Boehringer Ingelheim

Boehringer Ingelheim
Pharmaceuticals Inc.

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Food and Drug Administration
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Docket No. 02D-0526, Draft Guidance for Industry on Drug Product: Chemistry Manufacturing and Controls Information

Comments submitted electronically to fdadockets@oc.fda.gov

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Dear Sir or Madam:

Boehringer Ingelheim appreciates the opportunity to give comments on the subject draft guidance. Our comments are provided on the following pages, identified by section number/title of the guidance and line number.

Please contact the undersigned with any questions or comments on this correspondence.

Sincerely,

Patricia Watson

Patricia Watson
Head, Technical Drug Regulatory Affairs

Comment 1
Section III.B. Container Closure System
Lines 249 - 250

An overfill in the container should not be included in the brief description of the container closure in this section of the application. The overfill should be identified in the statement of composition (in cases where the composition is expressed on the basis of the unit container, (*e.g.*, vial). The overfill should also be identified in the description of the manufacturing procedure in P.3.3.

The brief description in P.1 of the container closure system proposed for marketing should be consistent with the description of the market package given in the "How Supplied" section of the drug product labeling.

The information on the size(s) of the market package is generally expressed as the number of units, number of doses or deliverable volume from the container. If an overfill is needed in order to ensure that the claimed (labeled) amount is delivered from the container, this is not needed in the description of the market package, and could cause confusion.

Comment 2
Section III.C. Composition Statement
- **References to Quality Standards**

Lines 307 - 309

The guidance states, "The compendium should be cited even if an in-house specification that provides for more testing than that of the compendial monograph is used to evaluate the component."

For clarity, reference to both the compendial standard and the additional requirements is needed so that the information in the composition statement is consistent with the information on the quality requirements for this component given elsewhere in the application (P.4).

We suggest revising this sentence to read as follows:

"For compendial components with requirements that exceed the compendial monograph (either additional tests or tighter acceptance criteria for a compendial test), reference should be given to the compendial standard with a footnote to the company's in-house quality standard, *e.g.*, "USP*" and footnote *additional tests performed".

Comment 3
Section III.C. Composition Statement
- **Reference to Quality Standards**

Lines 309 – 311

The guidance states, "For noncompendial components, the type of standard used to evaluate the component should be listed (e.g., in-house standard, Code of Federal Regulations (CFR) citation, DMF holder's standard)."

We recommend that the actual testing that the company/applicant performs should be referenced in the composition table, and suggest that this sentence be revised to read as follows:

"Noncompendial excipients should be referenced to the company's in-house quality standard."

Only in cases where the supplier, not the drug product manufacture, does the testing (*e.g.*, components of a capsule shell), the DMF for the component should be referenced. Otherwise the in-house standard should be listed.

Comment 4
Section III.C. Composition Statement
- **Amount**

Lines 341 - 342

The guidance states that "any overages" of drug substance in the unit should be listed in the composition statement. We agree that an overage used to compensate for stability losses should be shown in the statement of composition. However, a manufacturing overage should not be included in the quantities of ingredients in the statement of composition in P.1, since the manufacturing overage is presumably lost and does not appear in the unit of the drug product. (The overage should appear in the batch formula in P.3.2.

We propose that the sentence be revised to read as follows:

"The amount of drug substance in the specified unit should be listed. If an overage of drug substance is used to compensate for stability losses, the amount listed should include the overage."

Comment 5
Section III.C. Composition Statement
Line 358, Table 1

358

Table 1: Example Target Composition Statement

Component	Reference to Quality Standard	Function	50 mg tablet	100 mg tablet	150 mg tablet
Core Tablet					
Drug substance	In-house standard	Drug Substance	55 mg[1]	110 mg[1]	165 mg[1]
Excipient X	NF	Diluent	30 mg	60 mg	90 mg
Excipient Y	NF	Disintegrant	22 mg	44 mg	66 mg
Excipient Z	In-house standard	Binding Agent	5 mg	10 mg	15 mg
Magnesium Stearate	NF	Lubricant	1.5 mg	3 mg	4.5 mg
Core Tablet Weight	[redacted]	[redacted]	113.5 mg	227.0 mg	340.5 mg
Film Coat Solution					
Purified Water	USP	Processing Agent	-		--
Hydroxypropyl Methylcellulose	USP	Film Coat	4.5 mg	9 mg	13.5 mg
Color Red™[2]	DMF Holder Y standard	Film Coat Color	—	0.2 mg	—
Color Blue™[2]	DMF Holder Y Standard	Film Coat Color	0.05 mg	—	0.45 mg
Titanium Dioxide	USP	Opacifier	0.1 mg	0.1 mg	—
Total Tablet Weight	[redacted]	[redacted]	118.15 mg	236.30 mg	354.45 mg
Print Ink Solution					
Printing Ink Solution[3]	DMF Holder Z Standard	Identification	—	—	—

[1] Equivalent to 50, 100, and 150 mg, respectively, on the anhydrous basis
[2] The qualitative and quantitative composition statements for the two colors are incorporated by reference from DMF 99999. The information is located in the January 21, 2001 amendment to the DMF, Volume 2, page 104 and 105. See the letter of authorization from DMF Holder Y in Module 1.
[3] The qualitative and quantitative composition of the ink is provided in Table XYZ in the application.

An example composition table is helpful for applicants, and we appreciate that FDA has provided an example.

We agree that the ingredients used in manufacturing should be listed even if they do not appear in the final product, *e.g.*, the purified water.

However, it could be misleading to identify the film coat and ink on the tablet as solutions, since these are not solutions in the final drug product. For clarity, the composition table example should state "Film Coat" instead of "Film Coat Solution, and should state "Print Ink" instead of "Print Ink Solution".

Also, as per our Comment 3, the reference to the DMFs would be appropriate only if the drug product manufacturer purchases and tests the film coat solution and printing ink solutions themselves. If the components of these solutions (*e.g.*, the colorants) are tested by the drug product manufacturer, the in-house quality standard should be referenced.

Comment 6
Section IV.A. Components of the Drug Product (P.2.1)
1. Drug Substance (P.2.1.1)
a. Key Physicochemical Characteristics
Lines 392 - 405

We recommend that the information located in P.2.1.1 be limited to a discussion of the physicochemical characteristics of the drug substance that were prospectively considered in the development of the formulation.

We suggest that all drug product characterization studies should be located in P.2.2.3. Therefore we recommend P.2.2.3 be the location for the drug product development studies that investigate "the potential effect of key drug substance physicochemical characterisitics on the performance of the drug product." For example, the effect of particle size and/or polymorphic form of the drug substance on the drug product performance characteristics such as dissolution, stability (including interconversion of polymorphic forms in the drug product on stability), and bioavailability, should be located in Section P 2.2.3.

Comment 7
Section IV.A. Components of the Drug Product (P.2.1)
1. Drug Substance (P.2.1.1)
b. Compatibility
Lines 409 - 418

The compatibility of the excipients with the drug substance is one aspect of the justification for the choice of the excipients in the formulation. We suggest that information on compatibility of excipients with the drug substance, and compatibility between excipients would be better located in P.2.1.2. We suggest relocating the text in Lines 409 – 418 to the guidance section *2. Excipients (P.2.1.2).*

Comment 8
Section IV.A. Components of the Drug Product (P.2.1)
2. Excipients (P.2.1.2)
Lines 420 - 430:

As per Comment 7 on Lines 409 – 418, we suggest that information on compatibility of excipients be located in this section P.2.1.2.

In addition, we suggest adding the sentence "The compatibility of the excipients with other excipients (*e.g.*, in a dual preservative system) may also need to be discussed."

The justification of excipient ranges, and the demonstration of excipient functionality throughout shelf life, will be data derived from studies on the drug product performed

during formulation development (and possibly also during manufacturing process development).

For ease of review and understanding, these drug product studies would be better located with other formulation development studies in P.2.2.1 Formulation Development.

Therefore, please re-locate the following text (Lines 424 – 430) to guidance section **IV.B.*1. Formulation Development (P.2.2.1).***

"Any excipient ranges included in the batch formula (P.3.2) should be justified in this section of the application (P.2.2.1). Excipient ranges can often be justified based on the experience gained during the development of the formulation and manufacturing process. The ability of functional excipients (e.g., antioxidants, penetration enhancers) to perform throughout the intended drug product shelf life should also be discussed. The information provided should be used, as appropriate, to justify the excipient (P.4.4) and drug product (P.5.6) specifications."

Comment 9
Section IV.A. Components of the Drug Product (P.2.1)
2. Excipients (P.2.1.2)
- **Noncompendial–Non-novel Excipients**

Lines 454 - 456

We do not object to locating supporting CMC information on noncompendial–non-novel excipients in Appendix A3. However, we suggest that the section title for Appendix A3 should be re-titled to be consistent with the information to be located there. The ICH M4 guideline and the ICH M2 guideline explicitly prohibit any alteration in section titles by the applicant. We suggest that Appendix 3 be re-titled in the first revision to the ICH M4/M2 guidelines.

Comment 10
Section IV.A. Components of the Drug Product (P.2.1)
2. Excipients (P.2.1.2)
Lines 460 - 461

The guidance establishes a category of excipients as those "used at higher levels than in previously approved products with the same route of administration, or components used as tracers or markers".

We would appreciate more information from FDA on how applicants can easily determine the levels of excipients used in previously approved products. A definitive source of this information that is kept current is needed by industry.

Comment 11
Section IV.B. Drug Product (P.2.2)
1. Formulation Development (P.2.2.1)
Lines 489 - 490

We suggest that the brief summary of the drug product development should focus on the development of the proposed market formulation.

Early development studies may be conducted with initial formulations that are not directly related to development of the to-be-marketed product. For example, Phase 1 studies may be conducted with a powder, whereas a tablet may be proposed for marketing. Information on the early clinical trial formulations will be submitted in this section, but we recommend that this summary should focus on the development of the to-be-marketed drug product.

Please revise the sentence to read, "A brief summary describing the development of the proposed market product should be provided, taking into consideration the proposed route of administration and usage."

Comment 12
Section IV.B. Drug Product (P.2.2)
1. Formulation Development (P.2.2.1)
Line 495

We suggest that the "summary of formulations used in clinical trials" should be provided as a tabulated summary of the composition of each clinical trial formulation. Please add statements to the guidance saying that the composition of each clinical trial formulation should be provided in a tabular format, in a manner consistent with that given in P.1 for the proposed commercial formulation.

Where formulation numbers are used, these should be included in the tabulation of the clinical trial formulations.

We have also customarily provided in NDA applications a tabulation of the clinical studies (by study number), the specific batch numbers of the clinical materials used in each study, and formulation reference number of the clinical materials. This tabulation has encompassed all clinical studies supporting the application, *i.e.*, Phase 1 to Phase 3. We have included this tabulation in the CMC section as well as the Biopharmaceutics section of the application.

It has been our understanding that this linkage between clinical study, batch number and formulation number is a requirement for submission. Does FDA still require tabulations of the specific batches correlated to the clinical studies in which they are used? If so, we suggest that these tables be located in P.2.2.1.

Please note that the Batch Analysis tabulations in P.5.4 do not address this topic, since the clinical batches in the P.5.4 tables will be limited to pivotal clinical, bioavailability, and bioequivalence batches. The study/batch tabulations mentioned above encompass all clinical studies documented in the NDA from Phase 1 to 3, and list all batches of materials used in the studies, including placebo and comparators. We request that FDA provide clarification on whether or not this detailed information is required.

Comment 13
Section IV.B. Drug Product (P.2.2)
1. Formulation Development (P.2.2.1)
Lines 495 - 497

We suggest that the focus here should be on the formulations used in pivotal clinical studies, and the primary stability studies. We recommend the same language used in Lines 575 – 576, *i.e.*, "the clinical safety and efficacy, bioavailability, bioequivalence, or primary stability batches".

Please re-word the sentence to read: "The differences between the **pivotal clinical safety and efficacy, bioavailability, bioequivalence, or primary stability batches** and the proposed commercial formulation described in P.1 (*i.e.*, composition statement) should be discussed."

Comment 14
Section IV.B. Drug Product (P.2.2)
1. Formulation Development (P.2.2.1)
Lines 497 - 499

As per Comment 13, please re-word this sentence to read: "Any changes between the proposed commercial formulation and those formulations used in **pivotal clinical safety and efficacy, bioavailability, bioequivalence, or** primary stability batches should be clearly described and the rationale for the changes provided."

Comment 15
Section IV.B. Drug Product (P.2.2)
1. Formulation Development (P.2.2.1)
Lines 526 – 527

This draft guidance and the ICH guideline M4Q: *The CTD - Quality* recommend a separate P section for co-packaged diluents. Please clarify how much information on the diluent is expected to be located here. Please also clarify if a separate development report would be expected for a diluent if manufactured by the applicant (not purchased as a commercial product).

Comment 16
Section IV.B. Drug Product (P.2.2)
2. Overages (P.2.2.2)
Lines 532 – 533

We agree that all overages used in the formulation should be justified.

As explained in Comment 4, the composition statement should not include any manufacturing overage, and therefore P.1 should not be the point of reference here.

We suggest rewording the sentence to read, "Any overages included in the proposed market formulation should be justified."

Comment 17
Section IV.B. Drug Product (P.2.2)
2. Overages (P.2.2.2)
Lines 529 / Footnote 13

Footnote 13 states that the justification for a proposed excipient range should be included in section P.2.1.2. With reference to Comment 8 on Lines 424 - 430, we suggest that P.2.2.1 is a more appropriate location for the justification for a proposed excipient range.

Please revise the footnote to read:

[13] Justified ranges, rather than overages, can be used for excipients. The justification for a proposed excipient range should be included in section P.2.2.1.

Comment 18
Section IV.B. Drug Product (P.2.2)
3. Physicochemical and Biological Properties (P.2.2.3)
Lines 558 - 560

The sentence is not clearly written. We suggest the following wording:

"The solid state form of the drug substance in the drug product may need to be investigated, and studies performed to demonstrate whether or not a routine control over the form is needed in the drug product specifications."

Comment 19
Section IV.C. Manufacturing Process Development (P.2.3)
Lines 572 - 574

Section P.2.3 should also contain the rationale for the selection of the method of sterilization. Please consider adding the following sentence in this section of the guidance:

"For sterile drug products, the choice of the method of sterilization should be explained and justified."

Comment 20
Section IV.C. Manufacturing Process Development (P.2.3)
Lines 574 - 577

For clarity and consistency with other sections of the guidance, please add the word "pivotal" so that the sentence reads, "During the development phase, the process should be well documented so differences between the manufacturing processes used to produce the **pivotal** clinical safety and efficacy, bioavailability, bioequivalence, or primary stability batches and the process described in P.3.3 can be identified."

Comment 21
Section IV.C. Manufacturing Process Development (P.2.3)
Lines 580 - 587

The first sentence of the paragraph should be revised to state that it is not only a comparison of equipment that is to be tabulated, as is made clear in the subsequent lines of the paragraph.

The first sentence might be re-worded to read, "A table should be provided that compares the manufacturing information (manufacturing site, batch size, manufacturing process, equipment used, etc.) for the pivotal clinical batches that support efficacy or bioequivalence and primary stability batches, to the manufacturing information for the proposed production batches."

Please consider adding an example of this table to the guidance, to aid applicants in understanding what information is to be tabulated.

Please add a statement in this section of the guidance that the equipment should be described using the class and subclass terminology in FDA's SUPAC guidances.

Comment 22
Section IV.D. Container Closure System (P.2.4)
Lines 591 - 594

The guidance should be expanded to clarify the location of information on the development and suitability of *associated packaging components*[1]. These include devices which deliver the dose of the drug product, but are considered a packaging component of the drug product.

Comment 23
Section IV.D. Container Closure System (P.2.4)
Lines 596 -597

Please revise this sentence to make it clear that a description of the container closure system used for storage and transportation is required only for protein drug products.

As a suggestion, the sentence might be revised to read, "Provide a brief description of the container closure systems listed in P.7. For protein drug products, also provide a description of the container closure system used for storage and transportation."

Comment 24
Section IV.F. Compatibility (P.2.6)
Lines 656, 661 - 663

Line 656: Compatibility with "dosage devices" should not be located here. A "dosage device" is an *associated packaging component*, as defined in FDA guidance on container closure systems[2]. The demonstration of compatibility of the associated packaging component with the drug product is part of establishing suitability for the intended use of the component. The information on compatibility of the associated packaging component with the dosage form should be located in P.2.4 Container Closure System.

Lines 661 – 663: Similarly, the language on compatibility studies with administration sets is out of place here, since administration sets are also associated packaging components which should be discussed in P.2.4. Please relocate and incorporate the following text into the guidance section **IV.D. Container Closure System (P.2.4)**:

"Compatibility studies should assess, for example, precipitation, sorption onto injection vessels or devices, leachables[17] from containers and administration sets, and stability. The design and extent of the compatibility studies depend on the type of drug product and its anticipated usage."

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[1] FDA Guidance for Industry, *Container Closure Systems for Packaging Human Drugs and Biologics*
[2] FDA Guidance for Industry, *Container Closure Systems for Packaging Human Drugs and Biologics*

Comment 25
Section IV.F. Compatibility (P.2.6)
Line 655 - 658

Clarify that this section is only for *in vitro* compatibility with drug products that are physically mixed prior to administration, not *in vivo* compatibility of drug products that are co-administered.

Please add "*in vitro*", and delete "dosage devices" (per Comment 24), so that the sentence reads:

"The ***in vitro*** compatibility of the drug product with any diluents (i.e., constitution, dilution of concentrates, admixing),[16] specified in the drug product labeling and the ***in vitro*** compatibility of the drug product with likely coadministered drug products should be addressed to provide appropriate and supportive information for the labeling.

Comment 26
Section V.A. Manufacturer(s) (P.3.1)
Lines 685 – 708

The guidance does not specify a location for the name/address of manufacturers of excipients. In some cases, applicants are required to provide this information. Please clarify where this is to be located.

Comment 27
Section V.A. Manufacturer(s) (P.3.1)
Lines 692 - 693

The building number should be required only for critical operations in the manufacture of biologic and/or sterile drug products. For these types of drug products, the specific buildings in which operations are performed is important information, but this information should not be routinely required for all drug products. Furthermore, it should not be necessary to identify the specific building for a test laboratory.

Please re-word the sentence to read, "For biologic and/or sterile products, the building numbers or other specific identifying information should be provided for the locations where critical manufacturing and packaging operations will be performed."

Comment 28
Section V.A. Manufacturer(s) (P.3.1)
Lines 696 - 697

The Quality section (Module 3 of the CTD format) of the application should not contain the name, address and phone number of the U.S. agent for a foreign drug establishment. This would require unnecessary maintenance of the application with updates if this information changes.

The information on the U.S. agent is provided to FDA as part of the registration of the drug establishment under 21 CFR 207.40(c). The application will contain the establishment registration number, *i.e.*, the FEI (Foreign Establishment Identifer) number. FDA can access the name of the U.S. agent through the FEI number.

Comment 29
Section V.A. Manufacturer(s) (P.3.1)
Lines 710 - 712

The Quality section (Module 3 of the CTD format) of the application should not contain the name, telephone number, fax number and e-mail address of a contact person for each site listed in the application. This information is located on the FDA Form 356(h). Please refer to the instructions (copied below) for completing the Establishment Information section of the FDA Form 356(h).

FDA Form 356(h)
ESTABLISHMENT INFORMATION This section should include information on the locations of all manufacturing, packaging and control sites for both drug substance and drug product. If continuation sheets are used, please indicate where in the submission they may be found. For each site please include the name, address, telephone number, registration number (Central File Number), Drug Master File number, and the name of a contact at the site. The manufacturing steps and/or type of testing (e.g. final dosage form, stability testing) conducted at the site should also be included. Please indicate whether the site is ready for inspection or, if not, when it will be ready. Please note that, when applicable, the complete establishment description is requested under item 15.

Comment 30
Section V.B. Batch Formula (P.3.2)
- **Amounts**

Lines 741 - 746

We suggest the guidance be expanded with the following statements:

When the quantity of active ingredient is calculated from the "as is" assay value of the batch of that active ingredient ("factorisation"), this must be indicated. If the quantity of

another ingredient is adjusted to compensate for the variable input quantity of the active ingredient, this must also be indicated.

Comment 31
Section V.B. Batch Formula (P.3.2)
- **Amounts**

Line 743

Please make this section consistent with Lines 335 – 339 on the composition statement (P.1) and clarify that the amount of the following components need not be provided in the batch formula: (1) processing agents, (2) purposefully added gases that are intended to remain as part of the finished drug product (e.g., nitrogen added to head space).

Comment 32
Section V.B. Batch Formula (P.3.2)
- **Reference to Quality Standards**

Lines 748 – 761, 769

The "reference to quality standards" is located in the composition statement (P.1), and is also located in P.4. We suggest that this information is not needed in the batch formula, and recommend that Lines 748 – 761 be deleted, and that the column "Reference to Quality Standard" be deleted from Line 769, the example Table 2 Proposed Batch Formula

Comment 33
Section V.C. Description of Manufacturing Process and Process Controls (P.3.3)
Line 777 - 780

Please insert the word "pivotal" so that the sentence reads, "Differences in the manufacturing process described in this section and the manufacturing processes used to produce the batches used for **pivotal** clinical efficacy, bioavailability, bioequivalence, or primary stability studies that can influence the performance of the product should be discussed in P.2.3."

Comment 34
Section V.C. Description of Manufacturing Process and Process Controls (P.3.3)
1. Flow Diagram
Line 782

Please consider adding an example of the flow diagram to the guidance, to aid applicants in understanding what information is to be depicted in the flow diagram.

Comment 35
Section V.C. Description of Manufacturing Process and Process Controls (P.3.3)
1. Flow Diagram
Line 792

It is not clear what is meant by "noncontinuous process" since the timeframe of production of drug products may extend over several days and may be interrupted by weekends. Further clarification is needed on what is expected here would be helpful.

We also suggest that FDA consider adding a definition for "Noncontinuous Process" to the Glossary section of the guidance.

Comment 36
Section V.C. Description of Manufacturing Process and Process Controls (P.3.3)
1. Flow Diagram
Line 796

Please make it clear that the "type of equipment used" may be described in the terminology given in FDA's SUPAC guidances[3] [4]. We suggest revising this bullet point to read as follows:

- the type of equipment used (described in terms of class and subclass as defined in the FDA's SUPAC Guidances); equipment model is not needed)

The use of FDA's SUPAC class and subclass nomenclature for equipment description will facilitate the evaluation of post-approval changes for their regulatory significance.

Comment 37
Section V.C. Description of Manufacturing Process and Process Controls (P.3.3)
2. Description of Manufacturing Process and Process Controls
Line 808 - 809

Please make it clear that equipment may be described using the terminology given in FDA's SUPAC guidances. As per Comment 36, the use of FDA's SUPAC class and subclass nomenclature for equipment description will facilitate the evaluation of post-approval changes for their regulatory significance.

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[3] FDA Guidance for Industry, *SUPAC-IR/MR: Immediate Release and Modified Release Solid Oral Dosage Forms, Manufacturing Equipment Addendum* (Revision 1)
[4] FDA Guidance for Industry, *SUPAC-SS: Nonsterile Semisolid Dosage Forms, Manufacturing Equipment Addendum*, Draft Guidance

We suggest that the sentence be revised to read, "The type of equipment should be described using the class and subclass terms from FDA's SUPAC guidances (*e.g.*, Diffusion Mixer/V-Blender, Dry Granulator/Roller Compaction) and the working capacity where relevant."

Comment 38
Section V.C. Description of Manufacturing Process and Process Controls (P.3.3)
2. *Description of Manufacturing Process and Process Controls*
Line 824 - 830

The concern of cross-contamination with potential adventitious agents is a cGMP issue and should be addressed through the appropriate inspections of the facility. We consider that the requested broad statement in the application ["ruminant-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"] is unlikely to be a satisfactory solution to the regulatory concern. If the statement is required, we propose that it should be limited to biological drug products.

The guidance states that submission of information on the manufacturing facility may be warranted for multi-use facilities where there is a potential for cross-contamination with adventitious agents.

Both the requested statement, and the additional facilities information, would be better located in Appendix A.1 on facilities and equipment. We suggest that the text in Lines 624 – 830 be relocated to guidance section **XI.A. Facilities and Equipment (A.1)**.

Comment 39
Section V.C. Description of Manufacturing Process and Process Controls (P.3.3)
2. *Description of Manufacturing Process and Process Controls*
Lines 835 - 836

It would be helpful for the guidance to include some examples of an "in process material". The definition in the **GLOSSARY** (Lines 2197 – 2199) for **In-Process Material** seems quite broad. Some examples of an "in-process material" might be 1) uncoated cores for a tablet, 2) pellets used in manufacture of capsules, and 3) micronized drug substances.

A glossary definition (and examples) for "process tests" would be helpful, in particular to differentiate them from "operating parameters".

Comment 40
Section V.C. Description of Manufacturing Process and Process Controls (P.3.3)
2. *Description of Manufacturing Process and Process Controls*
Lines 911 - 912

We agree that any reworking operation should be justified by data, but do not agree that validation data are necessarily warranted, or that validation data should be submitted in the application.

The term "validation data" is generally understood to mean the test results obtained under a defined protocol for three (usually three) full-scale production batches made to target operating parameters, that demonstrate the process is capable of reproducibly delivering the drug product of the defined quality. Validation data are not required for submission to support the method of manufacture.

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A proposed reworking operation should be demonstrated to be suitable for its intended use. Process development / process evaluation data should be adequate to support a proposed reworking procedure, and these data should be located in P.2 or P.3.5.

Comment 41
Section V.D. Controls of Critical Steps and Intermediates (P.3.4)
Lines 927 - 930

There is considerable redundancy (and therefore lack of clarity) on the location of information to justify that a process control is considered "critical".

The relevant batches and batch analysis data that justify the designation of certain process controls as "critical" are not necessarily limited to those provided in P.5.4. We suggest that the parenthetical phrase concerning the "relevant batches" be changed so that the sentence reads:

"Critical process control values from relevant batches (***e.g.*, batches made specifically to evaluate certain aspects of the manufacturing process for criticality to the quality of the final drug product**) should be provided as part of the justification.

Comment 42
Section V.D. Controls of Critical Steps and Intermediates (P.3.4)
- **In-Process Tests Used in Lieu of Finished Product Tests**

Lines 945 - 946

The data referenced in these lines are derived from tests on the finished drug product, and form part of the justification of the finished product specifications. We recommend that

these data be located in P.5.6 not here. The analytical validation information should be in P.5.3

Comment 43
Section V.D. Controls of Critical Steps and Intermediates (P.3.4)
- **In-Process Tests Used in Lieu of Finished Product Tests**

Lines 948 - 950

We do not agree that the acceptance criterion for the in-process test "should be identical to or tighter than" that for the finished product specifications. The sampling plan and the type of acceptance criterion must be taken into consideration in evaluating whether this would be appropriate. We recommend this sentence be deleted.

Comment 44
Line 951

Please add FDA's SUPAC guidances to those listed.

Comment 45
Section V.E. Process Validation and/or Evaluation (P.3.5)
Lines 954 - 970

With the exception of sterile process validation, all of the information described in this section appears to already be located in P.2 and P.3.4. We recommend that the guidance clearly state that only sterile process validation information is to be located in.P.3.5.

With reference to Comment 40, we do not agree that manufacturing validation information for reprocessing or reworking operations should be submitted in the application.

Comment 46
Section VI. CONTROL OF EXCIPIENTS (P.4)
- **Compendial–Non-novel Excipients**

Lines 982 - 983

We appreciate the regulatory relief provided to applicants by allowing cross-reference to the compendial monograph requirements for compendial – non-novel excipients, where no additional testing is performed. The guidance states that in this case, the excipient can be listed in P.4 with no detailed information provided in P.4.1 through P.4.4. This is a welcome provision as it will obviate the need to submit changes to the application as the compendial monograph requirements change.

However, we are concerned that the guidance states this approach will only be acceptable if the applicant intends to perform full testing on each batch received. Otherwise, the guidance states that information should be included in P.4.1 through P.4.4

The basis for this position is not clear. The quality control inspection program for excipients is an aspect of current Good Manufacturing Practices (cGMPs). The excipient may be accepted by the applicant / drug product manufacturer on the basis of a certificate of analysis from a supplier, and at minimum the performance of an appropriate identification test, provided that the supplier's results have been qualified and are periodically re-qualified [21 CFR 211.84(d)(3)].

The extent of GMP acceptance testing that the applicant/drug product manufacturer performs on a compendial – non-novel excipient should have no bearing on a cross-reference in the application to the USP/NF monograph requirements. Please also refer to Comment 48 below.

We request that the guidance be modified to read as follows:

- **Compendial Non-novel Excipients**: When a compendial excipient is tested according to the monograph standard with no additional testing, the excipient (e.g., Sodium Chloride, USP) can be listed under P.4 with no detailed information provided in P.4.1 through P.4.4.

Comment 47
Section VI.A. Specifications (P.4.1)
Lines 1011 - 1012

The specifications for all excipients should be located in P.4.1, regardless of whether or not the excipient is novel. We see no rationale for segregating specifications for novel excipients apart from other classes of excipients. This causes too much fragmentation of the information in the dossier.

We would like to point out that after NDA approval, the excipient would no longer be considered "novel". For ease of post-approval changes and maintenance of the NDA, the most straightforward approach is to locate all excipient specifications in P.4.1.

Comment 48
Section VI.A. Specifications (P.4.1)
Lines 1022 - 1024

We do not agree that the specification sheet is the appropriate location to identify those tests which may be accepted from the excipient manufacturer's certificate of analysis (COA).

The quality control inspection program for excipients is an aspect of current Good Manufacturing Practices (cGMPs). The excipient may be accepted by the applicant / drug product manufacturer on the basis of a certificate of analysis from the supplier, and at minimum the performance of an appropriate identification test, provided that the supplier's results have been qualified and are periodically re-qualified [21 CFR 211.84(d)(3)]. In the frequent cases where there are multiple suppliers of a single excipient, the tests that may be accepted from the supplier's COA may be different for the different suppliers. As suppliers change, the acceptance testing is also changed in conformance with the requirement to qualify the supplier's test result.

It is impractical to identify the acceptance testing on the specification sheet. We suggest the language of the guidance be modified to allow the applicant to identify the acceptance testing by the applicant / drug product manufacturer in somewhat more general terms, and in a location apart from the specification sheet. For example:

"If the applicant / drug product manufacturer may accept test results for the specifications from a qualified supplier's certificate of analysis (COA), this should be stated. The minimum testing that will be performed by the applicant / drug product manufacturer should be identified."

Comment 49
Section VI.A. Specifications (P.4.1)
Lines 1032 - 1035

Please refer to Comments 46 and 48.

We do not agree that the in-house specification for a compendial excipient should be provided if the applicant / drug product manufacturer intends to accept tests from the excipient manufacturer's certificate of analysis. For compendial excipients where no additional tests are performed, it should be adequate to simply give a citation to the current compendial standard. With reference to Comment 48, we suggest that the application should contain a statement on what minimum acceptance testing will be performed by the applicant / drug product manufacturer, but that the specification sheet is not the appropriate location to designate which tests will be accepted from the supplier COA.

We suggest that the guidance be revised to delete the phrase "or test results will be accepted from the excipient manufacturer's COA,", so that the sentence reads:

"Only a citation to the appropriate official compendium need be provided when the excipient specification is identical to the compendial monograph[28].

Please also modify footnote 27 accordingly.

Comment 50
Section VI.A. Specifications (P.4.1)
Lines 1035 - 1038

For compendial excipients with additional tests, we recommend provision of only the additional tests, acceptance criteria and reference to the associated analytical procedure, plus citation of the compendial standard. This approach would avoid updates to the application as the compendial monograph standard is revised.

We suggest these lines be revised to read:

"When the specification for a compendial excipient differs from the compendial monograph (*e.g.*, additional tests, tighter acceptance criteria than in the monograph, different analytical procedures) a specification sheet should be provided listing the additional / different controls for the excipient, in addition to giving reference to the compendial monograph standard.

Comment 51
Section VI.A. Specifications (P.4.1)
Lines 1043 - 1046

Lack of harmonization between the major pharmacopoeia continues to cause great difficulty for industry. We suggest that the guidance allow the procedures of the *European Phamacopoeia* (Ph. Eur.) and the *Japanese Pharmacopoeia* (JP) to be designated as alternate procedures for control of excipients.

Comment 52
Section VI.B. Analytical Procedures (P.4.2)
Lines 1051 - 1053

We do not agree that the analytical procedures for novel excipients should be located in Appendix A.3.

Please refer to Comment 47 on the location of specifications for novel excipients. The analytical procedures for all excipients should be located in P.4.2, regardless of whether or not the excipient is novel. Segregation of the analytical procedures for novel excipients into Appendix A3 causes too much fragmentation of the information in the dossier.

We would like to point out that after NDA approval, the excipient would no longer be considered "novel". For ease of post-approval changes and maintenance of the NDA, all excipient analytical procedures should be lcoated in P.4.2.

Comment 53
Section VI.C. Validation of Analytical Procedures (P.4.3)
Lines 1062 - 1066

Please add a clarification that "verification" of the suitability of official compendial procedures, or other FDA recognized standard procedures, need not be submitted in the application.

Comment 54
Section VI.C. Validation of Analytical Procedures (P.4.3)
Lines 1066 - 1067

The language in the guidance is not clear as to what circumstances would require submission of validation data for excipients. We propose that submission of analytical validation data should be required only for analytical procedures that are not part of an official compendium (including the Ph. Eur. and JP) or other FDA recognized standard references (e.g., AOAC International Book of Methods). We suggest the following language:

"Submission of validation information in the application is normally not needed for excipients. Validation information should be submitted for analytical procedures that are not part of an official compendium or other FDA recognized standard references (e.g., AOAC International Book of Methods)."

Comment 55
Section VI.D. Justification of Specifications (P.4.4)
Lines 1089 - 1092

A certificate of analysis from the excipient manufacturer should be provided only if the drug product manufacturer does not perform full regulatory testing on the component.

We agree that COAs should be provided only for those excipients used to produce the batch described in the executed batch record (located in R 1.P). We suggest that R.1.P would be a more appropriate location for these COAs.

Comment 56
Section VII.A. Specifications (P.5.1)
Lines 1162 and 1174

Line 1162: FDA has traditionally not required submission of separate release and shelf life acceptance criteria as regulatory requirements, but has considered that release acceptance criteria are "in-house" criteria. As stated in the ICH Q6A guideline, "in these [U.S.]

regions, regulatory acceptance criteria are the same from release throughout shelf life; however, an applicant may choose to have tighter in-house limits at the time of release to provide increased assurance that the product will remain within the regulatory acceptance criteria throughout its shelf life."

Line 1174: Since a release regulatory acceptance criteria has not been a usual and customary requirement for submission, we suggest that the example Table 3 should delete the release acceptance criteria for assay.

Comment 57
Section VII.A. Specifications (P.5.1)
Lines 1147 - 1149

It is not clear how to interpret the following statement in the guidance:

"If an analytical procedure will be used only to generate stability data, the analytical procedure should be described in P.8.3."

It is our understanding that the regulatory specifications for the drug product should be located in P.5.1, and that the "regulatory specifications" are those to which the drug product must conform over its shelf life.

Therefore, all regulatory tests to which the drug product batch must conform should be listed on the specification sheet in P.5.1. There may be some tests in the regulatory specification that are performed only during stability testing. An example might be a test for "Weight Loss", which would not be performed at batch release, but only on the stability samples. Yet the "Weight Loss" test is a regulatory test, and should be listed on the specifications sheet in P.5.1. We do not agree that the regulatory analytical procedure associated with such a stability test should be located in P.8.3.

In another situation, there might be different analytical procedures used for release and stability testing a single test attribute (where one procedure is not classified as an alternate procedure). Both analytical procedures would be considered regulatory procedures, and should be listed on the specification sheet in P.5.1.

All regulatory analytical procedures (used for release and stability testing) should be listed in the specification sheet in P.5.1, and all of the analytical procedures referenced in the specification sheet should be located in P.5.2. We do not agree that regulatory analytical procedures used for stability testing should be located in P 8.3.

There may be some situations where there is a stability test, or analytical procedure used for stability testing, that is not a regulatory test/procedure. For example, certain development tests that are not part of the regulatory specification may be performed during stability testing. (Development tests might be performed to obtain additional information

so that a determination could be made whether or not the test should be added to the regulatory controls for the drug product.). In those circumstances, we would agree that the development stability test should be located in section P.8.3.

Comment 58
Section VII.A. Specifications (P.5.1)
Line 1174

The acceptance criterion for Identification Test #1 shown in the example Table 3, does not conform to the ICH Q6A guideline, which states "Identification solely by a single chromatographic retention time, for example, is not regarded as being specific. However, the use of two chromatographic procedures, where the separation is based on different principles, or a combination of tests into a single procedure, such as HPLC/UV diode array, HPLC/MS, or GC/MS, is generally acceptable." We suggest that the example be modified accordingly.

Comment 59
Section VII.A. Specifications (P.5.1)
- **Periodic Quality Indicator Tests**

Lines 1223 - 1225

The guidance should clarify how the list of PQITs should be presented in P.5.1. We assume that there should be a separate tabular presentation (similar to the specifications sheet) for the PQITs.

An example for the presentation of the list of PQITs, and the protocol for performing the tests would be helpful in the guidance.

Comment 60
Section VII.A. Specifications (P.5.1)
- **Periodic Quality Indicator Tests**

Lines 1204 - 1205

More guidance on what data would justify the PQIT approach would be helpful.

The guidance should clarify that the justification for the periodic testing should be located in P.5.6.

Comment 61
Section VII.C. Validation of Analytical Procedures (P.5.3)
Line 1276 - 1277

Submission of validation information would not normally be required for official compendial procedures. We suggest the sentence be revised to read:

"This information should be provided for all non-compendial analytical procedures listed in the specification (P.5.1) for which validation is required according to ICH Q2A."

Comment 62
Section VII.C. Validation of Analytical Procedures (P.5.3)
Line 1277 - 1278

Forced degradation samples should be used to support the validation of chromatographic analytical procedures, but these forced degradation studies may be separate and independent of the stressed studies used to characterize the drug product (P.8.3). Forced degradation experiments are not applicable to the validation of some analytical procedures.

We suggest the sentence be revised to read, "Data from stress studies (either the stress stability studies [S.7.3., P.8.3] or separate forced degradation studies) should be used support the validation of the analytical procedures."

Comment 63
Section VII.D. Batch Analyses (P.5.4)
Line 1288 - 1289

Please add the word "pivotal" so that the sentence reads as follows:

"Batch analysis data should be provided for all batches used for **pivotal** clinical efficacy and safety, bioavailability, bioequivalence, and primary stability studies."

Comment 64
Section VII.D. Batch Analyses (P.5.4)
Line 1291 - 1292

We recommend that the preferred presentation for the batch analyses data should be a tabular presentation. Alternatively, Certificates of Analysis for the individual batches may be provided here. Please revise the language in the guidance to state that the preferred presentation of the data is in a tabular format. Suggested text is the following:

"A tabular format for the presentation of the batch analyses data is preferred. Alternatively the Certificates of Analysis for each individual batch may be provided."

Comment 65
Section VII.D. Batch Analyses (P.5.4)
1. Batch Analysis Reports
Line 1324 – 1326

We recommend that the more detailed summary describing changes in the analytical procedures be located with the justification of specifications in P.5.6. We suggest that the batch analyses P.5.4 section provide for cross-reference to P.5.6 as follows:

"If there are significant differences in the analytical procedures (*e.g.*, different fundamental principles such as titration and HPLC), cross-reference the information in P.5.6 where a more detailed summary describing the changes in analytical procedure is provided."

Comment 66
Section VII.D. Batch Analyses (P.5.4)
2. Collated Batch Analyses Data
Line 1328 - 1289

We agree that the presentation of results from all batches for a particular test in tabular or graphical form is helpful to justify the acceptance criteria. However, we recommend that this collated data would be better located in P.5.6, where the collated data presentation can be viewed in the context of the discussion on the justification of specifications.

Comment 67
Section VII.E. Characterization of Impurities (P.5.5)
1. List of Expected Impurities
Line 1343 - 1351

The guidance appears to have coined a new term, *i.e.*, "Expected Impurities". A glossary definition for "Expected Impurities" would be helpful.

For added clarity, we suggest that the text of these lines might be revised as follows:

"All expected drug product impurities should be listed in this section of the application whether or not the impurities are included in the drug product specification. The expected drug product impurities may include:

- drug substance process impurities
- degradation products of the active ingredient

- residual solvents
- enantiomeric impurities
- excipient degradants
- leachables from the container closure system

The drug substance process impurities that could carry over to the drug product should be listed here even if they are normally controlled during drug substance testing and will not be included in the drug product specification. When qualified, the qualified level of an expected impurity with a cross reference to the appropriate studies (include study numbers) should be provided."

Comment 68
Section VII.E. Characterization of Impurities (P.5.5)
2. Identification of Impurities
- **Degradation Products**

Line 1372 - 1377

The ICH Q3B guideline does provide a framework for the identification of degradation products, and FDA has publicly stated their commitment to ICH guidance. We are concerned to find language in this draft guidance that suggests FDA will set requirements different from those agreed within the ICH process.

Comment 69
Section VII.F. Justification of Specification(s) (P.5.6)
Line 1420 - 1423

Please add the word "pivotal" so that the sentence reads as follows:

"Data from the **pivotal** clinical efficacy and safety, bioavailability, bioequivalence, and primary stability batches and, when available and relevant, development and process validation batches should be considered in justifying the specification.

Comment 70
Section VII.F. Justification of Specification(s) (P.5.6)
Line 1426 – 1427

We recommend that the justification for an in-process test that is used in lieu of a finished product test is more appropriately located here in P.5.6.

Please refer to Lines 1153 – 1155 of the guidance where it is stated that the specification sheet should identify tests that can be performed in-process in lieu of testing the finished product.

The tests listed in the specification sheet are the regulatory tests for the finished product, but there may be some tests where the result may be accepted from in-process testing instead of testing the final drug product.

An example of this situation might be a regulatory test for pH in the finished product, where the test result may be accepted from an in-process pH test. However, pH is considered a regulatory specification for the finished product.

Therefore, the justification for the finished product specifications in P.5.6 should include the justification for using an in-process result to satisfy a regulatory specification for the finished product. The justification may cross-refer to in-process data in P.3.4.

Please revise the language in the guidance to read as follows:

"Justification for an in-process test that is used in lieu of a finished product test should also be included in P.5.6."

Comment 71
Section VII.F. Justification of Specification(s) (P.5.6)
- **Acceptance Criteria**

Lines 1480 – 1482

The concept *of interim acceptance criteria* is welcomed. The guidance says "occasionally" an applicant may wish to propose interim acceptance criteria. It would be helpful for the guidance to clarify why this approach is considered to be occasional, and under what circumstances FDA would see the approach to be appropriate.

Comment 72
Section VII.F. Justification of Specification(s) (P.5.6)
- **Analytical Procedures**

Please add text to the guidance to clarify that P.5.6 is the location for a description of the changes in the analytical procedures during development. For example, an HPLC analytical procedure used for determination of degradation products may have been changed during development to improve selectivity (e.g., separation of co-eluting degradants.) These changes should be discussed and explained as part of the justification for the proposed regulatory analytical procedure.

Comment 73
Section VIII. REFERENCE STANDARDS OR MATERIALS (P.6)
Lines 1518 – 1521

In the examples of standards for which information should be provided, please consider adding a reference material of an excipient if the finished product specification includes a control for that excipient. For example, some products are tested for ethanol content using an ethanol (Dehydrated Alcohol USP) reference material.

Please also consider adding a sentence to the guidance saying that if USP reference standards are used, the application should state that these standards are the current lots of the USP.

Comment 74
Section VIII. REFERENCE STANDARDS OR MATERIALS (P.6)
Lines 1523 – 1524

In Line 1523, we suggest the word "standards" be changed to "standards or materials".

We suggest that the guidance provide further clarification on what types of standards are not required to be documented in the application, *i.e.*, information on secondary (working) standards[5] and reference standards used exclusively for system suitability testing should not be submitted. Please consider adding the following sentence to the guidance:

"Information need not be included on secondary (working) standards and reference standards used exclusively for system suitability testing."

Comment 75
Section IX. CONTAINER CLOSURE SYSTEM (P.7)
Lines 1531 - 1533

We suggest that the guidance add the requirement for submission of the analytical procedures used by the applicant for testing the primary packaging components. Please revise the sentence to read as follows:

"A description of the container closure system for the drug product should be provided, including the identity of materials of construction of each primary packaging component and the specification and analytical procedures used by the applicant to accept each batch of primary packaging component."

[5] The ICH Q7A definition for Secondary Working Standard is "A substance of established quality and purity, as shown by comparison to a primary reference standard, and used as a reference standard for routine laboratory analysis."

Comment 76
Section X.A. Stability Summary and Conclusion (P.8.1)
Lines 1548 – 1556

The guidance requires too much detail in the stability summary that is redundant to the information presented in section P 8.3. For example, in P 8.1, there should be a statement that a statistical analysis was performed, but the actual statistical treatment of the data would be presented in detail in P 8.3.

Please add text to make clear that this is a comprehensive overview of the entire body of information of the stability of the drug product, and would encompass the data from stress, supporting and formal stability studies.

Please also make clear that any special storage precaution based on the stability dataset should be given here (*e.g.*, protect from moisture, protect from light), with reference to the data on which the statements are based.

Comment 77
Section X.A. Stability Summary and Conclusion (P.8.1)
Lines 1569 – 1571

The language here is not clear. The sentence, "Stability study reports should also be included", seems to suggest that the stability results are not provided as stability reports. Please consider deleting this sentence.

Comment 78
Section X.C. Stability Data (P.8.3)
1. Formal Stability Studies
Lines 1573 – 1582

Please refer to Comment 57. As explained previously, we do not agree that regulatory analytical procedures used for stability testing should be located here.

If there are **development** procedures which are used to test the stability samples, but are not proposed for stability testing of the commercial product, these should be given here. For example development tests performed to justify the absence of a control for commercial product.

Analytical procedures that are performed only on stability, but not part of the batch release testing should **not** be provided here; they should be part of the regulatory specification in P 5.1 and the analytical procedures given in P 5.2. Validation of development procedures is not normally submitted.

Comment 79
Section X.C. Stability Data (P.8.3)
1. Formal Stability Studies
Lines 1597 - 1599

Please add "*in vitro*" to this sentence to clarify that the information on compatibility with coadministered drug products does not include *in vivo* data:

"Information regarding the ***in vitro*** compatibility of the drug product with any diluents (*i.e.*, constitution, dilution of concentrates, admixing), dosage devices, or coadministered drug products should be provided in P.2.6."

Comment 80
Section X.C. Stability Data (P.8.3)
2. Supporting Stability Studies
Lines 1607 - 1609

Please clarify that this is the location for submission of bulk drug product stability data, in cases where these data should be provided. FDA's guidance[6] on container closure systems suggests that this is required only for biological/protein drug products

Comment 81
Section X.C. Stability Data (P.8.3)
3. Stress Studies
Lines 1617 - 1618

The ICH Q1A(R) Guideline defines "stress" testing of the drug product as follows:

> *Stress testing (drug product)*: Studies undertaken to assess the effect of severe conditions on the drug product. Such studies include photostability testing (see ICH Q1B) and specific testing on certain products (e.g., metered dose inhalers, creams, emulsions, refrigerated aqueous liquid products).

Other than photostability data and thermal cycling data, the type of stress data that may be reported will vary depending on the dosage form being studied. The ICH Q1A(R) guideline states "Any available studies carried out on the drug product outside its immediate container can form a useful part of the stress testing of the dosage form". Note that stress testing of a reconstituted product may also be required.

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[6] FDA Guidance for Industry, *Container Closure Systems for Packaging Human Drugs and Biologics, Questions and Answers*, May 2002

These studies may be more appropriately located in the P2 Pharmaceutical Development section. This section should allow for cross-reference back to P2.

Comment 82
Section XII.A. Executed Production Records (R.1.P)
Lines 1793 - 1795

The CFR reference (21 CFR 314.50(d)(1)(ii)(*b*)) does not require the submission of executed batch records for Phase 3 clinical batches. We suggest the guidance be revised as follows:

"Executed Production Records (EPRs) and supporting production information must be provided for bioavailability, bioequivalence, and primary stability studies [21 CFR 314.50(d)(1)(ii)(*b*)], and should also be provided for representative batches used in Phase III clinical studies."

Comment 83
Section XII.A. Executed Production Records (R.1.P)
2. Information on Components
Lines 1811 - 1822

Lines 1811 – 1816: The information requested on names/addresses should be required only for the primary stability batches and bioequivalence batch. This information should not be required for Phase 3 clinical batches.

Lines 1817 – 1819: A certificate of analysis (COA) from the component manufacturer should only be required if the drug product manufacturer accepted test results from the supplier's COA.

Line 1822: It is not clear what information in P 4.4 can be cross-referenced. P 4.4 does not currently require the names/addresses of excipient manufacturers.

Comment 84
GLOSSARY
Specification
Lines 2242 - 2246

The glossary definition for "Specification" differs from that given in the ICH Q6A Guideline. As ICH Q6A defines "specification" it is a "list of tests, references to analytical procedures, and appropriate acceptance criteria that are numerical limits, ranges, or other criteria for the tests described."

Please revise the glossary definition to be consistent with the ICH definition for "Specification". Please consider adding a comment that the "specification sheet" described in this draft guidance is consistent with the ICH definition for "specification".