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Quality Assurance Programme  
Quality Assurance and Safety: Medicines (QSM)  
Department of Medicines Policy and Standards (PSM)  
World Health Organization  
CH-1211 Geneva 27  
Switzerland

**WHO DRAFT PHARMACEUTICAL DEVELOPMENT FOR MULTISOURCE (GENERIC)  
PHARMACEUTICAL PRODUCTS**

ISPE welcomes the opportunity to comment on the WHO document QAS/08.251: Draft Pharmaceutical development for multisource (generic) pharmaceutical products. Our comments are attached and should be read in conjunction with the attached line-numbered pdf document. We generally support the proposal and our specific comments are intended to clarify its provisions.

If you have any questions please do not hesitate to contact me.

Thank you for the opportunity to comment.

Yours sincerely,

Robert P. Best  
President/CEO

Attachments: ISPE Regulatory Comment Form, QAS/08.251  
Line-numbered QAS/08.251

**ISPE Regulatory Comment Form**

**Proposed Regulation/Guidance Document:**

**PHARMACEUTICAL DEVELOPMENT FOR MULTISOURCE (GENERIC) PHARMACEUTICAL PRODUCTS, QAS/08.251, January 2008**

No.	LINE NUMBER	CURRENT WORDING	PROPOSED CHANGE	RATIONALE
1.	After 80	Table	Suggest delete last row	The row may not show a formulation difference between Innovator and Multisource FPPs, but indicates different FPPs.
2.	93	The information and knowledge gained from pharmaceutical development studies and experience with the manufacture of primary batches provide scientific understanding to support the proposed critical quality attribute(s) (CQA(s)) of the FPP (quality control (QC) and in-process control (IPC) acceptance limits) and critical process parameter(s) (CPP(s)) and their manufacturing controls, which can be essential inputs for quality risk management.	The information and knowledge gained from pharmaceutical development studies, experience with the manufacture of primary batches, and quality risk management, provide scientific understanding to support the proposed critical quality attribute(s) (CQA(s)) of the FPP (quality control (QC) and in-process control (IPC) acceptance limits) and critical process parameter(s) (CPP(s)) and their manufacturing controls.	Quality risk management is used, in an iterative way, to confirm the appropriateness of CQAs, and CPPs etc. The current guideline is ambiguous, but suggests the process is the other way around.
3.	100	This guideline.....	The guideline QAS/08.251	With original wording, 'this' applies to the ICH CTD guideline, which would be incorrect.
4.	113	Uses of risk, risk factors, quality risk, risk classification etc	It is recommended that this section be re-written using the terminology provided in ICH guideline Q9. The tables do not present risk factors (although there is no agreement on what a risk factor would be), given that there is no reference to harm.	
5.	132	The initial risk assessment of CQAs and CPPs of a generic company should be based .....	The initial risk assessment used to establish which variables and unit operations are likely to have the greatest impact on product quality should be based.....	It is not a risk assessment of CQAs, nor CPPs. There is a misunderstanding of the process here.

6.	146	. . . only if it can detect changes (discriminate) between different formulations.	Insert reference to documented requirement in order to have the method "discriminating." (e.g., reference to FDA Guidance for Industry, August 1997.	Better definition
7.	147	To determine if a dissolution method can discriminate formulation changes,	To determine if a dissolution method can discriminate between formulation or manufacturing process changes,	It is important to recognise that a change in a process can lead to a change in availability of the active ingredient.
8.	165	All the attributes of the dosage form should be analysed in the QC laboratory	A risk analysis should be conducted to identify those attributes most likely to be useful in controlling the quality of the finished product. These should then be tested in the QC laboratory according to a relevant sampling scheme.	It is inappropriate to state 'all'. Many attributes of the innovator sample are also likely to be specified and controlled during the manufacturing process. It therefore also becomes important to specify the number of units to be tested.
9.	187	The specifications of the API manufacturer should be completed with potentially critical properties of the API, together with acceptance criteria, as applicable, e.g. solubility at 37oC to permit BCS classification of the API,	The specification of the API manufacturer should be complimented with potentially critical properties of the API, as applicable, e.g. solubility at 37.....,	There are several issues with this sentence. Presumably the guidance is to ADD to the specification of the manufacturer? Here, and elsewhere in the document, specification should be used in its ICH meaning, and therefore should not be plural. For API attributes that are intrinsic to the molecule, there is no value in setting acceptance criteria (e.g. solubility). Solubility on its own is insufficient for BCS classification – permeability is also needed.
10.	195	Stress testing of the API should be designed to simulate as far as possible the conditions that may be encountered during the manufacturing process of the FPP (an example is illustrated in Annex 3).	Stress testing of the API should be designed to ensure that degradation products likely to arise through manufacture and storage of both the API and finished product are produced, and so that the specificity of the analytical procedure can be verified.	Stress testing is used to establish the validity of analytical methods. The Annex 3 has very limited relationship to the manufacturing process for a wet granulated product. It is also not clear that the outcome of the studies would be used to verify the analytical procedures.

11.	209	When an excipient is critical for manufacturability of the FPP, batch or supplier variations should be minimized through including user requirements in the pharmacopoeial specifications.	At a minimum, those aspects of the excipients that are critical to product quality should be determined and control strategies justified. When a quality attribute of an excipient is identified as being critical, an understanding of the impact of variability should be demonstrated, and appropriate specification criteria established in addition to the pharmacopoeial specification.	There is no agreed definition of the word 'critical' in this context, and so it should be used in conjunction with eg, quality attribute. Furthermore, unless there is an understanding of the impact of variability on product quality, there is no rationale to back any limits that might be set. Simply 'minimising' does not have scientific credibility.
12.	220	When the container and closure system is a critical factor of FPP stability, batch or supplier variations should be minimized through tight specifications and extended sampling plans for QC testing.	Experimental studies should be conducted to identify any critical attributes of the container closure system. Where critical quality attributes are identified, appropriate tests and acceptance criteria should be added to the specification, together with appropriate sampling plans.	While there may be narrow ranges of acceptance criteria, one cannot have a 'tight specification'. In addition, the science is needed to identify which aspects of the container closure system have an effect upon stability.
13.	224	Once the qualitative composition of the comparator FPP has been identified the individual excipients should be quantified. Screening laboratory batches with different proportions of excipients to match innovator dissolution profile is the best method to select the final formula for scale up (typical ranges of excipients are illustrated in Annex 5).	Once the qualitative composition of the comparator FPP has been identified the quantitative composition of the product should be determined. Formal experimental designs, evaluating the impact of different proportions of excipients on the CQAs and CPPs, are an appropriate method to select the final formula for scale up (typical ranges of excipients are illustrated in Annex 5).	The current text lacks scientific justification, and is certainly not the 'best' method. There is more to designing a formulation than matching a dissolution profile, especially if that profile does not relate to clinical performance. The word 'quantified' (known by measurement) is inappropriately used.
14.	228	The final formula should be stress-tested (e.g. as illustrated in Annex 3) to identify CQA(s) and to establish tentative acceptance limits for their control.	Delete this paragraph.	Stress testing is a procedure to establish degradation pathways and the suitability of analytical procedures. Annex 3 does not indicate appropriate stress testing for a drug product (which is often limited to photostability testing). CQAs are not identified through stress testing, but by a science and risk based assessment of what is required to assure quality. Acceptance criteria should be based on safety and efficacy, not on stress testing.

15.	289	. . . which is frequently identified . . .	. . . which may be identified . . .	It is not always easy to identify this in publicly available information sources.
16.	290	. . . manufacturing process can also be established . . .	. . . manufacturing process could also be established . . .	May not be possible in the "majority of cases."
17.	304	The dissolution profile of the generic FPP should be similar to the dissolution profile . . .	The term "similar" should be defined.	May be ambiguous.
18.	480	Potentially critical physical attributes include clarity of solution, water content and particle size.	Potentially critical physical attributes include water content and particle size.	Clarity of solution is a test, not an attribute of the API. Failure of that test may indicate a GMP problem (particulate contamination). Additionally, for a solid oral dosage form, solution clarity is unlikely to be critical.
19.	497	The free moisture in the tablets is minimized both during the manufacturing process and in the packaging.	Given the sensitivity of the API to hydrolysis, the use of a wet granulation process carries the risk of degradation.	It is not true that the free moisture is minimized. A dry granulation process would carry less risk.
20.	502	Manufacture commences with a conventional wet granulation process, followed by a drying step to dry the granules (to LOD $\leq$ 3%) to reduce the intragranular moisture content. Finally the film coating (aqueous-based) is applied.	Manufacture commences with a conventional wet granulation process, followed by a drying step to dry the granules (to LOD $\leq$ 3%) to reduce the intragranular moisture content. Finally the film coating (aqueous-based) is applied. Given the sensitivity of the API to hydrolytic degradation, both these steps carry the risk of producing degradation products.	Line 502 illustrates that a number of the statements in the Annex do not indicate the risk, they are more statements of fact. The example here is intended to show what the risk associated with the statement is.

21.	507	The proposed specification limits for total impurities and degradation products in both the release and shelf-life specifications are very high and remain to be tightened or further justified by reference to the original toxicological studies.	The proposed specification limits for total degradation products in both the release and shelf-life specifications are very high and remain to be tightened or further justified by reference to the original toxicological studies.	Can delete 'impurities' as it is tautology. It is interesting to see the statement that the criteria should be tightened or justified. If there is insufficient safety/toxicology evidence to justify the level of an impurity, this would be contrary to current regulatory guidelines. When reviewed in addition to the stability issues (8% degradation product limit), this suggests further safety concerns for this product, based on the information provided. The guideline authors are urged to review this section.
22.	520	This table is based on ICH Q9 Quality risk management, Annex II – Potential applications: "Risk Management approach to focus on critical attributes" and has been modified to comply with multisource (generic) pharmaceutical products.	Delete footnote	ICH Q9 does not have any illustrative tables. In addition, the phrase 'critical attributes' is not used in the guideline.
23.	547	Comparator product – bench mark (Hypothetical example - Ph. Int., paddle, 75rpm, 900ml)	See line 155, where it states "...The comparator/reference product should be selected by dissolution profile tests using 12 units or more for three batches of the innovator FPP by the paddle method at 50 rpm."	Reconcile the differences in paddle speed.