

APIC Comments on: Draft FDA Guidance "DS CMC Information"

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**Guidance for Industry:
Drug Substance, Chemistry, Manufacturing and Controls Information**

Introduction

CEPIC is the organization representing national federations, companies and more than 100 affiliated associations and sector groups, located in Europe. All together CEPIC represents directly or indirectly more than 40,000 large, medium and small chemical companies in Europe, which employ about 2 million people and account for more than 30% of the world's chemical production.

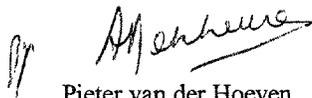
APIC is one of CEPIC's sector groups, comprising producers of active pharmaceutical ingredients (APIs) and intermediates in Europe. The major part of the total volume of APIs and intermediates imported into the USA originates from Europe. For this reason, CEPIC/APIC considers itself to be a very important stakeholder in new FDA Regulations and Guidelines related to APIs and intermediates.

We, therefore, highly appreciate this opportunity for submitting our members' comments on the above mentioned Draft Guidance which contains requirements which are of direct relevance and of great importance to our products.

Our comments hereunder have been categorized into "General Comments" and "Specific Comments". The comments that are in our view of the highest importance have been highlighted by **bold** text.

We trust that you will take this matter into consideration and look forward to reading from you very soon.

Yours sincerely,



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APIC General Comments:

These comments address general issues noted during the review of the guidance. Comments on specific issues follow these comments.

APIC welcomes the FDA initiative to update the 1987 Drug Substance Guidance and we would further welcome an opportunity to meet to discuss our feedback to the draft guidance.

The principles of a *risk-based* approach to drug substance chemistry, manufacture & controls are largely absent from the draft guidance and it is our position that this is inconsistent with current FDA direction. APIC members appeal to the opportunity that the 21st Century GMP Initiative will foster a regulatory environment for innovation and continuous improvement. Within this context it is our position to avoid requirements for submitting very detailed information that discourages these opportunities. Innovation and continuous improvement are a means to ensure continued drug substance and drug product quality. The majority of the general and specific comments below propose risk-based alternates to those in the draft guidance.

The industry sector of dedicated API manufacturers is suffering heavily under extremely strong regulatory restrictions on its possibilities to implement continuous improvement and innovation. Considering multi-customer supply situations for APIs, these restrictions form a difficult barrier to progress. These restrictions threaten the continuity of the companies within our sector that are in full regulatory compliance. Based on the requirements of the draft guidance it is apparent that there are increased CMC details that do not improve the Quality of the drug substance. The more detail is included in drug substance regulatory submissions (DMFs), the higher the regulatory restrictions on change and improvement thereafter.

We acknowledge that the FDA understands these difficult challenges for DMF holders in multi-customer supply systems and we once more express our hope and urgent need for an adequate solution to be implemented the soonest.

In addition, this strong increase in the amount of detail to be included in submissions will overall lead to a probably dramatic increase of the number of Supplements, because even changes in minor details will then affect the content of the approved Application. We believe that this important increase in workload at the FDA would be contrary to FDA’s current 21st Century Initiative that, amongst others, aims for an important decrease in the number of to be submitted Supplements.

Throughout the Draft Guidance reference is made to many different ICH Guidelines. The scope of these ICH Guidelines is restricted to new drug substances whereas the Draft Guidance is intended to apply to both new and older approved drug substances. This inconsistency should be resolved by either rewriting of the Draft Guidance in such a way that reference to the ICH Guidelines that have a broader scope will be deleted or by revising the scope of the Draft Guidance such that it will be identical to the scope of the ICH Guidelines.

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CMC requirements for large protein drug substances and small synthetic drug substances differ and a preamble to the guidance should clarify these differences where appropriate.

APIC Specific Comments

1. Inconsistency with ICH guidelines

Throughout the Draft Guidance, reference is made to many different ICH Guidelines. Many inconsistencies between the draft guidance content and current ICH guidance were noted. The scope of these ICH Guidelines is restricted to new drug substances whereas the Draft Guidance is intended to apply to both new and older approved drug substances. These inconsistencies should be addressed in order to promote alignment with ICH.

For impurities, the guidance should reference the appropriate ICH guidance rather than include specific numerical limits. The glossary should be aligned with ICH guidance documents including definitions for qualification, residual solvent, specification, intermediate and retest period.

2. Registration of process controls, parameters, tests, steps, etc.

In several instances within the draft guidance, reference is made to the inclusion of ‘all/any’ process controls, parameters and ranges. It is suggested that “all / any” be changed to “process controls, parameters and ranges that are *critical to quality*”.

3. Process scale and expected yields

Under Section IV. Manufacture, there are two references to “yield”. Yield, as an indicator of the process performance, should be indicated as a *typical or expected percentage range*, not as a single number.

Under Section IV. Manufacture, the guidance requires a description of the manufacturing steps undertaken *and the scale of production*. We agree that the narrative description should include information about the scale at which the manufacturing process has been operated, but the guidance should indicate that subsequent changes in scale are a GMP issue, covered by validation requirements, and should require not regulatory notification. Note that BACPAC I guidance does not require registration updates for scale changes up to and including the final intermediate.

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4. Starting Materials Selection Criteria

A general comment on Attachments 1 and 2: It would be appropriate if a harmonized approach on how to select the Starting Material for regulatory submissions would be pursued within the ICH program.

We recognize that the bullet points described in lines 1730-1733 are important selection principles for starting materials that ensure the quality of drug substance. However, we disagree with the distinction regarding significant and non-significant non-pharmaceutical use. The selection of starting materials should be based on risk-based scientific criteria and all subsequent comments are predicated on this premise.

4.1 "Significant non-pharmaceutical use"

The subdivision of potential starting materials into those that have or don't have a “significant non-pharmaceutical use” should be abandoned. The focus for selecting starting materials should be the capacity of the applicant to determine the suitability of the proposed compounds based upon the applicant's knowledge of the impact of the starting materials quality upon the quality and safety of the drug substance. With the use of this science-based principle, materials that are both commercially available and not commercially available can be considered to be suitable starting materials.

4.2 Flow diagrams for Starting Material synthesis

The requirement that the applicant supply a detailed flow diagram that includes the route of synthesis of the starting materials significantly expands the regulatory commitment beyond the core drug substance synthesis. As long as the applicant has demonstrated that the starting materials (which may be from more than one route of synthesis) meet their specifications and have been qualified to show that there is no impact on drug substance quality, there should be no *requirement* to provide the synthetic scheme for the starting materials. Information, in the form of a flow chart, indicating the starting material synthetic process(es) *may* be useful to evaluate the suitability of its specification and to help clarify the justification of the starting material, but this should not be a requirement.

4.3 "Propinquity"

As presented in the draft guidance, the starting material selection criterion of propinquity is overly restrictive, and exclusionary of certain commercially available, well characterized materials. It is our position that any processing activity (e.g. crystallization, extraction, salt formation, etc.) that removes impurities, reactants, or post-synthesis materials to the benefit of the quality of the drug substance should be considered a “step” towards meeting the propinquity criterion for a particular drug substance. Further, we believe that there may be circumstances where a drug substance *may* be appropriate to use as a starting material.

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4.4 "Isolated and purified"

It is appropriate to expect that starting materials typically should be isolated but there are circumstances where this may not be possible or desirable. For example, if a starting material is hazardous, it may be preferable to use it *in solution* to avoid solid handling safety issues. The central tenet for a starting material should always be that its quality is adequate and appropriate, and has been justified and qualified for its intended use. The requirement that starting materials must have been subjected to a purification procedure is overly restrictive and potentially exclusionary.

4.5 Starting materials for semi-synthetic drug substances

The guidance needs to differentiate between semi-synthetic drug substance starting materials and drug substances obtained directly from biological sources, and recognize that starting materials for semi-synthetic drug substances need not be the precursor biological materials. Well-characterized semi-synthetic molecules can be considered as starting materials for drug substances. Information assessing the TSE-risk of a starting material can and should be provided, but the point of TSE-risk should not be a criterion for starting material selection. Consideration should be given to developing a separate guidance on TSE-risk.

4.6 Carryover of impurities

The position that “a chemical proposed as a starting material should not be the source of significant levels of impurities in the drug substance” contradicts ICH Q3A (Impurities in New Drug Substances) by excluding the accepted practice of qualifying impurities in drug substances. The carryover of the starting material or its impurities into the drug substance is an important point to consider in selecting a starting material; however this should not be an exclusionary criterion. Impurities in the drug substance should be qualified as defined in ICH Q3A (Impurities in New Drug Substances).

4.7 Complexity of structure

The guidance states that if “advanced” analytical techniques are required to differentiate a proposed starting material from its isomers, analogues, etc., then the material is too structurally complex to be a starting material. Several of the analytical techniques listed as ‘advanced’ are commonly used and widely available. An applicant should have the option of justifying the use of either a structurally more complex starting material using “advanced” techniques or a larger number of structurally less complex starting materials using traditional characterization techniques. The analytical technology used should be appropriate to the complexity of the starting material.

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5. Definitions of, and requirements for, Reworking/ Reprocessing/ Recovery operations

We see a discontinuity between the draft guidance and ICH Q7A for the definitions of reprocessing and reworking. The key scientific differentiation between reprocessing or reworking should be the registration holder's knowledge of the process' capacity to remove process impurities and degradation products. If it can be demonstrated that repetition of a part of the registered process can adequately improve the quality of a batch of an intermediate or API, then this should be considered reprocessing. Correspondingly, improving the quality of any batch by a means not described in the registered process is reworking and requires adding the rework procedure to the registration.

6. Requirements for irrelevant impurity data (e.g., in S.3.2)

We believe that Section B impurities (lines 1006 – 1074) should be replaced by a reference to Q3A(r)

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APIC Specific Line-by-line Comments:

Line#	Item	Concerns	Proposed change
27-28, 100, 105	Applicability of guidance	<ul style="list-style-type: none"> This guidance applies to NADAs and ANADAs while previously published DP guidance does not. 	Revise companion guidances to be consistent with the DS guidance.
53	Semisynthetic DS	<ul style="list-style-type: none"> Limits starting point of semi synthetic DS to intermediates 	We propose that the words "or starting material" will be inserted after "intermediate". This will secure the flexibility to choose for this option if there is a sound rationale to do so.
53-54	Conventional Fermentation	<ul style="list-style-type: none"> Definition Unclear We would like to emphasize that it is important to consistently adhere to the ICH Q7A principle that fermentations as herewith defined are conventional ones, also when rDNA derived production strains are being used. 	The term "Conventional fermentation" should be defined in the Glossary. We propose the following definition be adopted, consistent with the ICH Q7A Guideline, "The production of APIs of low molecular weight, such as antibiotics, amino acids, vitamins and carbohydrates (as opposed to high molecular weight APIs such as proteins and polypeptides) irrespective of whether production strains are being used that have been selected by either classical mutation or by r-DNA techniques."
67	Conventional Fermentation	<ul style="list-style-type: none"> Harmonize with concerns noted above 	Operations involving <u>conventional</u> fermentations... delete (...or using r-DNA technology)
111	Grammatical		Delete "the" in "...will be the provided..."
213	Master Files	<ul style="list-style-type: none"> Letter of Authorization (LOA) 	The established procedures are that the DMF holder submits the original LOA in duplicate to the FDA and forwards a copy of the LOA to the applicant. Therefore, the wording should be changed from "...to the applicant and the..." to "...to the FDA and a copy to the applicant..."
274	Typo		"used" should be "uses"
383-4	Use of building numbers as identifiers	<ul style="list-style-type: none"> According to "Changes to an Approved NDA or ANDA," moving between buildings within a site does not have to 	"Building numbers" should be deleted and the sentence should be modified to "Other specific identifying information should be

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		be reported except for sterile drug substances. Therefore, including building numbers in the initial application is unnecessary in most cases.	provided as appropriate."
390-393	Inclusion of site contact information for PAI	<ul style="list-style-type: none"> This information is not appropriate for inclusion in the file since (a) it is only for the initial PAI and is not a registration commitment (b) in the CTD this information is region specific, and (c) this information is also provided in Module 1 (356H Form). 	This paragraph pertaining to contact person, FAX number, etc for PAI purposes should be deleted from S.2.1.
392-3	"Facilities should be ready for inspection when the application is submitted to FDA."	<ul style="list-style-type: none"> Change 'submitted' to 'filed' to allow for 45-60 day window. 	"Facilities should be ready for inspection when the application is filed to FDA."
399	"A flow diagram and a complete description of the processes and process controls that will be used"	<ul style="list-style-type: none"> The depth to which the process and controls must be provided is not clear. (If wording were similar to Guidance provided previously for CMC sections of an NDA, then our history of providing acceptable descriptions would provide the needed benchmark on depth.) 	"A flow diagram and description of the processes and process controls that will be used"
406-36	Items to be included in Flow diagram	<ul style="list-style-type: none"> General concern with this section: too much information in the flow chart leads to a cluttered presentation that is less useful. E.g., "Auxiliary materials" are not usually included in a flow diagram. 	Need to reduce some of these requirements to obtain clearer and more useful Flow diagrams. We suggest the focus should be upon materials reagents, solvents and catalysts, e.g.: 414: Each manufacturing step with identification of those steps that are critical. Remove rest of this bullet. 1425: "Solvents and reagents, used in each manufacturing step." 426: Remove (critical process controls are discussed elsewhere). 427: Remove (operating parameters are discussed in the narrative).
421-422	"Structurally complex reagents"	<ul style="list-style-type: none"> The term "structurally complex reagents" should be defined in the Glossary. An undefined term such as this one will cause widely diverging interpretations. 	
410, 417	Depicting drug release testing in synthetic	<ul style="list-style-type: none"> Flow diagrams normally depict steps 	Delete "through drug substance release

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	flow diagram	ending with the final drug substance. Release testing of the API is addressed under S.4 and should not be included in a flow diagram.	testing"
427	Operating Parameters	<ul style="list-style-type: none"> Space constraints of flow diagram 	We propose to delete this sentence. The operating parameters will already be included in the process description and may be too "bulky" to fit into the flow diagram.
431, KC	"Expected yield (percent) for each reaction step"	<ul style="list-style-type: none"> Yield is a CGMP issue, and as such is a crude indicator of process performance, not usually a necessary or critical parameter for inclusion in a registration. 	Change to: "Expected yield range (percent) for each appropriate reaction step."
434-6	Reactions resulting in a mixture of products (e.g. two or more isomers)...each component should be indicated in the flow diagram.	<ul style="list-style-type: none"> Isomer presentations in a flow diagram should be included in the flow diagram only if all isomers are intended as the desired intermediate composite for conversion in the next chemical step. Presentation of other isomers in a flow diagram is also acceptable if the manufacturing process includes a recycling operation that converts the undesired isomer to a previous intermediate or to a desired isomer in the manufacturing process. 	<p>Undesired isomers as potential side products or impurities should be discussed only in the impurity section (S.3.2) of the CTD.</p> <p>Delete: "If a reaction results in a mixture of products (e.g., two or more isomers), each component of the mixture should be included in the flow diagram."</p> <p>Revise line 436 to: "Information on side products and impurities, including isomer impurities, should be provided in S.3.2"</p>

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440-7, 457-8	Description of the Manufacturing Process and Process Controls	<ul style="list-style-type: none"> • Overly burdensome to require commitment in the registration to a specified "scale of production". [Note: BACPAC I allows for changes of scale for steps up to the final intermediate without any update to the file.] • It is unreasonable to include <u>all</u> process controls (as defined in the Glossary of the Guidance) in the registered process description. During the development of the drug substance process by the drug substance manufacturer, critical process controls such as critical processing parameters, reaction end points, and critical intermediate testing are identified. Some controls, such as agitator speed, milling speed, or specific instrumentation controls, need not necessarily be included in the registered process description. A few non-critical controls may be included in the process description to give the FDA chemistry reviewers an idea of certain conditions involved in the chemical processing. For example, certain crystallization temperature ranges may be developed to maximize product yield rather than to assure product quality. These temperature parameters, although not critical to assure product quality, may in fact be considered for the registered process description. • Critical process controls should be identified as such in S.2.4, but it is unnecessarily redundant to "highlight" them in the process 	<p>"Scale of production" should be provided for information and the guidance should clarify that future changes in scale are a GMP issue, not requiring supplementary filings.</p> <p>Change third sentence (lines 441-4) to: "This description should include critical process controls and their associated numeric ranges, limits, or acceptance criteria as well as non-critical process controls necessary to describe the manufacturing process."</p> <p>Delete fourth sentence:</p> <p>Change bullet point at 457-8 to:</p> <ul style="list-style-type: none"> • Process controls and their associated numeric ranges, limits, or acceptance criteria. <p>Also delete phrase on line 458.</p>

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		description.	
443-4	"description should identify ... associated ... acceptance criteria."	<ul style="list-style-type: none"> We question why "acceptance criteria" are mentioned here (i.e. within S.2, Manufacture). We propose that it would be more appropriate to include acceptance criteria in section 3.2.S.2.4 (Control of Critical Steps and Intermediates). 	Delete "or acceptance criteria" in line 444.
450-1, 452-3	"Starting materials or intermediate ... quantities specified", "Solvents, reagents, and auxiliary materials used in each step, with ... quantities specified"	<ul style="list-style-type: none"> Concerns on "scale" above are also applicable to "quantities specified". 	Clarify that "quantities" listed should be understood as molar quantities or ratios that are descriptive of the actual scale used routinely in commercial DS manufacture.
454-5	"Type of equipment ... used"	<ul style="list-style-type: none"> Overly burdensome to require commitment in the registration to a particular type of equipment when equipment type is not critical. 	Suggest replacing sentence with: "Identification of typical equipment."
459	"Type of analytical procedure..."	<ul style="list-style-type: none"> No Emphasis on PAT 	To better reflect current FDA thinking we recommend stating here: "(e.g. HPLC or PAT)"
460-1 (and elsewhere)	"Identification of intermediates, post synthesis materials, and unfinished drug substance that are tested (details should be provided in S.2.4)."	<ul style="list-style-type: none"> It should be clarified that FDA does not intend to require the manufacturer to register any and all testing that it may choose to do for internal information purposes. 	Suggest: "Identification of intermediates, post-synthesis materials, and unfinished drug substance that are routinely tested in connection with critical process controls (details should be provided in S.2.4)."
466-7 (and 622-6: IV.B.3.c)	"Identification of ... steps that use recovered solvents or auxiliary materials."	<ul style="list-style-type: none"> The quality of recovered solvents is assured by testing the quality of the recovered solvent against the specification given for the solvent in the NDA for use in the manufacturing process it is sufficient to state solvent quality criteria within the dossier without identifying where such recovered materials may be used. 	Remove lines 466 – 467 Lines 630 – 631: Remove "including the point at which they might be used in the process"
471-2	"Identification of processes that involve combining intermediate or DS batches, etc."	<ul style="list-style-type: none"> cGMP requirements provide adequate assurance that if combining of batches is performed that it will be done appropriately. 	Remove lines 471 – 472.
473	"Yield ranges (weight and percent) for each manufacturing step."	<ul style="list-style-type: none"> Yield is a cGMP issue, and as such is a crude indicator of process 	Delete this line.

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		<p>performance. Yield, especially as a single number rather than a range, could be interpreted as a registration commitment and therefore generate supplements as it is refined through process experience without adding value to the registration process.</p> <ul style="list-style-type: none"> • Yield ranges should be provided only where appropriate • It is necessary to allow flexibility to manufacture at different scales, especially before the final intermediate. 	<p>If necessary to retain, change to: "Typical yield ranges (weight and percent) for each appropriate manufacturing step."</p>

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475-84, also 1994-2020	"biological starting material"	<ul style="list-style-type: none"> The guidance needs to differentiate between semi-synthetic drug substance starting materials and drug substances obtained directly from biological sources. The guidance should also recognize that starting materials for semi-synthetic drug substances need not be the precursor biological materials. In lines 2008-10, excluding (from recommendations) "highly purified chemicals" of biological origin as starting materials on the basis of their not having a "significant nonpharmaceutical market" seems an arbitrary non-science-based criterion. We request that the option will be available to define the substance produced by fermentation as the starting material for a semi-synthetic API, for cases when there will be a sound rationale to do so. 	<p>In lines 475-6 change "derived" to "obtained" and delete "or a semi-synthetic drug substance".</p> <p>Chemical substances derived from biological sources should be allowed to be designated as starting materials provided they are "well-characterized" or "highly purified", irrespective of whether they have "significant nonpharmaceutical markets."</p> <p>See comments on lines 1994-2020 provided below.</p>
488-493	A statement should be provided that bovine-derived materials from bovine spongiform encephalopathy (BSE) countries as defined by the U.S. Department of Agriculture (9 CFR 94.11) are not used or manipulated in the same facility . Submission of additional facility information could be warranted for multi-use facilities where there is a potential for cross-contamination with adventitious agents (see sections X.A and X.B).	<ul style="list-style-type: none"> Cross Contamination with Adventitious Agents 	This statement should not be required. Cross contamination is controlled by cleaning validation which is a cGMP issue.
510-1	"Environmental controls— conditions associated with the manufacturing facility (e.g., temperature, humidity, clean room classification)"	<ul style="list-style-type: none"> This is GMP...not a filing issue Inconsistent with lines 532-4 and prone to erroneous interpretation that formal classification is required for other processing environments. 	Delete lines 510-511. If necessary to retain, after "...classification" add "for aseptic operations."
521-4	"All process controls, critical or otherwise, should be included"	<ul style="list-style-type: none"> It should not be a requirement for all process controls to be listed. Sponsors should be free to conduct 	Suggest changing to "Critical process controls should be included in the description of the manufacturing

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		<p>additional testing for internal information</p> <ul style="list-style-type: none"> All process controls are not normally critical to drug substance quality. Required disclosure should be limited to "controls critical to quality" only. Lines 397-8 state that the description of the DS manufacture process represents the applicant's commitment for the manufacture of DS; concern that filing of all process controls, critical or not, would be a commitment. Same for other operating parameters. 	<p>process."</p> <p>Need clarity around ALL process controls vs. non-critical controls that would be filed, vs. critical controls. For clarification purposes, a comment should be added before line 524, such as "The manufacturer of the drug substance identifies the process controls that are critical during the development of the manufacturing process."</p>
538-45 and Figure 1	<p>Process Controls "All of the operating parameters, environmental conditions, ...", "All tests ... should be listed"; Requirement to include the same information in both S.2.2 and S.2.4.</p>	<ul style="list-style-type: none"> Focus should be on critical process controls necessary to ensure that the DS meets its specification Often the testing for these materials includes tests that are not critical. A description of these tests should be included in S.2.4 and need not be duplicated in S.2.2. Should not be necessary to include same information in more than one place. 	<p>Change second sentence to: "Appropriate tests on intermediates, post-synthesis materials, and unfinished drug substance should be listed and described in S.2.4 and reference to these tests should be included in S.2.2."</p> <p>Delete in 538-45 the requirement to identify in S.2.2 those parameters, conditions and process tests considered to be critical, since this will be done in S.2.4. In Figure 1, delete "List in S.2.2", or modify to "Include as appropriate in S.2.2"</p> <p>Omit "environmental conditions" (see above)</p>
550-664	<p>Section 3: Reprocessing, reworking, recycling, regeneration and other operations</p>	<ul style="list-style-type: none"> There are significant concerns over the content of this section (see "Key Comments"). Comments below (on lines 550 – 664) illustrate our concerns but are not exhaustive. 	<p>Revise section to ensure clarity and consistency with ICH definitions.</p> <p>Include appropriate terms within Glossary (we note, for example, that definitions of "reprocessing" and "reworking" are not currently included in the Glossary)</p>
552-3 (also 645-53)	<p>Reprocessing, Reworking, Recycling, Regeneration, and Other Operations</p>	<ul style="list-style-type: none"> Overly restrictive 	<p>Ancillary operations such as regeneration or recycling of processing materials (e.g. resins, solvents) need not be described in</p>

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			the registration if appropriate acceptance criteria for their use have been established and are stated or monitored by an in-process test described in the registration. For example, if it is stated that a resin is discarded after a fixed number of uses or when loading capacity drops below a threshold, this should be adequate to control the process. Similarly, if a solvent that is recycled meets in-process or other appropriate control specifications, this should be adequate and a description beyond a statement of the nature of the recycle process (e.g. by distillation) is unnecessary.
552-3	Reprocessing, Reworking, Recycling, Regeneration, and Other Operations	<ul style="list-style-type: none"> We suggest that, if these operations are described within S.2.2, then, by definition, this is part of the registered manufacturing process, hence not "reworking". (We note that "salvage" is not defined) 	Delete 'salvage' from the guideline
555-558	"Moreover, reprocessing and reworking operations should be capable of producing an improvement in one or more quality attributes without having an adverse effect on others"	<ul style="list-style-type: none"> Reworking may improve one quality attribute but have a slight negative adverse effect on another. Despite the adverse effect, if all specifications are met the material is acceptable. ICH Q7A does not require non-conformance to standards or specifications for material to be reprocessed. Reprocessing may be legitimately pursued for reasons other than improving "one or more quality attributes" 	<p>Replace with:</p> <p>"Moreover, reworking operations should be capable of producing an improvement in one or more quality attributes without having a significant adverse effect that could lead to a specification failure."</p>
558-60, also 587	"Information ... to support the appropriateness of these operations included in S.2.2"	<ul style="list-style-type: none"> Section S.2.2 should remain as a standalone manufacturing process description without justification discussions. Next page states that generally, no need to provide justification for reprocessing.... 	Suggest: "Information (e.g., comparative analytical data) to support the appropriateness of rework operations should be cross-referenced in S.2.2 to Section S.2.6 (Manufacturing Process Development) in the application."

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571-2	Reprocessing	<ul style="list-style-type: none"> Concerns because of association with lines 658-664 and the comments applied thereto (Guidance is inconsistent with "reworking" in ICH Q7A and with industry practice). 	Delete the full sentence that begins with "See section..."
578-9	"Repetition of multiple reaction steps is considered to be reworking"	<ul style="list-style-type: none"> We question why repetition of multiple reaction steps is considered to be reworking, rather than reprocessing. Repeating multiple steps should be considered reprocessing, consistent with ICH Q7A. 	Delete lines 578-579.
581	"For most intermediates and drug substances, reprocessing need not be described in the application."	<ul style="list-style-type: none"> We appreciate this statement, which shows good consistency with ICH Q7A. 	It is important that this sentence stays in the final guidance.
584-7	Justification for reprocessing	<ul style="list-style-type: none"> Section S.2.2 should remain as a standalone manufacturing process description without justification discussions. 	Delete this sentence.
611-6	"In general, reworking operations are developed post-approval, and the application is updated through submission of a prior approval supplement that provides test results and, if appropriate, new or updated analytical procedures that are demonstrated to be appropriate to evaluate the effect of the reworking procedure on the ... drug substance".	<ul style="list-style-type: none"> It is not necessarily true that reworks are generally developed post-approval or that post-approval reworks need always be submitted by the PAS mechanism. It is not uncommon that at the time of filing manufacturing experience will have identified one or more desired rework procedures 	Revise lines 611-616 to clarify that a post-approval change to add a rework process might be added by means of a CBE or Annual Report mechanisms under the BACPAC I guidance.
616-18	However, if reworking operations are anticipated at the time of the original submission, they should be described in this section of the application (S.2.2) with justification for the reworking operation.	<ul style="list-style-type: none"> Section S.2.2 should remain as a standalone manufacturing process description without justification discussions. A rework procedure may be developed for a specific purpose, but at time of filing, there may be limited information available on other purity or quality issues which might be resolved by that same rework procedure All rework needs are not generally anticipated at time of filing and, thus, a comprehensive justification for a particular reworks use is often 	Revise lines to: "If reworking operations are developed and available at the time of the original submission, they should be described in this section of the application (S.2.2)."

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Line#	Item	Concerns	Proposed change
		unavailable.	
618, 642	"with justification for the reworking operation." "should be provided to justify recycling of filtrates"	<ul style="list-style-type: none"> Justification of rework and recycling operations should not be in S.2.2 but in S.2.6. 	Add the words "described in S.2.6 (Manufacturing Process Development)" to the end of the sentence at line 618. Add "in S.2.6 (Manufacturing Process Development)" between "provided" and "to justify" in line 642.
622	Recovered solvents	<ul style="list-style-type: none"> Clarification should be included in line 622 that recovered solvents under discussion are those generated by recovery operations from the same drug substance synthesis. 	Revise to: "The use of recovered solvents and recycling of filtrates (mother liquors) to recover reactants, intermediates, or drugs substance, including for the purpose of producing or isolating additional crystals (i.e., second crops), should be described in S.2.2."
633-7	Recovered solvents	<ul style="list-style-type: none"> Solvent recovery operations that originate from the synthesis of the same drug substance should be described in S.2.2. All other recovered solvent sources should be identified in S.2.3 with appropriate specifications and where used in the drug substance synthesis. Only operations directly associated with the synthesis of the drug substance should be included in S.2.2. 	Delete "or can come from other sources" (for recovered solvents) and revise these lines as follows: "However, information should be provided on whether (1) any processing is done to improve the quality of the recovered solvent with a brief description of the process (e.g., distillation) and (2) the recovered solvent comes only from the manufacture of this drug substance. Recovered solvents from other sources should be identified in S.2.3 with the material title and the step where the recovered solvent is used."
640	"Recycling of filtrates should be included in the description of the manufacturing process if these operations are performed. Information should be provided on the maximum number of times material will be recycled and for the process controls for such operations."	<ul style="list-style-type: none"> If literally interpreted, this could be applied to recycling of filtrate during a batch filtration. 	Clarify that this refers to recycling/reuse from one batch to another To include this in filing, data need to be filed on impurity levels to justify recycling.
643	Recovery of solvents, regeneration of column materials, catalyst, etc.	<ul style="list-style-type: none"> A requirement to describe recovery of solvents and regeneration of column materials, catalysts etc., including also process controls is far more restrictive than what has 	We propose that appropriate specifications should suffice for materials such as recovered solvents, column materials catalyst...

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		<p>been common practice thus far. It is another example of a sharp increase in the required detail of information to be submitted and contrary to new, emerging FDA policies (see also our above General Comment on this).</p>	
645-52		<ul style="list-style-type: none"> We challenge the necessity (and practicality) of requiring information concerning the maximum number of times that a "regenerated material" may be regenerated. We assert that such materials can be controlled via their specification. Practically, we note that a supported noble metal catalyst, for example, may be regenerated "indefinitely", making the request to supply information concerning maximum number of regenerations impossible to comply with. 	<p>Modify text to indicate that regenerated material quality should be controlled via specification; remove reference to "maximum" number of permissible regenerations.</p> <p>Clarify that this does not apply to metal catalysts recovered by manufacturer</p>
658-62	Reworking/ Reprocessing	<ul style="list-style-type: none"> Guidance is inconsistent with "reworking" in ICH Q7A and with industry practice The application of the term "reworking" rather than "reprocessing" to further processing of "released" material that doesn't require more than repetition of the purification and/or final crystallization is overly restrictive. Sometimes expired, or post-retest date, or returned materials may need to be reworked by using an alternate set of crystallization solvents or by conversion to an intermediate and processing forward to the API, but this is not always the case. If the material in question can be returned to a quality state equivalent to that of a virgin batch by repetition of the registered purification and crystallization procedures, this should be considered 	<p>Clarify so as to conform with ICH Q7A definition of reworking. Also, for the sake of clarity we think it will be useful to specifically mention here that combining tailings of released batches into a new batch is not reworking but reprocessing.</p>

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Line#	Item	Concerns	Proposed change
		reprocessing. Consider for example the recovery of tag ends of batches where they are combined and recrystallized from the same solvent by the same procedures as a virgin lot.	
665-6	Text Box	<ul style="list-style-type: none"> Incomplete references. 	Add ICH Q7A as a reference because the section draws significantly from that guidance.
683-96	Control of Materials (S.2.3): Entire paragraph	<ul style="list-style-type: none"> Should not be necessary or usual to distinguish between an "API" (i.e., GMP) starting material and "Application" starting material for a synthetic DS. Too restrictive to require all semi-synthetic DSs -- regardless of their synthetic distance from biological material -- to have SMs that are the actual biological material. It is appropriate when an API is obtained directly from a biological substance and where the API starting material is that biological substance that information on source country, genus, species, parts, pathogens, herbicides, pesticides be discussed in the application. Similarly, materials with potential TSE risk should be defined as to country, species, parts, and rigor of processing. However, when there is no TSE risk and API starting material is significantly removed from its biological substance of origin the presentation and regulatory documentation of this information is inappropriate. 	<p>It should be sufficient, in this paragraph, to merely state that the SM for GMP purposes, and the "Application" SM need not always be the same but that they "often will be the same" (rather than "in general will be the same") for synthetic DSs.</p> <p>If necessary to retain the latter part of the paragraph beginning with "However ...", limit the comments to SMs for DSs obtained directly from biological sources (i.e. obtained without substantial modification of the covalent DS structure).</p> <p>Suggest it may be desirable to insert new paragraph to allow for "Application" starting materials derived from biological sources when the SM is a highly purified or well-characterized chemical substance -- regardless of whether it has a substantial non-pharmaceutical market. A discussion of the remoteness of the API starting material to its biological substance of origin is appropriate here and bears on the justification of appropriate specifications for a remote API starting material.</p>
698	Starting Materials	<ul style="list-style-type: none"> Degree of contribution to the structure of the drug substance needs clarification 	We recommend that, for the sake of clarity, at the end of this sentence a reference will be made to Attachment 1, where the degree of contribution to the structure of the drug substance is further

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Line#	Item	Concerns	Proposed change explained.
701-6	"FDA considers [list of biological sources] ... from which the DS is derived to be the SM for a DS derived from a biological source..etc"	<ul style="list-style-type: none"> Same objection as above. Too restrictive to require all semi-synthetic DSs -- regardless of their synthetic distance from biological material -- to have SMs that are the actual biological material. 	Limit to SMs for DSs obtained directly from biological sources (i.e. those obtained without substantial modification of the covalent DS structure) and to those DSs that cannot establish a highly purified or well-characterized chemical substance derived from a biological source as SM. If necessary, may require info on biological source of SM without biological source being the SM.
710-4	Requirement for flow diagrams for starting materials	<ul style="list-style-type: none"> A list of proposed starting materials and/or information on plant or animal starting materials is redundant information. In most cases a flow diagram for a starting material is not relevant. 	Reference back to key starting material comments. We recognize that the bullet points described in lines 1730-1733 are important selection principles that ensure the quality of drug substance. However, we disagree with the distinction regarding significant and non-significant non-pharmaceutical use. All subsequent comments are predicated on this premise.
739	"The specification sheet should list all tests to which the material will conform"	<ul style="list-style-type: none"> May be interpreted to disallow for any additional testing or internal targets to be employed by the sponsor without their being listed as part of the registered specification. 	Delete "all" so that it reads: "The specification should list acceptance criterion to which the material will conform."
764	Section IVC3	<ul style="list-style-type: none"> Include Q7A in Additional Guidance (reference to water appropriate for intended use) 	Include Q7A in Additional Guidance
767-774	Controls of Critical Steps and Intermediates: Listing of all tests and acceptance ranges critical and non-critical, use of word "all"	<ul style="list-style-type: none"> Too burdensome to list all non-critical tests. Agency does note that it is the critical tests that constitute the specifications; however, historically, all tests presented in regulatory files have been considered as commitments. The term non-critical implies that optimization, variation, or excursion beyond stated (registered) criteria for these parameters will have minimal or no effect on the quality of the intermediate or API produced. 	On lines 769-70, change to read: "In this section of the application, critical operating parameters, controls and process tests should be listed and their associated numeric ranges, limits, or acceptance criteria should be identified." Delete rest of paragraph (i.e., lines 775-777).

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		<p>Typically, these non-critical parameters describe optimal operating conditions or process monitoring criteria. We would only provide tests which we believe are sufficient to appropriately test and characterize an intermediate. Suggest removal of references to "non-critical" here.</p> <ul style="list-style-type: none"> • Non-critical tests and limits are already provided in S.2.2, so no need to include them here. 	
785-7	<p>"Critical process control values from relevant batches ... should be provided as part of the justification."</p>	<ul style="list-style-type: none"> • Process controls used in actual production batches are usually well within critical values and are often irrelevant with respect to justifying critical control ranges. Control limits are normally established in lab-scale testing. • The data-based justification of the numeric ranges, limits, or acceptance criteria for critical process controls is a new requirement. Use of only in-process data from the "registration" lots of API will result in overly restrictive in-process control ranges, limits, or acceptance criteria. 	<p>Use of in-process data to justify these parameters should not be restricted to control values (test results) for intermediates and final API steps leading to the lots listed with batch analysis results in S.4.4. The justification must include use of laboratory and pilot-scale data that better test the limits of failure of the process for a particular parameter.</p> <p>Suggest replacing "should" with "may", and insert "if relevant" at the end of the sentence: "Critical process control values from relevant batches ... may be provided as part of the justification if relevant."</p>
795-812	<p>Tests Used in Lieu of DS Tests</p>	<ul style="list-style-type: none"> • Although lines 797-807 describe a valuable tool for the industry, we find the rest of the paragraph confusing. • Line 807 – 810: We assert that it is not necessary to have the acceptance criterion for the in-process test tighter than that for the drug substance. There are many instances where it can be shown that the downstream process improves quality. • This sentence should be revised to indicate that the acceptance criterion for the in-process test should be demonstrated to be appropriate to ensure that the drug substance will 	<p>We see lines 797-807 as a positive and helpful guidance.</p> <p>Revise (lines 807 – 810) sentence to read:</p> <p>-</p> <p>"When the same analytical procedure is used ... , the acceptance criterion for the in-process test should be demonstrated to be appropriate to ensure that the drug substance will meet its acceptance criterion."</p>

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		meet its acceptance criterion.	
818	Specification for an intermediate	<ul style="list-style-type: none"> Relevant testing 	It should not always be required to test for assay for intermediates. It is much more relevant (and often sufficient) to monitor the impurity profile.
822, 828, 830	Use of words "intermediate" and "obtained from"	<ul style="list-style-type: none"> Should allow for possibility that a highly purified or well-characterized chemical substance of biological derivation might be acceptable as a starting material. Suggest reserving use of "obtained from" for compounds obtained directly from biological sources without substantial modification of their covalent structure (e.g., use "derived from" to describe derivation from biological sources for semi-synthetic compounds). 	Suggest replacing "intermediate" with "chemical substance"; in line 830 suggest "is obtained or derived from ..."
852-4 (see also Glossary's "Intermediate" 2160-6)	"no distinction between intermediates, final intermediates, and postsynthesis materials for DSs derived from biological sources."	<ul style="list-style-type: none"> These distinctions are reasonable and useful and should be retained for semi-synthetic compounds synthesized from SMs which are highly purified chemical compounds (whether the SM is bio-derived or not). E.g., these distinctions are necessary if the BACPAC I guidance is to be applicable for changes to registrations of semi-synthetic DSs. 	<p>Suggest deletion of this paragraph.</p> <p>Or, if necessary to retain, limit its scope to DSs obtained directly from a biological material.</p> <p>We propose appropriate modification of glossary definitions (see comments on lines 2160-6).</p>
856	Unfinished Drug Substance		Under normal cGMP control, the specification of the drug substance is the API which comes from the supplier and is tested and released for use in the manufacture of the drug product. As part of manufacture of the drug product, the API may be purified, dried, milled, micronized, etc. These steps are considered to provide an intermediate in the drug product manufacture. Appropriate specifications are provided in P3.4 to control the quality of the processed drug substance.

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			FDA should clarify if the current practice of identifying the unfinished drug substance as the drug substance in the specifications section S.4.1 and the primary stability section S.7.3 and identifying the processed drug substance as a drug product manufacturing intermediate may continue.
877	Section IVE Footnote #15: "All manufacturing processes should be validated."	<ul style="list-style-type: none"> Only critical process steps need be validated. 	Recommend revision footnote to say "All critical process steps should be validated."
883-4	"Submission of validation information for reprocessing and reworking operations usually is not warranted."	<ul style="list-style-type: none"> We appreciate the inclusion of this statement. 	Please retain this statement in the final guidance.
890-911	Process Development	<ul style="list-style-type: none"> Section does not consider older established DS 	This section does not take into account that for quite old, well-established drug substances the original process development information may not be available anymore or may not be (fully) in line with current requirements. It should be stated in this section that in such situations this information would not be required.
900-3	"If in vitro studies ... or in vivo studies ... on the drug product were warranted because of a change in the drug substance manufacturing process, the study results should be summarized, and a cross-reference ... provided in S.2.6."	<ul style="list-style-type: none"> We suggest that use of the word "warranted" is inappropriate, since bioequivalence studies are conducted at the sponsors' risk. Also, we believe the placement of this requirement to be wrong 	Substitute "conducted" for "warranted" Move requirement to P2. Pharmaceutical Development
905-907	The primary stability batches should be manufactured using the same manufacturing processes (e.g., synthetic route) and procedures and a method of manufacture that simulate the process intended for production batches	<ul style="list-style-type: none"> Replace with language as suggested at right 	The primary stability batches should be manufactured using the same (synthetic route)-and a comparable method of manufacture that simulates the process intended for production batches
911	Additional guidance	<ul style="list-style-type: none"> We believe ICH Q1A (R) should be cited within "Additional guidance....." 	Include reference to ICH Q1A (R)
925-938	Elucidation of Structure	<ul style="list-style-type: none"> The use of many of the described techniques to confirm the chemical structure should relate to new 	For APIs for which a monograph exists in the USP the compendial identification test method should

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Line#	Item	Concerns	Proposed change
		chemical entities and not to existing APIs.	suffice.
965-970	Physicochemical Properties		We propose to include that the extent of physicochemical information should also depend on whether the API is a new one or an existing one.
986-989	"At an appropriate stage of development, the potential for interconversion of solid state forms should usually be investigated in stability studies."	<ul style="list-style-type: none"> We agree that this step needs to be done but that there may be alternate methods to primary stability studies 	<p>Allow for a rationale for not summarizing solid state interconversion based on solid state/polymorph screen</p> <p>Suggest 'At an appropriate stage of development, the potential for interconversion of solid state forms should usually be investigated'</p>
1006-1065	Impurities	<ul style="list-style-type: none"> Scope of requirements for impurities discussion expanded to include potential impurities as well as those present in the past but are no longer present due to synthesis changes. Then on page 28 (1049-1065), information is requested for impurities. Scope here could be massive. Need to reduce, limiting to impurities that are specific to the proposed commercial synthesis. 1049: Statement needs qualification: "The following are typical of the information that should be provided for impurities" 	Delete this entire section and cross refer to ICH Q3a(r)
1082-8	Specification S.4.1: "If the drug substance is processed (e.g., micronized) before it is used to manufacture the drug product, the specification for the unfinished drug substance, if there is one, should be included in section in S.2.4."	<ul style="list-style-type: none"> This passage is confusing. It appears to state that for any API that undergoes mechanical/physical operations such as milling, micronization, and/or blending to generate alternative grades, there must be a specification (tests and limits) filed for the unfinished API. Correspondingly, this implies that a full range of testing for parameters other than particle size or content uniformity would be performed on the unfinished material and then repeated 	<p>The API manufacturer should have the option of providing complete specifications and testing to these specifications for the finished API without also having to provide and perhaps test to specifications for the unfinished API.</p> <p>It would be useful if it would be explained here what the interrelation should be between the specifications of the drug substance manufacturer and the specifications of the applicant.</p>

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		<p>on the finished API unless the applicant made use of the "Tests Used In Lieu of Drug Substance Tests" option in Lines 795-812.</p> <ul style="list-style-type: none"> • DS Specification for multiple applicant customers 	<p>The drug substance has been the item manufactured by the drug substance manufacturer, tested and release to the drug product manufacture. This is the item subject to storage and transport for which stability data is generated. The drug product manufacturer may perform additional manipulations of the drug substance to make it suitable for use in the dosage form such as milling, micronization, drying, purifying, etc. The manipulated drug substance is considered a manufacturing intermediate controlled by specifications that assure the continued quality of the drug substance plus the additional attributes obtained during manipulation. These manufacturing intermediates are subject under the GMPs to be used within 30 days or require the provision of stability data for longer storage.</p> <p>We recommend that the guidance recognize this regulatory paradigm and permit flexibility in the presentation of the information for the drug substance provided by the supplier. The specifications for the unfinished drug substance should be permitted to be submitted in Section S.4.1.</p>
1090-1	"The specification for the mixture should be included in P.3.4 of the application."	<ul style="list-style-type: none"> • We question why a specification is needed for a mixture of specified drug substances used in the manufacture of a drug product, controlled via a specification. 	remove requirement
1105	"specification sheet"		Delete the word "sheet"
1110	"sunset provisions"		We welcome FDA acknowledgment of sunseting and suggest reference to the definition in ICH Q6, we also recommend

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Line#	Item	Concerns	Proposed change
			to include "sunset provisions" in the glossary
1111-4	"The specification from the applicant and/or DP manufacturer should identify the tests that it will routinely perform and the test results that will be accepted from the DS manufacturer's COA"	<ul style="list-style-type: none"> Inappropriate for this section. 	These lines should be deleted and included in the drug product section of the CTD
1121-3	(footnote #19): "Certain <i>General Chapters</i> in the USP contain a statement that the text of the USP is harmonized with the corresponding texts of the <i>European Pharmacopoeia</i> (EP) and the <i>Japanese Pharmacopoeia</i> (JP). However, where a difference appears, or in the event of dispute, the result obtained from the USP procedure is conclusive."	<ul style="list-style-type: none"> This footnote does not seem to fully embrace pharmacopoeial harmonization as we would envisage this. We assert that harmonization principles should be honored. It seems inconsistent to embrace harmonization on one level, yet default to USP methodology – as is apparent from Footnote 19 – in case of "difference" or "dispute". 	Delete footnote 19 (and reference to it in line 1123)
1126	"Release and shelf-life acceptance criteria when both are used"	<ul style="list-style-type: none"> Release and shelf life criteria apply only to drug products 	"Release- and end of retest period (or if applicable: end of shelf-life-) acceptance criteria when both are used"
1129	Example Appearance Specification: "White crystalline powder" (Also appears as an example in Lines 1257-1258)	<ul style="list-style-type: none"> Assessing crystallinity by eye is not appropriate Heavy Metals Limit 	Appearance should be part of the description rather than a specification test. Heavy Metals NMT 0.001%
1129-30	Table 2 detail: Brand X Particle Size Analyzer	<ul style="list-style-type: none"> Overly restrictive to expect provision of the brand of an instrument as part of the specification. 	Suggest "Type of " Particle Size Analyzer rather than "Brand X"
1135-90	"Occasionally ... other tests and associated acceptance criteria ... that assess drug substance quality can be included in the application and not be listed in the drug substance specification. These tests, referred to as periodic quality indicator tests (PQITs), augment the drug substance specification."	<ul style="list-style-type: none"> PQITs: this appears to be a helpful proposal, especially if a PQIT can be designated for use exclusively for process change-control and re-validation purposes. It may be helpful to provide some examples of what typical PQITs might look like. 	Provide examples of PQITs.
1137	"The CGMP regulations require that ... a batch that does not meet the specification must not be used to manufacture the drug	<ul style="list-style-type: none"> In order to avoid confusion, it should be clarified that it is indeed permissible to use CGMP batches that do not meet 	Add " (other than for use in non-clinical studies)" to the end of the first sentence, i.e. after "the drug product".

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	product (21 CFR 211/84)."	specification in non clinical studies (where CGMP does not apply)	
1142-1143	PQIT		We propose that no discrimination will be made between a drug substance specification and a PQIT. In other words, it should be possible to have PQITs as part of the total set of specifications, provided there will be a sound rationale for these.
1149	PQIT		Testing for heavy metals is an example of a test that may often be suitable for a PQIT approach or even for complete deletion. (see also lines 1316-1319 of the Draft Guidance). However, the reference to "impurities" in a general sense, as is done in line 1149, suggests that PQIT would not be appropriate for heavy metals testing. We suggest therefore that the term impurities will be narrowed down to e.g. "related impurities".
1173-5	"Any investigation will assess the effect on all batches produced, in particular, the batches between the last batch tested with a passing result and the batch that failed."	<ul style="list-style-type: none"> It should be necessary only to assess the effect on batches produced since the last batch tested with a passing result. For PQITs used only for process change control and re-validation purposes, there is usually no reason to question the acceptability of pre-change lots. 	Suggest "Any investigation will assess the effect on the batches between the last batch tested with a passing test result and the batch that failed." Add a sentence to clarify: "For PQITs used for process change control purposes, there is usually no need to assess the acceptability of pre-change lots that were not tested by the PQIT."
1176-8	If batch failure, must file CBE to include PQIT into the DS specification		Add a sentence to clarify: "If the batch failure include PQIT into the DS specification.
1186-1188	"It is recognized that only limited data may be available at the time of submission of an application. Therefore, this concept would generally be implemented post approval"	<ul style="list-style-type: none"> PQITs would not usually be proposed in an initial NDA. It would be more helpful if these sentences were moved to the beginning of the section. 	Move these sentences to beginning of the section. Any reference to supplemental criteria should be deleted so that other mechanisms can be implemented.
1198 (also in 1229)	"Information should be provided for all analytical procedures listed in the specification."	<ul style="list-style-type: none"> Avoid use of "all". E.g., information on compendial methods should not need to be provided. 	Delete "all" here, e.g.: "Information should be provided for analytical procedures listed in the specification (S.4.1)"
1229	Assay validation	<ul style="list-style-type: none"> Validation data should not be required for compendial methods for submission 	Change to: "This information should be provided for <i>noncompendial</i> analytical

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Line#	Item	Concerns	Proposed change
			procedures..."
1229-31	Validation of Analytical Procedures (S.4.3)	<ul style="list-style-type: none"> Since all analytical procedures listed in S.4.1 are to be accompanied by validation data, this would include PQITs. 	It should also be stated in the PQIT section that validation documentation is required.
1230-31	"Stability data...should be used to support the validation of the analytical procedures."	<ul style="list-style-type: none"> Circumstances in which inclusion of stability data from stress studies are desirable are already indicated in the existing validation guidances that are referenced. 	Suggest deleting this sentence. Otherwise, please substitute "can" for "should".
1241	"Batch analysis reports (e.g., certificates of analysis (COAs)) should be provided for all drug substance batches"	<ul style="list-style-type: none"> Batch data tables should be acceptable as an alternative to COAs. Requirement for a separate batch analysis report for each batch will add greatly to the bulk of the dossier without adding information. 	Allow for option to present data in tabular format: "e.g, certificates of analysis (COAs) or batch data tables..."
1257-1259	We discourage the use of terms such as <i>conforms</i> or <i>meets specification</i> .	<ul style="list-style-type: none"> In laboratory notebooks, observations are written numerically or qualitatively. The conclusion often is "Conforms" or "Meets specification" Should allow "Conforms" or "Meets specification" to be used as a conclusion when it is clear what specification the test results have been assessed against. 	Change to: "We discourage the use of terms such as <i>conforms</i> or <i>meets specification</i> except when it is clear what specification the test results have been assessed against (e.g., description, identity)."
1263-4	"The batch analysis reports should include results from all tests performed on the batch, including tests that are not part of the proposed specification."	<ul style="list-style-type: none"> Tests listed in the specification should be sufficient to characterize a batch. The guidance should recognise that some testing conducted may be omitted because it is no longer relevant to the proposed specification. The omission of this data will be discussed in the justification of the specification.<this comment sent to parking lot> 	Any batch data used to omit a particular spec will be in S.4.5 Suggest instead: "The batch analysis reports should include results from all tests listed in the Drug Substance specification, where available"
1264-1265	References to analytical procedures should be provided.	<ul style="list-style-type: none"> Need clarification. 	Delete the sentence asking that analytical procedures should be referenced in batch analysis reports.
1267-1276	"A summary of any changes in the analytical procedures should be provided if the analytical procedures"	<ul style="list-style-type: none"> Use of the word "any". There could be minor changes made with no impact on the data 	Only discuss the major changes in the analytical procedures that impact the data significantly.

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Line#	Item	Concerns	Proposed change
1309-11	"exclusion of ... one that was reported in the batch analyses (S.4.4)..."	<ul style="list-style-type: none"> • Related to comments on lines 1263-4. If all tests run are required to be reported in the batch analysis summary, then this is overly burdensome and the phrase should be deleted. • If only tests directly related to specifications are required in the batch analysis summary, then this phrase is superfluous and should be deleted. • If all tests associated with specifications are required in the batch analysis summary and also tests that are routinely performed, then insert "routinely" to clarify. 	<p>Delete phrase "one that was reported in the batch analyses (S.4.4)."</p> <p>Alternatively, modify phrase to "one that was reported routinely in the batch analyses (S.4.4)."</p>
1314-33	"sunset test protocols"	<ul style="list-style-type: none"> • We see this as a potentially positive and helpful proposal. A provision for sunset test protocols should not be used by the agency to justify a general expectation for increased numbers of initially-registered tests and limits, many of which may be of highly doubtful value. • Example of "manufacturing process change" circumstance under which sunset tests may be appropriate (line 1322) is adequately covered under existing guidances for GMP (e.g. ICH Q7A 11.22) and for post-approval changes (e.g., "the applicant should perform additional testing, when appropriate" to assess the effect of a process change). 	<p>Add a sentence to paragraph to clarify: "Sunset test protocols should not be proposed where existing information is sufficient to show that the test is not necessary or critical to quality."</p> <p>Delete "and/or (2) the manufacturing process for production batches will be different (e.g., scale, equipment) from that used to produce the batches used to support the application and the effect, if any, of the differences has yet to be characterized."</p>
1368	Acceptance criteria	<ul style="list-style-type: none"> • Acceptance criteria for organic impurities should be established in line with Q3A. • Impurity methods can have enough variability that setting a limit based on one determination is not scientifically sound. The limit must account for the 	<p>Change to read: "The proposed acceptance criteria for impurities should be based on ICH Q3A considering the precision of the test method and the levels qualified through nonclinical or clinical studies presented in the NDA."</p>

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1372-3	"Acceptance criteria for residual solvents should generally be based upon manufacturing capability."	<p>precision of the method.</p> <ul style="list-style-type: none"> We suggest that, to avoid ambiguity, it would be helpful to omit this sentence*, retaining instead the direct cross-reference to ICH Q3C to provide appropriate guidance. Instead of process capability, residual solvent specifications should be based upon ICH safety thresholds. 	<p>* Omit sentence: "Acceptance criteria for residual solvents should generally be based upon manufacturing capability"</p> <p>Alternatively, change sentence to: "Acceptance criteria for residual solvents should generally be based upon demonstration of acceptance to safety thresholds as determined by ICH."</p>
1401-2	List of any available reference standards for impurities and intermediates	<ul style="list-style-type: none"> Should clarify that this list is for those available reference standards that are required for testing vs. the DS specification. 	Suggest sentence should read: "A list of available reference standards for drug substance impurities and intermediates (i.e., those that are required for testing versus the drug substance specification) should be included in S.5."
1412-4	Container Closure System (S.6) "nonfunctional secondary packaging components"	<ul style="list-style-type: none"> Only packaging components necessary to assure product quality should be described. 	The lines regarding the necessity to describe non-functional package should be deleted.
1431	Shelf Life	<ul style="list-style-type: none"> Consistency with ICH Q7A 	<p>We propose that "shelf-life" will be replaced by "retest period (or if applicable shelf-life)".</p> <p>Reason: Retest period is normally applicable for APIs and shelf-life only if there are specific reasons (quite unstable APIs) not to apply retest period.</p>
1451-3	"Stability study reports should also be included."	<ul style="list-style-type: none"> Stability study "reports" would make the section unwieldy and difficult to focus on the data. 	<p>Tabulated stability data should serve the purpose.</p> <p>Change to: "Tabulated stability data should be included."</p>
1490	"Any results from DS stress testing should be provided"	<ul style="list-style-type: none"> "Any" may be too all-inclusive and lead to inclusion of irrelevant and potentially confusing data. 	<p>Should be sufficient to say merely "Results from DS stress testing should be provided"</p> <p>For clarification purposes it would be appropriate to explain here that stress testing results are not expected for older, well-established APIs for which the degradation pattern is well known.</p>

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1514-6	Emphasis on potential TSE concerns.	<ul style="list-style-type: none"> Stylistic improvement desired: this section and subsequent ones seem very focused on bovine TSE concerns to the exclusion of other agents that could present some concerns (such as other proteins, fungi etc). 	A general statement placed at the beginning of this entire section and then followed by more detailed comments on the cases where points of emphasis are needed would be more helpful as a guidance. E.g., lines 1537-8 appear to aim at this more general concern.
1599-1601	Virological safety		It should be clarified in which cases such an evaluation will be relevant and in which cases it is not. A reasonable way to limit the scope will be to restrict this to APIs directly obtained from animals or from humans.
1630-1	An executed batch record is not required, but if an executed production record is provided for illustrative purposes, it should be included in R.1.S.		Please retain this statement in the guidance.
1650-2	Methods validation package	<ul style="list-style-type: none"> More complete references to guidances are desired. 	Suggest adding reference to the 1987 guidance on "Submitting Samples and Analytical Data for Methods Validation" and the 2000 draft, "Guidance for Industry: Analytical Procedures and Methods Validation, Chemistry, Manufacturing, and Controls Documentation".
1666-2106	General Comment on Starting material Attachments: significant level of "NMT 0.10%"	<ul style="list-style-type: none"> The guidance repeatedly uses the 0.10% level of impurities as a significant level. Lines 1785, 1860, 1922 and 1945 (for example), each reference an impurity limit of NMT 0.10%. This appears inconsistent with and more stringent than the BACPAC guidance that describes limits of 0.1% (using less significant figures) and of 0.2% for veterinary-use-only materials. 	<p>Revise to be consistent with "qualified" levels (e.g., in line 1785) and also to be consistent with ICH Q3A/B:</p> <p>Delete lines 1855-1867.</p>
1666-70	Starting Materials for Synthetic Drug Substances	<ul style="list-style-type: none"> General concerns relative to dividing all DSs into "Synthetic" and "Derived from 	Starting materials for semi-synthetic DSs that are significantly removed from

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		biological source" categories, together with different SM criteria for each. Unnecessarily burdensome for many semi-synthetic DSs.	biological sources should be covered under Attachment 1 rather than Attachment 2.
1681-3	"A proposed starting material should be chosen so that sufficient information will be available to the FDA on the <u>manufacturing process</u> to evaluate the safety and quality of the drug substance"	<ul style="list-style-type: none"> A starting material with a significant nonpharmaceutical market may be made by a proprietary process by a company not regulated by FDA, so information about its manufacturing process may not be known. This situation should not prevent a pharmaceutical company from proposing a starting material, nor should it prevent FDA from accepting the proposal. We suggest that the emphasis is <i>incorrect here, and recommend the sentence be re-worded, as proposed.</i> 	Recommend that this sentence is deleted and replaced with a statement that industry is responsible for conducting a risk assessment of the starting material.
1683-5	Starting materials for synthetic drug substances: requirement that SM may not be itself a DS	<ul style="list-style-type: none"> We disagree with this restriction. The sentence too proscriptive. There is so much variety in chemical synthesis that is not realistic to rule out the use of drug substances as starting materials. The exclusion of any possibility of using a drug substance as a starting material regardless of the number and nature of subsequent chemical steps (propinquity) to reach the API of the subject application is unnecessarily restrictive. No scientific reason for this restriction. A DS used as SM may be well-characterized, commercially available, described in compendia, and sufficiently separated from the DS being filed. It would not likely have a significant nonpharmaceutical market, but this should not be an objection for such starting materials. 	Allow for the possibility of using a DS as a SM: we propose that Lines 1683-1685 should be deleted
1740	Propinquity	<ul style="list-style-type: none"> There is no scientific basis for propinquity as a criteria for selecting a 	Delete entire section on propinquity. Refer to general comment on propinquity

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		starting material.	above for rationale. Recommend that an Industry / FDA workshop may be the optimum way of resolving propinquity issues.
1764	Extraction Procedures	For example, evaporating solvent from a reaction mixture or the extraction work up of a reaction mixture is not considered to produce an isolated and purified intermediate.	Extraction procedures are generally considered as a purification.
1768-3	"Isolated and Purified". "A chemical proposed as a SM should be an isolated and purified substance. ID of an isolated and purified substance as the SM, as opposed to an in situ and/or crude substance reduces the risk of degradants and/or impurities affecting the ID, quality, purity, or potency of the DS."	<ul style="list-style-type: none"> The word "purified" does not offer specific guidance with regard to the extent of purification. There may be instances in which a well-characterized but impure substance would be an appropriate starting material. E.g., an impure (but well-characterized) SM that leads to a pure DS. Similarly, the requirement that a "crude" chemical should be not be used as a starting material should be deleted from this section. The word "crude" does not offer specific guidance with regard to quality requirements. Often a "crude" chemical can be demonstrated to be a suitable starting material. Also, there may be instances in which un-isolated (e.g., "in situ") materials may be more appropriate as a SM (e.g., more stable) than their isolated form. We suggest instead a criterion of "stable, well-characterised substance". 	<p>1768: Suggest "stable and well-characterized" rather than "Isolated and Purified". Also make this substitution in 1770-4. Suggest revision as follows:</p> <p>"A chemical proposed as a starting material should be a stable, well-characterized substance. Identification of a stable, well-characterized substance as the starting material-reduces the risk of degradants and/or impurities affecting the identity, quality, purity, or potency of the drug substance."</p>
1775-82	Carryover of Impurities: "A chemical proposed as a starting material should not be the source of significant levels of impurities in the drug substance."	<ul style="list-style-type: none"> 1777-1778: We strongly oppose this sentence since the fate of the significant impurities in starting materials can be understood, and, if they lead to significant impurities in the drug substance, appropriately qualified. There is no additional safety hazard or 	<p>Suggest to modify first sentence to read "A SM should not be the source of significant levels of un-qualified or un-specified impurities in the DS".</p> <p>Suggest insertion of the following sentence:</p>

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		<p>value to the patient in establishing this selection criterion as it is written. If significant levels of specified impurities are present both in SM and in the DS, this should be acceptable provided the impurities are appropriately qualified and controlled. The selection principle should be limited to the legitimate concern that potential new or uncontrolled SM impurities may carry over to DS.</p>	<p>"It is recognized that some impurities may originate from the starting material in which case the applicant should demonstrate appropriate control."</p> <p>We urge the Agency to re-phrase the rest of this section (lines 1778-97) to address the fundamental points raised (see also "Key Comments."</p>
1784-90	<p>"For purposes of selecting proposed starting materials, a significant level is considered to be greater than 0.10 percent in the drug substance (0.20 percent for veterinary drug substances not used in human drug products) of any of the following impurities: [bullet points]."</p>	<ul style="list-style-type: none"> • We suggest that the "significant level" limit for purposes of selecting SMs should be more in-line with the applicable ICH qualification threshold for DSs rather than the ICH identification threshold. • Should clarify that proposed "significant level" applies to individual impurities and not to collective measures of impurities. • Clarify in each bullet point that it is unqualified or unspecified impurities of these types that are in view. 	<p>This section should be revised to refer to ICH Q3 and VICH. Use qualification rather than identification thresholds</p>
1792-7	<p>Carryover of Impurities: SM must be at or before point at which TSE agents could be introduced</p>	<ul style="list-style-type: none"> • The placement of the starting material before the (first) point in the process where TSE risk materials are used is arbitrary and without scientific basis. • If TSE risk materials are used in the production of the starting material, and if adequate documentation is provided to assure that the proposed starting material carries a minimal risk of TSE, then the proposed starting material should be acceptable from a TSE carryover perspective. • Appropriate control can be demonstrated via a compliance statement provided from the starting material manufacturer. • To impose this requirement would 	<p>Potential TSE concerns are better handled by requiring that SMs and raw materials be assessed appropriately for TSE risk. This paragraph requiring that a starting material be chosen before the introduction of TSE risk materials should be deleted.</p>

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		<p>place a huge, unjustified regulatory burden upon the pharmaceutical industry, made even more questionable by the fact that similar requirements are not applied to starting materials with a significant nonpharmaceutical market</p>	
1799-1820	D. Complexity of Structure	<ul style="list-style-type: none"> • 1801-1805: Move under section B. • The rest of Section D should be deleted • 1805-7: While discussion of the subject of complexity is not included in Appendix II (which applies to starting materials of plant or animal origin), in fact a starting material may be derived via numerous steps from a material of natural origin that already bears significant molecular complexity. APIs bearing a steroidal carbon ring skeleton are valid examples, and may be derived from natural materials derived from plants. Registration of such processes should not be compelled to go back many, many synthetic steps to a material derived from a natural source, when a later intermediate may meet all the requirements established by the other provisions of Attachment I. • 1815-1818: This sentence disqualifies future pursuit of complex starting materials and seems unnecessarily confining, allowing insufficient room for future exploration. Several of the "advanced techniques" listed (e.g., 1H-NMR, 13C-NMR, mass spectrometry, elemental analysis, chiral HPLC) are now widely available and easily implemented and their use in an ID spec should not be a basis for rejecting a SM proposal. 	<p>Suggest 1801-1805 be moved to section B ("Isolated and Purified", which we have suggested be changed to "Stable and Well-characterized").</p> <p>Later in Section II (lines 1961 – 1971), reasonable requirements are established for documentation involving structural complexity and the ability of proposed tests to distinguish from isomers and analogs; these requirements are sufficient and appropriate to address what should be necessary for this aspect of a regulatory application.</p> <p>Suggest removal of the rest of this subsection.</p>

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1806	Grammar		"are" should be "is"
1831-41, 1834-1836	Flow Diagram of the Complete Synthesis "Each synthesis branch should begin with chemicals that have significant nonpharmaceutical market"	<ul style="list-style-type: none"> • Impracticable if there is more than one way that has been demonstrated to make SM. • "Significant nonpharmaceutical market" is a scientifically irrelevant criterion to which we object (see "Key Comments). • This requirement would effectively change the regulatory significance of what a SM is. • Proposal is especially onerous if all details (reagents, solvents, etc.) sought in DS flow diagram are also expected here for synthesis of SMs. • An unreasonable requirement for SMs that are themselves DSs. 	<p>Appropriate specifications should be sufficient to justify a proposed SM.</p> <p>Reduce the two paragraphs to: "A flow diagram should be provided showing the complete route of synthesis of the DS from the SM(s). The flow diagram in S.2.2 can be cross-referenced."</p> <p>Synthetic steps within the route towards the starting material may be confidential information of a supplier of the starting material (or even different sequential steps in such routes may be performed by different companies). In those cases this information may be unavailable for inclusion in the submission. Therefore, the insertion of the words "if such information on the synthesis of the starting material is available" will be appropriate.</p>
1845-8	Starting Material Specifications	<ul style="list-style-type: none"> • The requirement that specifications for the starting material be based solely on the starting material lots used to manufacture the API lots used to establish the API specifications is overly restrictive. 	<p>Modify the second sentence of this paragraph to address these concerns, for example:</p> <p>"The starting material specifications should be derived from the complete experience during development and commercialization and should incorporate demonstrated capability of the process to remove impurities originating from the starting materials."</p>
1851	"and any related compounds that are likely to be present"	<ul style="list-style-type: none"> • Related compounds could be construed to mean impurities. Or other similar materials in use at the manufacturing site. Neither of these should be supported. 	<p>Revise to indicate that the ID test should be specific, including presence of correct stereoisomer, counter ion, etc., as applicable.</p>
1856-1857	A limit on unspecified impurities should be considered.		<p>We understand that the FDA wishes to control the impurity profile even for trace level impurities. This requirement however exceeds the requirements of ICH Q3A which requires that there be</p>

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			<p>acceptance criteria for total impurities, specified impurities which exceed the identification threshold and for individual unspecified impurities. Tight limits on both the total impurities and the specified impurities should assure control on the amount and number of unspecified impurities. Therefore, we recommend that the Guidance be specific with respect to limits for "unspecified impurities" to clarify that a limit for Total Unspecified Impurities will not be required.</p>
1871-1893	<p>Whole section under D.1</p> <p>1883 "A description of the uses other than for drug substance production..."</p> <p>1884 "able to provide quantities suitable for both DS production and other markets";</p> <p>1886 DS manufacturer did not synthesize SM for Ph1&2;</p> <p>1888 Phase 1 & 2,</p> <p>1889 Did not scale up its process</p>	<ul style="list-style-type: none"> • 1883: An unreasonable requirement, as it is irrelevant to the preparation of the API what are the potential other uses of a given starting material. • 1884: "Quantities suitable ..." an unnecessary restriction. • 1886: It is a common occurrence for business reasons for the innovator company to prepare the DS from the SM for early batches, but once POC has been demonstrated to start looking for SM suppliers. Is there a scientific reason why SM made by innovator is not useful? • 1888: Amounts used for Ph 1&2 may vary tremendously depending on therapeutic area. Why is Ph 1&2 important? This seems to be not relevant. Should focus on commercialization. This requirement is not related to quality. • 1889: Scale-up not an important criterion. E.g., more important is the fraction of market related to capacity. A supplier could meet demand by making more batches without scaling up. Or several suppliers could be used. 	<p>Suggest deletion of this entire section (1871-1893).</p>
1899-1900	Starting Materials without a Significant	<ul style="list-style-type: none"> • We believe that it is critically important 	We propose that the following wording be

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	Nonpharmaceutical Market	for the successful implementation of this guidance that clear provision be made for a means by which a sponsor may address those cases where it is not necessary, for valid scientific reasons, to comply with the selection principles criteria exactly.	added at the end of this paragraph: 1899: "If an applicant can demonstrate that a proposed starting material complies with the selection principles, then it will be acknowledged as a regulatory starting material. Should it not be possible to fulfil all selection principles criteria, then further justification, based on scientific understanding, will be needed. Applicants are encouraged to discuss their proposed strategies/ justifications with the Agency at appropriate time points during the development process"
1966-8	Common techniques	<ul style="list-style-type: none"> • <i>More sophisticated techniques should be OK. See comments on lines 1815-1818.</i> 	In line 1966, place a period after "analogs" and delete the rest of the sentence.
1984-1988	It is valuable for drug substance manufacturers to maintain close communication with manufacturers of starting materials. The quality of a starting material can be affected by changes in manufacturing process (e.g., changes in solvents, purification, catalysts, route of synthesis), and knowledge that a change has taken place can assist a drug substance manufacturer in maintaining a valid starting material specification.	<ul style="list-style-type: none"> • We agree with this statement. Make sure it stays and include additional sentences 	It is recognized in the guidance that close communication with vendors is valuable for the purposes of understanding changes to the route of synthesis and potential impact on quality. There should be some provision in this guidance for justification of later starting materials if commitments are made around the manufacture of the starting material. For example, the level of rigor required with regard to carry-over of impurities and propinquity should be considered in the context of possible formal agreements with starting material suppliers, and/or commitments in the application to a particular route of synthesis for the starting material.
1994-2004	"DS derived from a biological source"	<ul style="list-style-type: none"> • <i>Unnecessarily burdensome to require the same amount of documentation for semi synthetic DSs far-removed from</i> 	Suggest, in lines 1995 and 1996, substituting "obtained" for "derived". Suggest rewrite of sentence in lines 1998-

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		biological sources as the amount required for DSs obtained directly from biological sources.	01: "The term <i>DS obtained from a biological source</i> includes DSs that are the chemical substance obtained directly from the biological source and semi-synthetic DSs that involve only minor modification of the chemical obtained from the biological source." The last sentence of the paragraph should then substitute "is obtained from a biological source" for "is of biological origin."
2000-1	Inclusion of all drug substances derived in any degree from a biological source under the guidance of Attachment 2.	<ul style="list-style-type: none"> This unnecessarily broad categorization would impact our entire steroid DS line and impose restrictions which have no bearing on the quality of these and similar semi-synthetic substances. 	See our key comments on needing to relax requirements for semi synthetic DSs that are significantly removed from biological sources.
2008	List of cases to which the Attachment 2 recommendations do not apply.	<ul style="list-style-type: none"> Attachment 2 recommendations should not apply to SMs that are well-characterized semi synthetic chemicals derived from biological and non-biological sources. 	Add bullet point: <ul style="list-style-type: none"> SMs that are well-characterized semi-synthetic chemicals derived from biological sources.
2016-8	Cases to which the Attachment 1 recommendations apply	<ul style="list-style-type: none"> Include SMs that are well-characterized semi-synthetic chemicals derived from biological and non-biological sources. 	Insert sentence after the first sentence: "The recommendations in Attachment 1 also apply to SMs that are well-characterized semi-synthetic chemicals derived from biological and non-biological sources."
2026	"For semi synthetic DSs the information recommended in Attachment 1 should be provided for the SMs of synthetic origin, if there are any ..."	<ul style="list-style-type: none"> Include SMs that are well-characterized semi-synthetic chemicals derived from biological and non-biological sources 	Change to "... should be provided for the SMs of synthetic origin or semi synthetic origin, if there are any ..."
2033	"variety"	<ul style="list-style-type: none"> Seems excessive to require not only "species" but also "variety" in all cases 	Suggest: "(i.e., Family genus, species, and where appropriate, variety)"
2038	"List of pesticides and herbicides that may be used in the geographic areas of harvesting"	<ul style="list-style-type: none"> Seems excessive. 	Suggest deleting "geographic" so that only those pesticides and herbicides approved locally for the particular type of agriculture of interest would need to be listed, not all those approved for any agricultural use whatever.
2141-46	Glossary: "Final Intermediate"	<ul style="list-style-type: none"> We find the proposed definition of "final 	The guidance should refer to the

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		<p>intermediate" flawed.</p> <ul style="list-style-type: none"> For example, if a starting material were introduced at step 2 of a 4 step synthesis, to react with an intermediate to generate a free base immediately prior to drug substance generation, then, since salt formation is not considered a reaction step, which intermediate is the final intermediate? We suggest that both the intermediate at step 2, and the starting material added at step 2 would fulfil the definition in this case. 	<p>BACPAC1 definition</p>
2158-66	Glossary: "Intermediate"	<ul style="list-style-type: none"> We note that this definition does not agree with those given within ICH Q7A and ICH Q3A (R) Not all semi synthetic DSs should have their "Intermediates" defined by the second bullet point, which seems more appropriate to reserve for DSs that are obtained directly from biological sources. 	<p>We recommend that an ICH-aligned definition should be developed.</p> <p>2160: change to: "For synthetic DSs and for semi synthetic DSs having no biological SMs, a material"</p> <p>2164: substitute "obtained" for "derived, and change end of sentence to be "... or that undergoes only relatively minor molecular modification before it becomes a DS.</p>
2160, 2188	Intermediate definition	<ul style="list-style-type: none"> Desirable to broaden definition. E.g., Believe a classical resolution should be considered a step and its product an intermediate. 	<p>Suggest a phrase be added to the definition to include products of steps such as (1) resolution of enantiomers or (2) salt formations done for the purposes of isolation and purification, in which a different material is isolated and purification usually occurs.</p>
2218-2219	Retest Period		<p>In a science-based approach it is not appropriate to link the stability characteristics of a drug substance to a completely unrelated characteristic such as its pharmacological activity (in this case: antibiotic activity). We therefore propose that the words "certain antibiotics" will be replaced by "certain other labile drug substances"</p>

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2207-9	Residual solvent definition	<ul style="list-style-type: none"> We note that this definition does not agree with that given within ICH Q3A (R) This definition could include any volatile chemical, but really is intended for those used as solvents or a by-product that corresponds to a common solvent. 	<p>A definition more in-line with ICH Q7A is preferred. I.e., "An inorganic or organic liquid <u>used as a vehicle</u> for the preparation of solutions or suspensions in the manufacture of an API."</p> <p>May be suitable to include a definition of "Organic Impurities" (consistent with ICH Q3A).</p>
2211-9	Retest Period	<ul style="list-style-type: none"> The definition of Retest Period given here is that from ICH Q1A. 	Please retain this statement in the guidance.
2222	"elements of biological origin"	<ul style="list-style-type: none"> Unclear 	Please clarify what is meant by this phrase.
2228-2232	Glossary: "Specification"	<ul style="list-style-type: none"> We note that this definition does not agree with that given within ICH Q6 A and B 	<p>We recommend that the agreed ICH definition should be used</p> <p>(It is unnecessary to refer to a specification "sheet" – as previously noted, this term should be deleted from the guidance)</p>
2235-2236	Definition of Starting Material	<ul style="list-style-type: none"> In-line with other comments, need to allow for semi-synthetic SMs in some cases 	<p>In line 2239, change "derived" to "obtained".</p> <p>- delete everything after the first sentence.</p> <p>Definitions included in Glossaries of major Guidelines such as this one are often used as such within other context and in other documents. Therefore, the further important explanation given in the first paragraph of Attachment 1 (that a minor contribution to the structure of the drug substance is not a criterion) should be also added here.</p>