PDA
Parenteral Drug Association
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31 August 2010

Katerina Bursikova, Scientific Administrator
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Reference:
Guideline on the Requirements for Quality Documentation Concerning Biological Investigational Medicinal Products in Clinical Trials, draft
(EMA/CHMP/BWP/534898/2008, 18 February 2010)
Deadline for comments: 31 August 2010

Dear Dr. Bursikova,

PDA is pleased to provide comments on this important draft CMC guidance. Our comments were prepared by an expert committee of members with practical expertise in the science, development and manufacture of biological products. We have attached a table in the EMA format that lists both our general and specific comments. Our general comments cover four concerns including: level of information, phase related information, use of prior knowledge, and storage time vs. shelf-life of drug substance. Please see the table for supporting details.

PDA proposes to have a scientific discussion with EMA representatives on the setting of re-test date/expiry date for biotechnological/biological drug substances/drug products. Such a discussion will allow consideration of the complex technical issues related to this topic. Please see the comment table for supporting details.

Again, we appreciate the opportunity to support the development of high quality CMC guidance. PDA is ready to provide support for any activities or discussions that are helpful in furthering the usefulness and interpretation of this guidance. For questions, or to pursue a scientific discussion on re-test date/expiry dates, please contact myself or James C. Lyda of the PDA Staff (lyda@pda.org).

With very best regards,

Georg Roessling, Ph.D.
Senior VP, PDA Europe
Roessling@pda.org

cc: J. Lyda, R. Levy, R. Dana, S. Roenninger, H. Willkommen

Attachment

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

31 August 2010

Submission of comments on:

Guideline on the Requirements for Quality Documentation Concerning Biological Investigational Medicinal Products in Clinical Trials

Draft, 18 February 2010
EMA/CHMP/BWP/534898/2008
End of consultation (deadline for comments) 31 August 2010

Comments from: Parenteral Drug Association (PDA)

Name of organisation or individual
James C. Lyda, lyda@pda.org Tel: 919 809 2411

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).

1. General comments

PDA No.	Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
		Note: PDA has attempted to show deleted text with the strikeout symbols (e.g. ~~strikeout~~), while added text is **bolded.**	
1		**Comment 1: Level of Information:** In general, PDA acknowledges that the current draft is a very comprehensive and well written guidance document. However, there is a concern that, in many instances, the type and level of information being requested is more appropriate for a marketing authorization dossier than for a clinical trial application. As noted in the Introduction of the draft guideline, information provided for an IMP should focus on quality attributes related to safety aspects. In our detailed comments in Section 2, we have provided specific suggestions where the type and level of requested information is inappropriate for a clinical trial application.	
2		**Comment 2: Phase related information:** Except in a few instances (e.g., validation of analytical procedures), the draft guideline does not distinguish between phase appropriate quality documentation requirements for IMPs. While in general we support the flexibility provided by the draft guideline in allowing the sponsor to consider product specific and trial specific aspects when determining an appropriate data package for assessment, the lack of phase specific information requirements can lead to inconsistent expectations among the competent authorities. In several areas we believe that more specific guidance is needed to identify phase appropriate information requirements. Addition of such guidance will help to ensure consistency of interpretation among sponsors and competent authorities. We have provided specific suggestions in this regard in our detailed comments.	

PDA No.	Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
3		**Comment 3: Use of prior knowledge**: The EMA should consider expanding guidance on opportunities where prior knowledge (prior in-house data including those derived from platform technologies) can be applied to meet proposed requirements set forth in the document. The draft guideline currently only refers to this in section S.7.3. We note that such guidance is provided in EMEA/CHMP/BWP/398498/05, Guidance on Virus Safety Evaluation of Biotechnological Investigational Medicinal Products, and recommend that similar provisions be included in this guideline (for example, within sections S.2.2 Description of Manufacturing Process and Process Controls, and S.3.2 Impurities).	
4		**Comment 4: Storage time vs. shelf-life of DS:** PDA is concerned that the application of the term "shelf-life" to biotechnological /biological drug substances is not completely in line with ICH Q1A nor is it applicable to all such substances. Guidances for clinical material should provide flexibility, taking into consideration the specific properties of the substance of the IMPD, and avoid restrictions which are not applicable to large groups of biotechnological /biological substances (like monoclonal antibodies). Please see the detailed comment on lines 408/409. PDA proposes to discuss the setting of retest date/expiry date for biotechnological/biological Drug substances/Drug products in a meeting with EMA representatives. The draft guidance only allows for extrapolations as normally applied to marketed products, which is not appropriate in a development setting. For some groups of biotechnological /biological substances (e.g. monoclonal antibodies), a wealth of supportive data is available to justify an alternative mode of setting retest date/expiry date. Please see the detailed comment on lines 431-432.	

2. Specific comments on text

PDA No.	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
5	98-100		Comment: The sentence is unclear; remove “in’ to improve clarity Proposed change (if any): In the EU, applications to conduct clinical trials are required to be submitted to the competent authority for approval prior to beginning a clinical trial ~~**in**~~ separately in each member state in which the trial is proposed to take place.	
6	110-112		Comment: Assuring the quality of biological medicinal products is challenging, as they consist often of a number of the desired product, its variants and process related impurities. It is difficult to predict the safety and efficacy profile of these variants and process related impurities. “Product variants” is not a commonly used term and no definition is provided in the document. In the interest of clarity the sentence should be changed to the following: Proposed change (if any): Assuring the quality of biological medicinal products is challenging, as often they consist of **the desired product and its variants** ~~product variants~~ and process related impurities. It is difficult to predict the safety and efficacy profile of these variants and process related impurities. It is important to demonstrate comparability between material that goes to pre-clinical and different phases of clinical study.	

PDA No.	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
7	165		Comment: Delete the word “comprehensive” and replace with “relevant” since it is acknowledged that, depending on the stage of development, the product knowledge may be limited. Proposed change (if any): The quality part of the IMPD should include ~~comprehensive~~ **relevant** information related to the quality, manufacture and control of the IMP based on the stage of product development.	
8	178-180		Comment: Reference to an Active Substance Master File or a Certificate of Suitability (CEP) of the European Directorate for the Quality of Medicines is not relevant for biological/biotechnological active substances. As the procedure for an Active Substance Master File is not available in Europe at present, the sentence may better express the current situation if the wording is changed to the following: Proposed change: Reference to an Active Substance Master File or a Certificate of Suitability (CEP) of the EDQM is ~~neither acceptable nor~~ **generally not** applicable for biological / biotechnological active substances **to be used in IMP manufacture.**	
9	187		Comment: Higher order structure information does not need to be provided in section S.1.2, since detailed information is provided in section S.3.1.	

PDA No.	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			Proposed change: The predicted structure including **a short description of** the higher order structure should be provided. The schematic amino acid sequence...	
10	202		Comment: PDA does not believe that details concerning the shipping conditions are appropriate for clinical trial applications. Monitoring and control of shipping conditions during clinical trials is controlled under GMPs. Shipping studies are typically conducted during Phase III to support temperature excursions in the final shipping container as part of the marketing authorisation application. Thus we recommend deletion of 'and shipping' from the text in this section. Proposed change: …..(harvest(s), purification and modification reactions, filling), and storage ~~and shipping~~ conditions.	
11	203-204		Comments: In early phases, in-process testing is often performed as "monitoring" for information only, without definition of acceptance criteria. The guideline should differentiate between requirements for early phases I and II, and the later phase III. The level of detail to be provided in the description of the manufacturing process should also be phase dependent. We proposed rewording this section as shown below. Proposed change:	

PDA No.	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			A flowchart of all successive steps ~~and details of~~ **including** in-process-testing ~~including appropriate acceptance criteria~~ should be given. **Acceptance criteria should be provided as appropriate.** ***Additional information for phase III clinical trials*** **Details of process controls and limits and in-process-testing including appropriate acceptance criteria should be given. Critical steps and intermediates should be identified.**	
12	205-206		Comment: In the interest of clarity the wording should be revised. Flexibility should be maintained during development. Proposed change: The sentence should be revised to the following: ~~Batch(es) and~~ Scale definition ~~should be provided including information on any pooling of harvests or intermediates~~ **and the definition of a batch should be provided including where pooling was performed.**	
13	211-217		Comment: The level of detail to be provided regarding the control of raw and starting materials for the active substance is burdensome and should be required only for critical materials. The text should therefore be amended by adding the word 'critical' in the last sentence as shown below. Proposed change:	

PDA No.	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			Information demonstrating that **critical** materials (including biologically-sourced materials, e.g. media components, monoclonal antibodies, enzymes) meet standards appropriate for their intended use should be provided, as appropriate.	
14	243-244		Comment: Genetic characterization for end of production cells should not be mandatory. The level of characterization is dependent on the stage of development and this should be clarified in the guideline. Replace therefore the current text in lines 243-244 with the following. Proposed change: ~~Any available~~ Data on genetic stability ~~including characterisation of End of Production Cells~~ should be provided. ***Additional information for phase III clinical trials*** **Data derived from characterization of End of Production Cells should be provided (if available) in accordance with the principles of the ICH Q5B Guideline.**	
15	246		Comment: Acceptance criteria of tests for the control of critical steps are not always available. This is especially the case in early stages of product development. Therefore, the first sentence in the paragraph should be amended accordingly: Proposed change: Test and acceptance criteria for the control of critical steps in the	

PDA No.	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			manufacturing process, **when available,** should be briefly summarised.	
16	248-249		Comment: For hold time studies of process intermediates, microbiological testing (such as bioburden) is not considered an appropriate parameter Storage should be based on relevant quality parameters, whereas microbiological controls should be considered as routine monitoring of the process. Proposed change: If holding times are foreseen for process intermediates, periods and storage conditions should be justified and supported by data on physico-chemical, and **biological** ~~and microbiological~~ characteristics/properties.	
17	262-265		Comment: Acceptance criteria of tests for the control of critical steps are not always available. This is especially the case in early stages of product development. Therefore, the last sentence in the paragraph should be amended as proposed already in the previous comment. Proposed change: It is acknowledged that process modifications may require adaptation of in-process and released tests, and thus these tests and corresponding acceptance criteria**, where available,** should be considered when changes are introduced.	

PDA No.	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
18	276-277		Comment: Optimization work on the process often occurs after production of material for non-clinical studies and is subsequently implemented to produce material for first in human clinical studies. The requirement to use material derived from the **same** process as the one used in non-clinical studies seems to be overly prescriptive. If the process is 'representative' changes can be made in the process (e.g. higher scale) but it is demonstrated that the process results in a product that is comparable in all quality attributes. It is proposed therefore to change this sentence accordingly. Proposed change: In the case of first in human clinical trial, it is recommended to use investigational product derived from ~~the same process as~~ **a process representative of** the one used in non-clinical studies.	
19	295-299		Comment: Provision should be made for the use of binding assays as a surrogate of biological activity when justified. The requirement as stated in the draft guidance for a "relevant, reliable and qualified method" prior to initiation of Phase 1 studies could be misinterpreted to imply a requirement for a cell-based assay prior to initiation of Phase 1 studies. Additionally, binding ELISA approaches may continue to be appropriate throughout development and for commercialization depending on the biological mechanism of action. Clarification should also be provided that information needed for product related substances is not required in early phases of development.	

PDA No.	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			Proposed change: For desired product ~~and product related substances,~~ all relevant information available on the primary, secondary, and higher-order structure including post-translational (e.g. glycoforms) and other modifications should be provided. **As product-related substances are characterized in later phases of development, information as described above should be provided for these substances in phase III at the latest.** Details should be provided on the biological activity (i.e. the specific ability or capacity of a product to achieve a defined biological effect). **Justification should be provided for the suitability of the method employed for evaluation of biological activity (e.g. cell-based assay or binding assay).** ~~Prior to initiation of phase I studies, the biological activity should be determined using a relevant, reliable and qualified method~~	
20	300		Comment: The meaning of "justified" is unclear. Characterization assays are not required to be validated or qualified. Change wording of line 300 to the following: Proposed change: ~~The suitability of the methods employed should be justified.~~ **The methods employed should be described and their suitability discussed, if needed.**	
21	315/316		Comment:	

PDA No.	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
	& 333		Product characteristics monitored for information only ('for information only' tests) should not be reported in the clinical trial application. This testing is conducted to understand the characteristics of the molecule and may or may not result in meaningful information. Therefore, it is not appropriate to report these results until relevancy to a critical quality attribute can be established. Proposed change: Add a phrase to the end of the first sentence of the paragraph (on line 315), and delete the last sentence of the paragraph, as follows: Product characteristics... should also be recorded for future evaluation**, but need not be reported in an IMPD**. ~~As a consequence, the results of...~~ Also, Revise line 333 to delete the last words of this sentence, ~~"including those tests reported FIO".~~	
22	320		Comment: The draft guidance states that biological activity assay is mandatory for drug substance. This is not consistent with ICH Q6B which states "When an appropriate potency assay is used for the drug product (section 4.2.4), an alternative method (physicochemical and/or biological) may suffice for quantitative assessment at the drug substance stage." Proposed change:	

PDA No.	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			Test for quantity, identity, and purity ~~and biological activity~~ are mandatory. **A test for biological activity should be included unless otherwise justified.**	
23	338-351		Comment: Validation of analytical methods should be performed during phase III clinical trials. As experience increases during early phases resulting, e.g. in modification of analytical methods, this strategy would be in accordance with the requirements of this guideline for the review and justification of specifications and acceptance criteria in paragraphs S.4.1 and 4.5. Proposed change: Line 342: For phase I/**II** clinical trials, the suitability….. Line 347: Information for phase ~~II and~~ III clinical trials	
24	357		Comment: As results of non-clinical batches are not reported in S.4.4 / P.5.4 and, depending on project schedules and timelines, release of further clinical batches might not occur before submission of the IMPD we recommend changing the word “all” to “relevant” as below: Proposed change: For early phase clinical trials, which are often characterised by a limited number of batches, results for **relevant** ~~all~~ non-clinical and clinical batches should be provided, including the results of batches to be used in the given clinical trial.	

PDA No.	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
25	372-373		Comment: The acceptance criteria will not necessarily reflect process capability even at Phase 3 since there are often a limited number of lots manufactured prior to Phase 3 initiation. Process capability consideration for acceptance criteria is more appropriate for setting specifications prior to marketing authorisation rather than during clinical trials. Proposed change: Change wording to Due to ~~a too~~ limited ~~data base~~ **process knowledge during clinical development** ~~at an early stage of development (phase I/II)~~, the acceptance criteria **at this stage** ~~are~~ **do** not necessarily reflect~~ing~~ process capability.	
26	374-375		Comment: The sentence “Correlation to *in vivo* biological activity should be described” is confusing and needs clarification. It is not clear whether this statement pertains to correlations based on pre-clinical animal studies, or based on human clinical studies. Proposed change: Insert replacement sentence as follows: **Relevance** ~~Correlation~~ to *in vivo* biological activity should be described.	
27	407		Comment:	

PDA No.	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			The term shelf life is considered the correct wording for final drug product (DP), but not for drug substance (DS). It should be carefully differentiated between the storage period of the DS and the shelf life of the DP. Also the applicable requirements are different. Proposed change: Replace the term “shelf life”, in line 407 and other areas of the guideline, with the term “storage period” when discussing the DS, reference is made to the comment No. 28 below.	
28	408-409		Comment: The draft guideline states that “The re-test period (as defined in ICH Q1A guideline) is not applicable to biological / biotechnology derived active substances.” As we understand it, ICH Q1A states, “For most biotechnological/ biological substances known to be labile, it is more appropriate to establish a shelf-life than a re-test period. The same may be true for certain antibiotics.” (Underlining added). Therefore assigning a re-test period is appropriate for those biotechnological/biological substances demonstrated to be stabile at their stipulated storage condition (for example: Monoclonal antibody bulk drug substance solutions are stored at or below -60 °C and are stable under these conditions). It should be left to the discretion of the sponsor to determine whether a biotechnological/biological substance is labile or not, based on the data generated. Proposed change:	

PDA No.	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			Delete Text lines 408-409 and add the following: **Depending on the data generated from controlled stability studies, a re-test period (as defined in ICH Q1A) or a shelf-life may be assigned to the biotechnological /biological substance. The establishment of a re-test period may be appropriate if the stability of the drug substance is supported by relevant data.**	
29	411-414		Comment: Clarification is requested regarding use of stability data from a previous manufacturing process to establish a storage period of the drug substance. If comparability has been demonstrated for material made with two different processes, it should be possible to use stability data collected from both processes for the establishment of the storage period. Allowing the use of such data 'only as supportive data' is overly prescriptive. Proposed change: Stability data should be presented for at least one batch representative of the manufacturing process of the clinical trial material. **If comparability has been demonstrated for material made with two different processes, stability data from both processes can be used for the establishment of the storage period.** Stability data of relevant batches or batches manufactured using previous manufacturing processes should be provided as well ~~but they are to be used as supportive data~~.	
30	420		Comment:	

PDA No.	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			It is not clear what is meant by 'Progressive requirements' in the sentence beginning in line 420. In the interest of clarity this should be reworded. Proposed change: Replace sentence beginning in line 420 with: **The proposed storage period should reflect the available data and emerging knowledge about the stability of the active substance during the different phases of clinical development.** For phase III …	
31	*Line 427, but comment applicable to drug product as well*		Comment: It should be possible to base storage time or shelf life on real-time data of a batch adequately representing the clinical material. Material should be considered representative if produced at smaller scale but with the otherwise identical process (e.g. material for toxicological studies). Especially during early, e.g. First-in-Human studies, often, there is only one clinical batch manufactured closely before start of the trial. Therefore it should be allowed to use stability data from development batches if comparability to the clinical material has been demonstrated. The reference to the Q5C guideline should be deleted as these are requirements for products on the market. Proposed change: Change wording to: The requested storage period should be based on long term, real-time and real-condition stability studies~~, as described in ICH Q5C~~. However,	

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			extension of the storage period beyond the period covered by real-time stability studies may be acceptable, if supported and justified by relevant data, including accelerated stability studies **and data from development batches with demonstrated comparability to the clinical trial material.**	
32	431-435 *but comment applicable to drug product as well*		Comment: The guideline specifies expiration dating not to exceed two-fold and not to be more than twelve months beyond the provided stability data obtained with representative batch(es). There is no doubt that stability data for the biotechnological /biological substance intended to be used in the clinical study have to be obtained. However, the options offered for setting an expiration date do not, unfortunately, take into account a potential wealth of experience available with certain molecule groups, e.g., monoclonal antibodies. For many of these, stability was proven under long-term storage conditions (< -60 °C, where degradation, aggregation and loss of biological activity is not to be expected). So, data for antibodies of the same subclass stored under the same conditions using related formulations can be used to set up a data base which allows for knowledge based alternative means of defining expiration dating schemes for both biotechnological /biological Drug substances and Drug products. A company documenting this experience should be allowed to use such knowledge-based alternatives and not be confined to schemes as defined in the current draft of this guidance, which may not fit all cases. Such alternative expiration dating is already applied for years and accepted in some Member States of the EU and other regions, e.g., US.	

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			Note also, that one advantage of this is avoiding many rounds of re-labelling of clinical material during clinical studies, especially during Phase I. Proposed change: Delete all of the paragraph ~~sentence 1~~ , lines 431-435, and replace with the following text: **The maximum storage period should be based on stability data presented for the batch(es) to be used in the clinical study. Normally, the maximum extension should not exceed two-fold and should not be more than twelve months. However, the sponsor may also present his database for related substances/products (e.g., for other monoclonal antibodies), which would support other, scientifically justified schemes of storage period definition.**	
33	446-447		Comment: Stability studies are performed at the intended storage temperature; also accelerated stability studies are performed. This is laid down in the agreed protocol. There may be cases that OOS results or trending may be observed in accelerated stability studies. It should therefore be clarified that only OOS results or significant trends in stability studies using the intended storage temperature be considered. Proposed change: Change the wording to the following:	

PDA No.	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			- no significant trend or out-of-specification results (OOS) has been detected in ongoing stability studies **at the designated storage temperature.**	
34	461		Comment: Line 461 refers to 'accompanying solvent(s)'. Should this be replaced with reconstitution diluents? Is it intended to refer any administration form e.g. infusion diluents**?** Proposed change: Change the text to • description of **reconstitution diluents** ~~accompanying solvents~~	
35	501-505		Comment: The reference in lines 504-505 does not provide details on content to be included but does provide the definition for "non-standard". As such, we suggest the reference is more appropriately inserted at the end of first sentence (current line 502). Furthermore, based on the current practice it is generally accepted that non-standard manufacturing process are not described in great detail since the process controls are subject to GMP regulation and GMP inspections. Proposed change: Delete all of the paragraph in lines 501-505 and insert the following replacement text: Most of the finished products containing recombinant proteins and	

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			monoclonal antibodies are manufactured by an aseptic process, which is considered to be non-standard **(see Annex II to Note for Guidance on Process Validation: Non-Standard Processes (CPMP/QWP/2054/03)).** Non-standard manufacturing processes, new technologies and new packaging processes should be described ~~in detail~~**.**	
36	513-516		Comment: The cited reference specifically excludes biological medicinal products such as vaccines, sera, toxins and allergens, products derived from human blood and plasma as well as medicinal products prepared biotechnologically (p1 of reference). This reference should therefore be deleted. Proposed change: Delete the reference in the first sentence of this paragraph.	
37	521-523		Comment: Validations of sterilization processes such as sterile filtration are often postponed due to lack of available material until relatively late in development when the commercial composition and other product details are finalized. Conducting filter validation on early clinical formulations that may be subject to multiple changes during the clinical phase can result in substantial delay to the start of early phase trials. As an alternative, sponsors should be allowed to support sterility assurance by the overall bioburden control strategy, pre-filtration bioburden specifications, in-process controls such as filter integrity	

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			testing and prior filter validation data on similar or platform formulations. We suggest utilizing the text contained in the existing guideline on Quality documentation for IMPs (CHMP/QWP/185401/2004) as this information in not unique to biologic IMPs. The requirement to provide media fill data for standard parenteral processes in the dossier should be removed since this would be subject to GMP regulation and inspection. Proposed change: Maintain the first sentence of this paragraph but delete current lines 521-523 and replace with the following text: **Data are not required during the development phases, i.e. clinical phases I to III, except for nonstandard sterilisation processes not described in the Ph. Eur., USP or JP and for non-standard manufacturing processes. In these cases, the critical manufacturing steps, the validation of the manufacturing process and the applied in process controls should be described (c.f. Annex II to Note for Guidance on Process Validation: Non-Standard Processes (CPMP/QWP/2054/2003)).~~Add:~~ During the early phase of development, where validation of the sterilising process for drug product has not yet been conducted, the sterility assurance should be supported by the overall bioburden control strategy including bioburden controls for drug substance and excipients, prefiltration bioburden limits, and in-process controls (e.g., pre and post filter integrity testing). This should be summarised in the dossier along with a brief description of the sterilization process for the packaging**	

PDA No.	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			components and the equipment used in manufacturing.	
38	566-567		Comment: The statement in this sentence is unclear. Proposed change: The text should be amended to clarify which impurities are to be considered in this paragraph.	
39	591-592		Comment: This statement does not acknowledge that the identity of impurities is dependent on stage of product development. Proposed change: Additional impurities and degradation products observed in the IMP, but not covered by section S.3.2, should be identified and quantified as necessary **consistent with the stage of product development**.	
40	609-610		Comment: Most parenterals could be considered to have a potential for interaction between product and container closure system. The guidance should be revised to indicate that details should be provided in cases where a specific interaction is known to occur. Proposed change: Revised this sentence as follows: For parenterals ~~having a~~ **with a known** potential for interaction	

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			between product and container closure system more details may be needed.	
41	424-435 and 611-617		Comment: See related PDA comment 32 (lines 431-435). The guidance specifies expiration dating not to exceed two-fold and not to be more than twelve months beyond the provided stability data obtained with representative batch(es). This, unfortunately, does not take into account that there may be a wealth of experience available with certain molecule groups, e.g., monoclonal antibodies. For these, data for antibodies of the same subclass stored under the same conditions and formulations, can be used to set up a database which allows for alternative means of defining expiration of Drug substances and Drug products. A company documenting this experience should be allowed to use such alternatives and not be confined to pre-defined schemes, as defined in the current draft of this guidance, which may not fit all cases. It is to be noted that such alternative expiration dating is currently applied and accepted in some Member States of the EU and other regions, e.g., US. Proposed change: Replace the first two sentences of this paragraph, in lines 612 -615, with the following revised text: **The maximum extension should be based on stability data presented for representative batch(es), with a justification of the proposed retest date. Normally, the maximum extension should not exceed two-fold and should not be more than twelve months.**	

PDA No.	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			However, the sponsor may also present his database for related substances/products, which would support other, scientifically justified schemes of expiration date definition. The presented data should justify …	
42	619-621		Comment: The principles described for active substance stability can be applied to in-use stability requirements. This negates the need to submit changes to in-use stability programs as substantial amendments (as described in line 721). Proposed change: After the two existing sentences in the text (lines 619 to 621) please add the following text to the end of this paragraph: … opening or reconstitution. **Changes to the in-use stability recommendations resulting from changes to the method of preparation would not be considered as substantial amendments if the in-use stability studies are covered and in compliance with the approved in-use stability protocol. In the event of unexpected issues, the Applicant should commit to inform the Competent Authority of the situation, including any corrective action proposed.**	
43	657		Comment: All manufacturing and testing sites are provided in S.2.1 and P.3.1. Repetition of this information in Appendix A.1 is unnecessary. Proposed change: ~~All manufacturing and testing sites should be listed~~. Premises and	

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			equipment have to be qualified…..	
44	721		Comment: Changes in the approved in-use stability recommendations should not be considered as a substantial amendment. Principles as described for active substance stability can be applied to provide sufficient assurance that the IMP will be stable during its intended in-use period. This proposal is in line with the proposed addition of the text in paragraph P.8 Stability. Proposed change: Delete text in current line 721 and replace with the following: • **in-use stability recommendations that goes beyond the accepted stability protocol**	
End of Comments				