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IPAC-RS COMMENTS ON USP <1220> ANALYTICAL PROCEDURE LIFE CYCLE[1]

For submission by email to: Horacio N. Pappa (hp@usp.org), Director, General Chapters, USP

The International Pharmaceutical Aerosol Consortium on Regulation & Science (IPAC-RS) reviewed with interest the new USP chapter <1220> Analytical Procedure Life Cycle.

IPAC-RS is a non-profit association of companies that develop, manufacture or market pharmaceutical products for delivery via respiratory tract - such as metered dose inhalers (MDIs), dry powder inhalers (DPIs), nasal sprays, and other product types - with the goal of advancing science-based and data-based regulations, standards, and practices for these products. A list of current members, and further information are available at http://ipacrs.org.

Overall, we commend USP for producing <1220>, which is a welcome, and clearly written, addition to the regulatory landscape for Analytical Life Cycle Management, and are pleased to offer a few key General and Specific comments below. IPAC-RS is willing to discuss these matters further with USP as needed.

[1] USP NF. PF 46(5), published September 1, 2020. Table of Contents at https://www.uspnf.com/pharmacopeial-forum/pf-table-contents. Chapter <1220> text downloaded from https://online.usppf.com/usppf/document/GUID-35D7E47E-65E5-49B7-B4CC-4D96FA230821_10101_en-US?highlight=1220

General Comments

1. IPAC-RS supports the concepts presented in the chapter, and encourages USP to ensure that future new and revised chapters on analytical methods are building on these life cycle approaches. In particular, tests for complex products, such as pharmaceutical aerosols, need to be described in pharmacopoeial chapters with the life cycle philosophy in mind. In support of that goal, IPAC-RS recommends that future revisions of <1220> include examples from testing aerosols and other drug-device combination products.

2. The document makes mention of replication strategy – but does not seem to give any cross-references to guide "good sampling practice"? The sampling uncertainty may potentially be by far the largest single component of overall uncertainty and the biggest factor in overall PPQ.

Specific Comments

Location	*Original Language*	*Proposed Changed Language*	*Justification of Proposed Change*
Page 1 Introduction	"The procedure life cycle approach described here is consistent with the quality by design concepts described in International Council for Harmonisation (ICH) guidelines."	"The procedure life cycle approach described here is consistent with the quality by design concepts described in International Council for Harmonisation (ICH) guidelines Q.., Q… and Q…."	**It might be useful to state which ICH guidelines are being referenced (e.g. Q2, Q12 and Q14, as outlined in the briefing).**
Page 4 Specification and Decision Rules	"**Scenarios 2 and 3**: In these scenarios, it is less clear that the true quality characteristic is actually above or below the upper acceptance criterion and there is significant probability that the true value of the quality characteristic is actually inside (Scenario 2) or	"**Scenarios 2 and 3**: In these scenarios, it is less clear that the true quality characteristic is actually above or below the upper acceptance criterion and there is significant probability that the true value of the quality characteristic is actually inside (Scenario 3) or outside (Scenario 2)	The example given uses an upper acceptance limit (U_a). In this situation, Scenario 3 would result in a significant probability that the true value of the quality characteristic is actually inside the specification acceptance range, whereas Scenario 2 would result in a significant probability that it is actually outside.

Location	*Original Language*	*Proposed Changed Language*	*Justification of Proposed Change*
	outside (Scenario 3) the specification acceptance range."	the specification acceptance range."	
Page 5: Figure 5 and associated text	"Managing these risks may be achieved by altering the type of decision rule that is used. In the situation where the safe and efficacious range is accurately known, guard bands can be applied to that range, based on the distribution of the total analytical error, to determine the acceptance range (Figure 5)"	"Managing these risks may be achieved by altering the type of decision rule that is used. In the situation where the safe and efficacious range is accurately known, guard bands can be applied to that range, based on the distribution of the total analytical error, to determine the acceptance range (Figure 5), thereby reducing the risk of false acceptance but increasing the risk of false rejection."	Guard bands, as shown in the figure, ensure we don't get a false acceptance, but it doesn't prevent a false rejection. This should be made clear in the associated text.
Page 8 PPQ: Protocol Study and design second bullet point	"The acceptance criteria needed to meet the ATP (accuracy, precision, range)…."	"The acceptance criteria needed to meet the ATP (e.g. accuracy, precision, range)….".	Minor amendment for clarification, and alignment to earlier text: It is understandable why accuracy, precision and range have been added, however it is critical to include the 'e.g.' since ATP criteria will be very dependent on method, approach to defining ATP etc.
Page 9 Routine Monitoring	"This stage includes an ongoing program to collect and analyze data that relate to analytical procedure performance. Monitoring may include tracking analytical performance attributes including SSTs, stability trends, analytically caused invalid results such as out-of-	"This stage includes an ongoing program to collect and analyze data that relate to analytical procedure performance. Monitoring may include tracking analytical performance attributes including ~~SSTs,~~ stability trends, analytically caused invalid results such as out-of-specification or out-of-trend results, SST failures,	SSTs are covered twice in the same sentence and only need to be covered once.

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	specification or out-of-trend results, SST failures, other procedure failures, and other attributes as appropriate."	other procedure failures, and other attributes as appropriate."	
Pages 2-3 and 6-7			Total Analytical Error (TAE) versus Standard Error, and their applicability to Decision Rules: The text regarding Decision Rules (page 3-5), refers to the EURACHEM/CITAC guide. This guide and other literature have the concept of "bottom-up" and "top-down" assessments of **Method Uncertainty** (or a **Standard Error**). The "top down" is broadly the same as Example 2 (TAE) in the ATP (page 2-3), and "bottom-up" utilises the concepts of Ishikawa diagrams, C&E, FMEA random and systematic variation etc. as detailed in the section on Quality Risk Management (QRM) (page 6-7). It would be useful to establish a link between these method uncertainty concepts, ATP and the decision rules and to clarify whether the USP see TAE as being the same as, or fundamentally different to, standard error. On the assumption that method uncertainty is considered different, can the EURACHEM guide be referenced in the QRM section (page 6-7) in addition to the method replication section (page 8) and consider providing a simple example.