage. While good manufacturing practices (GMP) regulations clearly outline what is required for active pharmaceutical ingredients, only a basic framework exists for ascertaining appropriate GMP for excipients through risk assessment.

In recognition of the criticality of excipients in the production of drug products, the European Commission (EC) Falsified Medicines Directive (2011/62/EU) revised Article 46(f) of Directive 2001/83 to require manufacturing authorization holders to verify that any excipients used in a product are made according to appropriate GMP standards ***(1).*** The Falsified Medicines Directive also committed the EC to publishing *Guidelines on the formalised risk assessment for ascertaining the appropriate GMP for excipients of medicinal products for human use* (EC Guidelines), which were published on March 19, 2015 ***(2)***. In 2018, PIC/S incorporated the same provisions for formalized risk assessment into a publication of the same name, extending the provisions to have global applicability ***(3)***. In the U.S., the 2012 Food and Drug Administration Safety and Innovation Act redefined "current good manufacturing practices" to include "the implementation of oversight and controls over the manufacture of drugs to ensure quality, including managing the risk of and establishing the safety of raw materials [and] materials used in the manufacturing of drugs," in addition to the final drug product ***(4).*** This change also emphasizes the criticality of excipients.

Although the accountability for risk assessment rests entirely with the manufacturing authorization holder, all parties in the supply chain are required to support the process by providing relevant information (e.g., Excipient Information Packages ***(5)***) to the manufacturing authorization holder. The risk management process is applicable throughout the excipient's lifecycle, that is, from selection through termination of use, and remains the responsibility of the manufacturing authorization holder at each stage.

Over the course of an excipient's lifecycle, there will be a broad array of drivers for risk assessment and reassessment. Those drivers may include, among others, product deviations, market recalls, changes in excipient use, supply chain amendments, and adverse trends in quality. The manufacturing authorization holder is responsible for providing evidence that the risk management approach adopted is commensurate with the level of risk to ensure the safety, purity and other quality characteristics of the excipient in use.

To comply with the EC Guidelines and PIC/S publication, each excipient used in a drug product must be assessed for the risks that it poses to the product's quality, safety, and purity. From these risks, the manufacturing authorization holder must determine the quality standards required for the manufacture of the excipient. The manufacturing authorization holder should communicate these quality standards to the excipient supplier and seek the supplier's agreement. Any confirmed gaps in quality standards determined by the assessment must be appropriately mitigated, which may require the manufacturing authorization holder to take action on its own or through collaboration with the supplier. To ensure that risk assessments remain effective during the excipient's lifecycle, the manufacturing authorization holder must incorporate a periodic review into the excipient risk assessment process.

Figure 1.0-1 illustrates this overall, iterative risk management process as it is used in supply chain management ***(6).***

1.1 Purpose

This report is based on the general principles of quality risk management (QRM) as outlined in ICH Quality Guideline *Q9 Quality Risk Management* ***(7).*** It has been developed to provide additional guidance on the excipient risk assessment process required by the EC Guidelines and incorporated into the PIC/S publication. In addition, TR 54-6 presents a model risk assessment and real-world examples