February 28, 2018

European Medicines Agency
30 Churchill Place
Canary Wharf
London E14 5EU
United Kingdom

via email to rp-stats-qa@ema.europa.eu

Dear Sir or Madam:

The International Society for Pharmaceutical Engineering (ISPE) would like to submit comments on the document *the EMA Reflection Paper on Statistical Methodology for the Comparative Assessment of Quality Attributes in Drug Development* (EMA/CHMP/138502/2017).

These comments were developed by an international team of ISPE subject matter experts working in collaboration with A3P. The comments on the following pages comprise ISPE's feedback. A3P will submit their comments separately.

ISPE is an individual membership Society of more than 18,500 professionals involved in the manufacture of pharmaceuticals and related products. All scientific and technical areas of the pharmaceutical manufacturing industry are represented among the ISPE membership.

We appreciate the opportunity to submit these comments for your consideration.

Sincerely,

John E. Bournas
CEO & President, ISPE

February 28, 2018

Submission of comments on 'Reflection paper on statistical methodology for the comparative assessment of quality attributes in drug development' (EMA/CHMP/138502/2017)

Comments from:

Name of organisation or individual
International Society for Pharmaceutical Engineering (ISPE) **7200 Wisconsin Avenue, Suite 305** **Bethesda, MD 20814 USA** **+1 301-364-9210** **regulatorycomments@ispe.org** **Transparency Register # 316626227774-56**

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).

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Send a question via our website www.ema.europa.eu/contact

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	We appreciate the opportunity to comment on the application of statistical methods to comparability assessments. We support the development of guidance for comparability assessments (especially for biosimilarity) and hope that our comments will prove useful to the EMA reflection paper authors. The paper contains a significant discussion on the limitations of the application of statistical methods to comparison situations. Non-statisticians may interpret the paper to mean that statistics is not helpful for comparability assessments. We believe that statistical assessments can be important components of such assessments even with the limitations discussed in the paper. We propose that statistical evaluations should not be considered the sole decider of comparability. Clinical relevance should be considered. Statistical comparison should be viewed along with the totality of the evidence for comparability especially the science and engineering used to develop the biosimilar, generic or process change. If statistics is deemed not suitable for this task, what approaches should be used? How will manufacturers and regulators agree on a subjective data analysis? To help address the challenges of using statistical methods for comparability assessments, we recommend obtaining additional input from non-clinical statisticians (those working in chemistry, manufacturing and control, CMC) that have substantial experience with this type of data and the issues the paper raises.	
	We suggest that the document be split into several documents instead of a large document which covers all three areas of application detailed in the paper. The scope of the paper is quite large and difficult to	

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	thoroughly cover. For example, a discussion of F2 calculations could take an entire paper to adequately cover. We suggest focusing on an initial paper for biosimilars since such guidance is urgently needed. The three areas of application discussed in the reflection paper are entirely different situations for patients and for manufacturers. The analysis approach might be very different in each of these situations and the issues raised in the paper may be more or less important.	
	We suggested adding references in Section 2: *e.g. ICH Q2 R1*	
	We suggest mentioning power and sample size in the general section of the document in addition to section 5.7	
	We suggest further clarifying the definitions for similarity, equivalence, comparability so that all stakeholders have a common understanding.	
	We suggest adapting the approaches based on the number of batches available. A comparability assessment using an equivalence approach (two-one sided test) is very relevant but this approach needs an appropriate sample size and well balanced design. These conditions are usually not achieved in the industrial context. Interval approaches should be allowed in this situation especially during the post change comparison.	
	If the paper continues to cover all areas of comparability assessment, we suggest the document provide guidance on equivalence of test methods.	
	We suggest adding discussion of the use of Bayesian methods for small sets of data in addition to the disclaimer section. It would be possible to introduce additional information into the comparison through appropriate use of Bayesian methods.	
	An assumption for most statistical methods is that the measurements on the lots are independent. Yet for many biological/vaccine processes which manufacture lots in campaigns, there is a campaign effect due to changes in process conditions (e.g., lots of raw materials) and some testing practices (batch testing). These kinds of effects are acknowledged as part of long-term, common cause variability, and should be taken into account in the comparability design and analysis.	

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	The impact of violation of this assumption of independence should be discussed. The lack of independence of the data is not in the control of the biosimilar manufacturer so the paper should discuss approaches that mitigate the impact. Robust analysis approaches should be considered and statistical assessment should not be viewed as the only input to the conclusion of similarity or not since such limitations can never be fully removed from the analysis.	
	We suggest that the paper provide examples of appropriate comparability evaluations.	
	We suggest clarifying that the issues discussed in the paper are present in all experiments and analysis of data. It is important for non-statisticians to understand the issues discussed are not unique to comparability situations.	
	We suggest that the document provide guidance on how to choose the appropriate quality attributes. All Quality attributes are not equal and it would enhance the paper if guidance on determining criticality of the quality attributes was included as well. Discussion should be in alignment with the concepts in ICH Q8 and Q11.	

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
78-79		Suggest the change from "the comparison of empirical data…is of importance in many areas of **drug development**" to "in many areas of **drug development and the lifecycle of a product**" which give a larger purpose for these comparison data.	
89-90		Suggest the change from: 'mostly based on information regarding known or expected variability to: "mostly based on scientific knowledge or impact to process capability" There are two possible ways to define the comparability criteria: 1- Using the scientific knowledge, product experience and/or clinical relevance; 2- Using the potential impact on the process capability when there is sufficient data available. The text seems to suggest defining the criteria by understanding the impact on the "variability of data", but in reality, the impact could be on both the average and the variability of the data. The criteria could be expressed as an impact on process capability if the specification limits and sufficient data are available.	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
106, 107		Suggested change from :'**comparability**' to '**similarity**'	
229		Suggested change: "manufacturing change or transfer", add analytical change. Changes to the analytical methods (including the reagents) could impact directly the measurement of the product.	
391/393		Suggested change: "Several methods are applied in this context, and not all of them might be considered suitable to take into account the uncertainty arising from the fact that specifications are often calculated based on data from sampled batches rather than based on clinical relevance."	
431		Suggested change from: "characterising underlying manufacturing processes" To "manufacturing and analytical procedure" We suggest that Analytical Changes are part of the process changes.	
482		Suggested change from: "representative for the underlying data generating process" to: Add at the end: process "(e.g. the last consecutive manufacturing batches before the change which are under control)"	
524		Suggested clarification to the discussion of Min, Max, Range and non-parametric methods. The Min, Max and Range should not be used as acceptance criteria but can be very useful to present a concise summary of the data. Non-parametric methods are used when the parametric distribution assumptions are not met.	

Please add more rows if needed.