Paul G. King Consulting/FAME Systems

Comments on Draft "CMC" Document *G:\1215dft.doc 12/16/02*

Friday, 9 May 2003

Copy 21

Documents Management Branch [**HFA-305**]
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

2544 '03 MAY 13 P1:18

RE: Docket No. 02D-0526

FORMAL COMMENTS ON:

Docket Number : 02D-0526
Comments On : "Draft Guidance for Industry on Drug Product: Chemistry, Manufacturing, and Controls Information; Availability"

Pursuant to a "request for comments" promulgated in ***FEDERAL REGISTER*, 68(18)**, pages 4219 – 4220, Tuesday, 28 January 2003

The comments being provided to Docket: "**02D-0526**" are based on a second reading and review of "**Draft Guidance for Industry on Drug Product: Chemistry, Manufacturing, and Controls Information; Availability** [G:\1215dft.doc – 12/16/02]" that attempts to add elements that connect various issues in the draft provided by the Agency to the CGMP regulations upon which they are supposed to be based.

In general, the comments are in the current font, "News Gothic MT."

When a wording change within existing wording is suggested, the comment text is entered in *italicized News Gothic MT*.

In general, original text is presented in a "Times New Roman" font and quoted references to CGMP and other recognized documents are presented in a "**Lydian**" font.

The current comments embody slight revisions and grammatical corrections from the original comments submitted earlier (posted on 8 April 2003).

Should anyone in the Agency who reviews said comments need clarification on a given suggestion, then they should e-mail me (**drking at dr-king.com**) their observation and, where possible, I will provide appropriate clarifying remarks.

Respectfully submitted,

9 May 2003

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Line "331" – "In general, a fixed amount for each component should be stated." **should be revised to read as follows:**

Except for the active ingredients and the filler or diluent used to balance the change in the weight of the weight of each "Drug substance" needed to ensure that the requirements of **21 CFR 211.101(a)** *are met,* a fixed amount for each component should be stated.

[**Notes:** To satisfy the requirements of **21 CFR 211.101(a)**, the amount of active should be determined by adding a small amount over the label claim (typically, 0.5 % to 1 %, or, if there are significant losses in processing, 0.5 % more than the worst-case processing loss) to the label claim amount and then dividing that weight by the "as is" weight-fraction **purity** of active in the lot or batch of the active pharmaceutical ingredient (API; "Drug substance") assigned to be used in a given batch of the drug product. The resulting weight should be rounded to the nearest 0.01 % of the weight calculated. Then, the weight of the largest "Filler" or "Diluent," or the one first blended with the drug substance should be appropriately reduced so that the weight of the drug substance plus that filler or diluent is a constant. For example, IF: **a)** the label claim is 1 mg, **b)** the firm adds a 1% overage, and the weight-fraction purity of the lot of API to be used is 0876, THEN, the formulation would need to be adjusted to 1mg x 1.01/0.876 = 1.152968037 or, rounding to the nearest "0.01 %," 1.153 mg. Then, 0.153 mg should be appropriately subtracted from the weight of the appropriate "Filler" or "Diluent."]

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Comments On "**Table 1**" at **Line "358"**

2.1 First the weights in the table should be uniformly expressed for each ingredient as shown in the **"Revised Table 1"** shown on the next page.

2.2 The weight of the "Drug substance" needs to be more than 100 % of the label claim to meet the requirements set forth in **21 CFR 211.101(a)**, **"The batch shall be formulated with the intent to provide not less than 100 percent of the labeled or established amount of active ingredient."** To do this a slight overage must be added and the drug substance must then be corrected for its "as is" fractional weight purity. **[Note: 21 CFR 211.84(d)(2)** requires the purity of components to be determined, **"Each component shall be tested for conformity with all appropriate written specifications for purity, strength, and quality."]**

2.3 Strictly, "**Excipient X**" is a "Filler" and not a "Diluent" because the term "diluent" applies to components that dilute actives by some integer multiple. Moreover, the level of this "Filler" must be reduced by the amount the correction for purity increases the weight of drug substance so that the total "Core Tablet Weight" is maintained without changing the level of disintegrant, binding agent or lubricant.

2.4 The changes proposed in "**Table 1**" are in a **bold** font.

"Revised" Table 1: Example Target Composition Statement

Component Referenced	Quality Standard	Function	50 mg Tablet	100 mg Tablet	150 mg Tablet
Core Tablet					
Drug substance	In-house standard	Drug Substance	**55.55 mg[1]**	**111.00 mg[1]**	**166.65 mg[1]**
Excipient X	NF	~~Diluent~~ **Filler**	**28.45 mg[2]**	**59.00 mg[2]**	**88.35 mg[2]**
Excipient Y	NF	Disintegrant	22.0 mg	44.0 mg	66.0 mg
Excipient Z	In-house standard	Binding Agent	5.0 mg	10.0 mg	15.0 mg
Magnesium Stearate	NF	Lubricant	1.5 mg	3.0 mg	4.5 mg
Core Tablet Weight			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	9.0 mg	13.5 mg
Color Red™[3]	DMF Holder Y standard	Film Coat Color	—	0.20 mg	—
Color Blue™[3]	DMF Holder Y Standard	Film Coat Color	0.05 mg	—	0.45 mg
Titanium Dioxide	USP	Opacifier	0.10 mg	0.10 mg	—
Total Tablet Weight			118.15 mg	236.30 mg	354.45 mg
Print Ink Solution					
Printing Ink Solution[4]	DMF Holder Z Standard	Identification	—	—	—

[1] Equivalent to 50, 100, and 150 mg, respectively, on the anhydrous basis – weight adjusted based on a processing overage of 1.0 % and corrected for purity by dividing resulting weight by "as is" fractional weight purity and rounding result up to nearest 0.01 mg. For example if the "as is" fractional weight purity is 0.987 %, and the active is to be formulated as a 100 mg tablet, the drug substance amount would be 112.45 mg.

[2] **The weight of filler is adjusted by subtracting the extra weight of Drug Substance added from the nominal fill weight in order to keep the total weight constant. In the example shown, an extra 1.45 mg of Drug Substance would reduce the weight of "Filler" from "59.00 mg" to "57.65 mg."**

[3] 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.

[4] The qualitative and quantitative composition of the ink is provided in Table XYZ in the application.

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3 Page "10"
Lines "364 – 367," "The Pharmaceutical Development section should contain information on the development studies conducted to establish that the dosage form, formulation, manufacturing process, container closure system, microbiological attributes, and usage instructions are appropriate for the purpose specified in the application." **should be revised as follows:**

The Pharmaceutical Development section should contain information on the development studies conducted to establish that:

a) *Components, and their identity, purity, quality and control specifications,*
b) *Dosage form and its statistical-quality-control-based batch-release specifications,*
c) *Formulation and the overages of actives added,*
d) *Manufacturing process and its representative-sample-based in-process control specifications,*
e) *Container-closure system and that system's acceptance and performance specifications,*
f) *Microbiological attributes, including, as appropriate, viral, and/or endotoxic attributes, and*
g) *Usage* instructions

are *scientifically sound and* appropriate for the purpose specified in the application.

[Notes:

"a)" Component **identity, purity, quality"** is required to satisfy **21 CFR 211.84** and "component **control specifications"** are required to satisfy **21 CFR 211.110**.

"b)" Dosage-form **statistical-quality-control-based release specifications** are required to satisfy **21 CFR 211.165** (specifically, **21 CFR 211.165(d)** and, for dosage forms containing ingredients that control (accelerate or retard) drug availability, **21 CFR 211.167(c)**.

"c)" Component **overages are required for the active ingredients to meet** the "provide not less than 100 percent" **requirement of 21 CFR 211.101(a)**.

"d)" Representative-sample **in-process testing is required** "at commencement or completion of significant phases" (**21 CFR 211.110(c)**) "to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product" (**21 CFR 211.110(a)**).

"e)" Container-closure system's **acceptance and performance specifications are required** to satisfy **21 CFR 211.84** and the implicit requirements of **21 CFR 211.130** governing "Packaging and labeling operations."

"f)" The phrase **"including, as appropriate, prionic, viral, and/or endotoxic attributes"** should be added to ensure that such are considered and, where such can affect product safety, reflected in the submission documents.

"g)" "are **scientifically sound and** appropriate" – **21 CFR 211.160**, "... controls shall include the establishment of scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity," requires all controls to be, first, **scientifically sound** and, second, appropriate – not just "appropriate" as the text currently reads.]

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4 Page "10"
Lines "367 – 368," "The studies included in this section are distinguished from routine control tests conducted according to specifications (e.g., release testing, stability testing)." **should be revised as follows:**

The studies included in this section are distinguished from routine control tests conducted according *to the scientifically sound and appropriate* specifications (e.g., *incoming testing, in-process testing,* release testing, and stability testing) *derived from the results found from the testing of the appropriate full-scale batch- or lot- representative samples during the final stages of development.*

5 Page "11"
Lines "369 – 371," "Additionally, this section should identify and describe the formulation and process attributes, including critical parameters, that can influence batch reproducibility, product performance, and drug product quality." **should be revised as follows:**

Additionally, this section should identify and describe the *component,* formulation and process attributes, including critical parameters, which can influence batch reproducibility, product performance, and drug product quality.

6 Page "11"
Lines "383 – 390," "Key physicochemical characteristics (e.g., water content, solubility, particle size distribution, polymorphic form, solvation or hydration state, pH, dissociation constant (pKa)) of the drug substance identified in S.3.1 that can influence the performance or manufacturability of the drug product should be discussed. If the drug substance is structurally modified from an active moiety (e.g., salt, endogenous protein) and the modification affects a key physicochemical (e.g., solubility) and/or biological characteristic, this should be discussed. These discussions should cross-reference any relevant stability data in S.7.3)." **should be revised as follows:**

Key physicochemical characteristics (e.g., water content, solubility, particle size distribution, *bulk and tap density, flow, surface affinity, hardness,* polymorphic form, solvation or hydration state, pH, dissociation constant [pKa]) of the drug substance identified in S.3.1 that can influence the performance or manufacturability of the drug product should be discussed. If the drug substance is structurally modified from an active moiety (e.g., salt, endogenous protein) and the modification affects a key physicochemical (e.g., solubility) and/or biological characteristic, this should be discussed. These discussions should cross-reference any relevant stability data in S.7.3).

7 Page "14"
Lines "511 – 512," "Data to support scoring should include content uniformity and dissolution studies comparing split versus whole tablet.[12]" **should be revised as follows:**

Data to support scoring should include *batch-representative* content uniformity and dissolution sample studies *comparing the batch active-uniformity and batch active-release properties of the split tablet fractions to the corresponding batch-representative samples of the* whole tablet.[12]

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8 Page "14"

Lines "521 – 524," "The amount of overfill should be sufficient to ensure that the finished dosage form meets appropriate pharmacopeial tests (e.g., *United States Pharmacopeia* (USP) *General Chapters* <1> *Injections*, <698> *Deliverable Volume*, <755> *Minimum Fill.*" **should be revised as follows:**

Full-scale-batch-representative sample testing should be used to establish that the minimum specified overfill is sufficient to ensure that *each and every article of the finished dosage form in that the batch* meets *the minimum CGMP batch-acceptance requirements set forth in* **21 CFR 211**, *and, if tested, will meet* the appropriate pharmacopeial tests (e.g., *United States Pharmacopeia* (USP) *General Chapters* <1> *Injections*, <698> *Deliverable Volume*, <755> *Minimum Fill.*

9 Page "14"

Lines "531 – 537," "An overage is a fixed amount of the drug substance in the dosage form that is added in excess of the label claim. Any overages included in the formulations described in P.1 should be justified. Information should be provided on the: (1) amount of overage, (2) reason for overage (e.g., compensate for expected and documented manufacturing losses, ensure proper dose delivery), and (3) justification for the amount of the overage. The overage should be included in the amount of drug substance listed in the composition statement (P.1) and the representative batch formula (P.3.2)." **should be modified as follows:**

An overage is a fixed amount of the drug substance *(active ingredient)* in the dosage form that is added in excess of the label claim. Any overages included in the formulations described in P.1 should be justified, *<u>including</u> the overage added to satisfy the requirement set forth in* **21 CFR 211.101(a)**. Information should be provided on the: (1) amount of overage, (2) reason for overage (e.g., compensate for expected and documented manufacturing losses, ensure proper dose delivery), and (3) justification for the amount of the overage. The overage should be included in the amount of drug substance listed in the composition statement (P.1) and the representative batch formula (P.3.2).

[Note: For overages arising from the variation in the weight of the "less than 100 % pure" API necessary to provide the required weight of active ingredient (drug substance) in the formulation, the amount of API listed in the composition statement (P.1) and the representative batch formula (P.3.2) needs to be appropriately increased based on the weight-fraction "purity" of the active ingredient (drug substance) in the API.

The formula for computing the required weight of each API should be:

(Required weight of active ingredient) / (weight-fractional purity of the API)

It is neither scientifically sound nor appropriate to use "100 %" divided by the Assay in place of the weight-fraction purity ("100 %" divided by the weight-percent purity). This is the case because the reported "Assay" of a given lot of API is NOT a valid measure of the purity of that lot of API. This is the reason **21 CFR 211.84(d)(2)** specifically requires, "Each component shall be tested for conformity with all appropriate written specifications for <u>purity</u>, strength, and quality." *This is the case because API purity is not the same as API strength (typically measured by an Assay).* In addition, the weight of the appropriate "Filler" or "Diluent" in the composition statement (P.1) and the representative batch formula (P.3.2) needs to be reduced by the additional weight of API required.]

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10 Page "14"

Lines "638 – 640," the indent "• for sterile products, the integrity of the container closure system as it relates to preventing microbial contamination" **should be followed by:**

- *For protein-based components and products derived from animal sources, the proof that such products are free of prionic contamination including any transmissible spongiform encephalopathy (TSE)*
- *For components and products derived from animal tissues subject to contamination by viruses, the proofs that such product are free of viral contamination*
- *For components and products that may contain endotoxins, the nature and level of such contaminants in such components and products and the pathways and levels of reduction by which are reduced to acceptable levels in the finished drug product.*

11 Page "20"

Lines "765 – 767," "Explanatory notes should be included as appropriate. For example, explanatory notes should be used to identify components that are removed during processing or the purpose of inert gases used during the manufacturing process." **should be revised to read**:

Explanatory notes should be included as appropriate. For example, explanatory notes should be used to*:*

- *Explain the adjustment of the weight of API required to ensure that the weight of active ingredient (drug substance) added is sufficient to meet the requirements of* **21 CFR 211.101(a).**
- *Explain the adjustment of the weight of the "Filler" or "Diluent" reduced to ensure that the total formulation weight is of the active ingredients plus the adjusted "Filler" or "Diluent" weight is a constant.*
- *Identify* components that are removed during processing or the purpose of inert gases used during the manufacturing process.

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12 Page "21"
Lines "769 – 770," "Table 2" should be revised as follows:

Table 2: Proposed Batch Formula[1] — 250 mg Trademark™ Tablets		
Core Tablet		
Component	Reference to Quality Standard	Amount (kg **or L**) per batch
Drug Substance	In-house Standard	**505.0 kg**[2]
Excipient X	**National Formulary (NF)**	**305.0 kg**[3]
Excipient Y	NF	**280.0 kg**
Excipient Z	In-house standard	**50.0 kg**
Magnesium Stearate	NF	**15.0 kg** (range 14.5 to 15.5)
Purified Water	**United States Pharmacopeia (USP)**	(200 **L**)[4]
Total Batch Size		**X**
Film Coat Solution[5]		
Component	Reference to Quality Standard	Amount (kg or L) per batch
Hydroxypropyl Methylcellulose	USP	**10.0 kg**
Purified Water	USP	(200 **L**)[4]
Color Red™	DMF Holder Y Standard	**10.0 kg**
Color White™	DMF Holder Y Standard	**1.5 kg**
Total Batch Size		**Y**
Print Ink Solution		
Colorant™	DMF Holder Z Standard	0.15 **kg**
Solvent	NF	(10 **L**)[6]
Total Batch Size		**Z**

1 Theoretical yield is 2,000,000 tablets **based on a 250 mg tablet weight and a 1 % formulation overage added to ensure that the "not less than 100 percent" requirement of 21 CFR 211.101(a) is met.**

2 **The actual amount of API to be weighed out for a given lot of API is given by the formula: 505.0 kg/(API Lot's weight-fraction purity) with the result rounded to the nearest 0.1 kg.**

3 **The actual amount of "Excipient X" to be weighed out is 305.0 kg minus (API kg weight computed in Footnote 2 minus 505.0 kg).**

4 Water is removed during processing.

5 Film coat weight may vary between 80% **and** 120% of target coating weight.

6 **Solvent evaporates after ink is applied.**

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[**Note:** The rationale for the preceding changes (in **bold**) should be self-evident. However, the proposed changes are required:

1. To ensure that **21 CFR 211.101(a)** is met, an overage must be added for the active ingredient. The "1 %" value was selected because this is the typical minimum value that permits a valid (*scientifically sound and appropriate*) determination of the *batch strength* (*as required by* **21 CFR 211.165(a)**, **"For each batch of drug product, there shall be appropriate laboratory determination of satisfactory conformance to final specifications for the drug product, including the identity and strength of each active ingredient, prior to release. ..."**) based on the "Assay" testing of a "few" (< 20 at the 95 % confidence level) aliquots from an appropriately homogenized *batch-representative* composite sample.
2. To ensure that the weight of a given lot of API added to this formulation is sufficient to provide the required weight of active ingredient, the API weight must be adjusted by dividing the nominal weight required by the weight-fractional "purity" of the API with respect to the active. This is required because no API is 100 % pure by weight; typically, the "active" purity of most APIs is less than 99 % and, in some instances (where the active is purchased diluted in a carrier) may be as little as 1 % of the component's weight.
3. To ensure that the overall weight of the formulation is approximately constant, the weight of some "excipient" that does not affect active availability (a filler or a diluent) must be reduced in weight by the amount added by the adjustment of the weight of the API required.

The weights of materials added by weight in the formulation table should be expressed to the level precision that the balance used to weigh them. For ingredients dispensed by volume rather than weight that do not remain in the formulation after the completion of the processing steps that add them, the volume (weight) added need only be expressed to the nearest liter (kilogram) unless less than a liter (or kilogram) is to be added (in such cases, the volume [weight] added should be expressed to the nearest 0.1 L [0.1 kg]).

13 Page "21"
Lines "774 – 776," "The description of the manufacturing process and process controls should include a flow diagram of the manufacturing process and a detailed description of the manufacturing process and process controls." **should be revised to read**:

The description of the manufacturing process and process controls should include:

- *Flow* diagram of the manufacturing process,
- *Detailed* description of the manufacturing process, and
- *Detailed description of the* process controls *that includes the rationale that establishes that the process controls specified satisfy:* ***a)*** *the in-process controls* (**21 CFR 211.110** and **21 CFR 211.160**) *and* ***b)*** *the batch release controls* (**21 CFR 211.160**, **21 CFR 211.165**, and **21 CFR 211.167**) *set forth in the minimum CGMP regulations for finished pharmaceuticals* (**21 CFR 211**).

14 Page "26"
Lines "948 – 950," "When the same analytical procedure is used for both the in-process test and the finished product test, the acceptance criterion for the in-process test should be identical to or tighter than the acceptance criterion in the finished product specification." **should be revised to read**:

When the same analytical procedure is used for both the in-process test and the finished product test, the acceptance criterion for *each scientifically sound batch-*

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representative-sample-based in-process test should be *appropriately tighter than the acceptance criterion in the finished product batch-acceptance specification unless the process steps subsequent to said in-process test cannot* adversely affect the variability of the finished product. In such cases, the acceptance criterion for the in-process test can be identical to the acceptance criterion for the finished product specification when the subsequent steps do not affect batch uniformity, or, when subsequent in-process steps are known to improve batch uniformity, appropriately wider than the acceptance criterion in the finished product specification.

15 **Page "28"**
Lines "1024 – 1026," "At a minimum, the drug product manufacturer must perform an appropriate identification test (21 CFR 211.84(d)(1))." **should be revised to read**:

At a minimum, the drug product manufacturer must perform an appropriate identification test *and, if specific identity tests exist, they must be used* (**21 CFR 211.84(d)(1)**, "At least one test shall be conducted to verify the identity of each component of a drug product. Specific identity tests, if they exist, shall be used."). *Moreover, all testing must be performed on a batch-representative set of samples* (**21 CFR 211.160(b)(1)**, "Laboratory controls shall include: (1) Determination of conformance to appropriate written specifications for the acceptance of each lot within each shipment of components, drug product containers, closures, and labeling used in the manufacture, processing, packing, or holding of drug products. The specifications shall include a description of the sampling and testing procedures used. Samples shall be representative and adequately identified. ..."). *In addition, the drug product manufacturer must appropriately determine the purity, not the Assay, of each shipment of each lot of component that has a discrete chemical composition. Each purity determination must be performed on an appropriate batch-representative sample from the lot tested.*

15 **Page "29"**
Lines "1053 – 1057," "When the analytical procedure used is in the current revision of an official compendium or another FDA-recognized standard reference (e.g., AOAC International Book of Methods) and the referenced analytical procedure is not modified, a statement indicating the analytical procedure and reference can be provided rather than the analytical procedure itself." **should be revised to read**:

When the analytical procedure used is in the current revision of an official compendium or another FDA-recognized standard reference (e.g., AOAC International Book of Methods) and the referenced analytical procedure is not modified, *enhanced, or its text changed in any way,* a statement indicating the analytical procedure and reference can be provided rather than the analytical procedure itself. *If the firm's implementation of an analytical procedure changes it in any way from the current FDA-recognized revision, the firm must include a copy of its analytical procedure in its filing.*

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16 Page "29"
Lines "1062 – 1066," "When analytical procedures from the current revision of an official compendium or other FDA recognized standard references (e.g., AOAC International Book of Methods, analytical procedures from EP or JP that are interchangeable with a USP *General Chapter*) are used, they should be verified to be suitable under actual conditions of use." **should be revised to read**:

When analytical procedures from the current revision of an official compendium or other FDA recognized standard references (e.g., AOAC International Book of Methods, analytical procedures from EP or JP that are interchangeable with a USP *General Chapter*) are used *without any modification, change, augmentation or interpretive language*, they should be verified to be suitable under actual conditions of use. *Otherwise, such analytical procedures must be appropriately validated.*

17 Page "30"
Lines "1079 – 1081," "For compendial excipients, justification of the acceptance criteria for tests beyond those included in the monographs is recommended (e.g., particle size, flow properties, impurities)." **should be revised to read**:

For compendial excipients, justification of *the scientific soundness and appropriateness of* the acceptance criteria for tests beyond those included in the monographs *or required in* **21 CFR 211.84** is *required* (e.g., particle size, flow properties, impurities).

18 Page "30"
Lines "1093 – 1094," "Use of terms such as *conforms* or *meets specification* is discouraged." **should be revised to read**:

Use of terms such as *"conforms"* or *"meets specification"* is *proscribed.*

19 Page "31"
Lines "1100 – 1106," "Excipients of human or animal origin should be identified. The genus, species, country of origin, source (e.g., pancreas), and manufacturer or supplier should be clearly indicated. Furthermore, for excipients derived from ruminant materials, the application should state whether the materials are from BSE countries as defined by the U.S. Department of Agriculture (9 CFR 94.11). Guidance is available from FDA on *The Sourcing and Processing of Gelatin to Reduce the Potential Risk Posed by Bovine Spongiform Encephalopathy (BSE) in FDA-Regulated Products for Human Use.* Use of terms such as *conforms* or *meets specification* is discouraged." **should be revised to read**:

Excipients of human or animal origin should be identified. The genus, species, country of origin, source (e.g., pancreas), and manufacturer or supplier should be clearly indicated. Furthermore, for excipients derived from ruminant materials *(or materials from other susceptible herbivores)*, the application should state whether the materials are from BSE countries as defined by the U.S. Department of Agriculture (9 CFR 94.11). Guidance is available from FDA on *The Sourcing and Processing of Gelatin to Reduce the Potential Risk Posed by Bovine Spongiform Encephalopathy (BSE) in FDA-Regulated Products for Human Use.*

20 Page "31"
Lines "1108 – 1110," "The potential adventitious agents should be identified, and general information regarding control of these adventitious agents (e.g., specifications, description of the testing performed, and viral safety data) should be provided in this section." **should be revised to read:**

The potential adventitious agents should be identified, and general information regarding control of these adventitious agents (e.g., specifications, description of the testing performed, and viral *and prion* safety data) should be provided in this section.

21 Pages "31" to "32"
Lines "1133 – 1142," "The proposed specification for the drug product should be provided. The specification establishes criteria to which each batch of drug product should conform to be considered acceptable for its intended use. *Conformance to specification* means that the drug product, when tested according to the listed analytical procedures, will meet the listed acceptance criteria. A specification is one part of the strategy to control drug product quality. They are proposed and justified by the manufacturer and approved by the Agency. Specifications are established to confirm the quality of drug products rather than to establish full characterization and should focus on those characteristics found to be useful in ensuring product quality as it relates to safety and efficacy. Information on periodic quality indicator tests is provided below." **should be revised to read:**

The proposed specification for the drug product *batch* should be provided. The specification establishes criteria to which each batch of drug product should conform to be considered acceptable for its intended use. *"Conformance to specification"* means that *batch representative samples from* the drug product *batch*, when tested according to the listed analytical procedures, will meet conform to the drug product CGMP requirements established in **21 CFR 211.110**, **21 CFR 211.160**, **21 CFR 211.165** and, where applicable, **21 CFR 211.167** and the listed acceptance criteria. A specification is one part of the strategy to control drug product quality. *The manufacturer proposes and justifies their scientific soundness, appropriateness, and conformance to the applicable CGMP requirements for the drug product batch. If and only if the Agency finds that the specification proposed complies with said CGMP requirements, the Agency can then approve it for use. [**Note:** As per a 1988 U. S. Supreme Court ruling (**Berkovitz v. US {486 US 531, 100 L Ed 2d 531, 108 S Ct 1954}**), the Agency has no authority to approve specifications that do not comply with any of the clear requirements set for in* **21 CFR 211**.*]* Specifications are established to confirm the quality of drug product *batches based on the results obtained from the testing of batch-representative samples therefrom* rather than to establish full characterization and should focus on those characteristics found to be useful in ensuring product quality as it relates to safety *(as measured by the batch's drug product identity, strength, and levels of the impurities)* and efficacy *(as measured by the batch's uniformity with respect to the active and the active release or release rate).* Information on periodic quality indicator tests is provided below.

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22 Page "32"

Lines "1144 – 1162," "The specification sheet should list all tests to which each batch of a drug product will conform and the associated acceptance criteria and should also include a reference to the analytical procedures that will be used to perform each test. Acceptance criteria are numerical limits, ranges, or other criteria for the tests described. If an analytical procedure will be used only to generate stability data, the analytical procedure should be described in P.8.3. Justified interim acceptance criteria and tests with sunset provisions should be included in the specification (see section VII.F). Presentation of information in a tabular format is suggested. The specification sheet should also identify:

- tests that can be performed in-process in lieu of testing the finished product (the results of such tests performed in-process should be included in the batch analysis report (e.g., certificate of analysis))
- all analytical procedures that will be used for a test; identifying which are regulatory and which are alternative analytical procedures when multiple analytical procedures can be used for a test[30]
- acceptance criteria for the test using the regulatory analytical procedure and alternative analytical procedures when the criteria are different (e.g., conformance to a spectrum for near infrared (NIR) or retention time for HPLC).
- release and shelf-life acceptance criteria when both are used.

The proposed specification for the drug product should be provided. The specification establishes criteria to which each batch of drug product should conform to be considered acceptable for its intended use. *Conformance to specification* means that the drug product, when tested according to the listed analytical procedures, will meet the listed acceptance criteria. A specification is one part of the strategy to control drug product quality. They are proposed and justified by the manufacturer and approved by the Agency. Specifications are established to confirm the quality of drug products rather than to establish full characterization and should focus on those characteristics found to be useful in ensuring product quality as it relates to safety and efficacy. Information on periodic quality indicator tests is provided below." **should be revised to read**:

The specification sheet should list all tests to which each batch of a drug product will conform and the associated acceptance criteria *for the batch-representative samples tested (as* **required by 21 CFR 211.160(b)(3)***) and the calculated batch statistical quality control values derived from the batch-representative sample results* (as required by **21 CFR 211.165(d)**). *The specification sheet* should also include a reference to the analytical procedures that will be used to perform each test and the recognized statistical standard used to evaluate the statistical acceptability of the batch. Acceptance criteria are numerical limits, ranges, or other criteria for the tests described. If an analytical procedure will be used only to generate stability data, the analytical procedure should be described in P.8.3. Justified interim acceptance criteria and tests with sunset provisions should be included in the specification (see section VII.F). Presentation of information in a tabular format is suggested. The specification sheet should also identify:

- *Tests* that can be performed in-process in lieu of testing the finished product (the results of such tests performed in-process should be included in the batch analysis report (e.g., certificate of analysis))

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- *All* analytical procedures that will be used for a test; identifying which are regulatory and which are alternative analytical procedures when multiple analytical procedures can be used for a test[30]
- *Acceptance* criteria for the test using the regulatory analytical procedure and alternative analytical procedures when the criteria are different (e.g., conformance to a spectrum for near infrared (NIR) or retention time for HPLC).
- *Release* and shelf-life acceptance criteria, when both are used.

23 Page "32"
Lines "1164 – 1170," "The ICH guidance *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances* provides recommendations on tests that should be included in the specification for solid oral drug products, liquid oral drug products, and parenterals (small and large volume). Some tests that are identified as appropriate for inclusion in the specification can be proposed as periodic quality indicator tests when there are sufficient data and justification. Recommendations on tests for other dosage forms are included in Attachment 1." **should be revised to read**:

The ICH guidance *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances* provides recommendations on tests that *can be used as the basis for the tests to be* included in the specification for solid oral drug products, liquid oral drug products, and parenterals (small and large volume). Some tests that are identified as appropriate for inclusion in the specification can be proposed as periodic quality indicator tests when there *is* sufficient data *to support such periodic rather than each batch evaluation provided the firm can demonstrate CGMP compliance without performing such tests on every batch. In general, the tests amenable to such treatment are those that evaluate factors, like appearance, that have no direct bearing on the safety and efficacy of the drug product. In general, the CGMP for drug product (finished pharmaceuticals;* **21 CFR 211**) does not permit omitting tests that bear on the identity, purity, strength and performance quality of the each drug batch. Recommendations on tests for other dosage forms are included in Attachment 1."

24 Pages "32" – "33"
Lines "1172 – 1175," "An illustrative example of a specification sheet is provided in Table 3." ➔ **"Table 3"**

1 The example provided in **Table 3** is deficient in several aspects including, failure to: **a)** specify that the sample tested must be batch representative, **b)** specify the number of sample units that must be tested for batch acceptance, **c)** specify if the tests should be on each unit or on a homogeneous composite (and if on the composite, how many aliquots).

2 In addition, as most do, the example confuses specification limits appropriate to a given post-release grab-sample test (the **USP** test for an *article*) with specifications appropriate to batch acceptance or rejection for the appropriate testing of a batch-representative sample.

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3 Finally, though appearance testing using **ANSI Z 1.4** (or the obsolete Mil Std 105E or 105F) is an integral part of the testing used by a firm for batch acceptance, no mention is made of it in the example table.

4. For compliance with **21 CFR 211.165(d)**, the reference standard **ISO 3951**:1989 and its acceptance criteria need to be addressed when statistical quality control acceptance decisions are to be made (typically required for active uniformity ("content uniformity") and the uniformity of the release ("dissolution") or the rate of release ("drug release") of the active ingredient

To address the preceding issues, the following alternate **Table 3**, shown on the next three pages, is proposed.

25 **Page "33"**
Lines "1178 – 1181," "The CGMP regulations require that for each batch of drug product, there will be appropriate laboratory determination of satisfactory conformance to the drug product specification. Drug product failing to meet established standards or its specification and any other relevant quality control criteria must be rejected (21 CFR 211.165)." **should be revised to read**:

For each batch of drug product being evaluated for acceptance, the CGMP regulations require:

- *The sampling and examination or testing of batch-representative samples* (**21 CFR 211.160(b)(3)**).
- *The laboratory evaluations to be performed on said batch-representative samples to establish the satisfactory conformance of said samples* "to final specifications for the drug product, including the identity and strength of each active ingredient, prior to release" (**21 CFR 211.165(a)**).
- *Appropriate* "laboratory testing, as necessary, of each batch of drug product required to be free of objectionable microorganisms" (**21 CFR 211.165(b)**).
- Any sampling and testing plans shall be described in written procedures that shall include the method of sampling and the number of units per batch to be tested; such written procedure shall be followed (**21 CFR 211.165(c)**).
- Acceptance criteria for the sampling and testing conducted by the quality control unit shall be adequate to assure that batches of drug products meet each appropriate specification and appropriate statistical quality control criteria as a condition for their approval and release. The statistical quality control criteria shall include appropriate acceptance levels and/or appropriate rejection levels (**21 CFR 211.165(d)**).
- The accuracy, sensitivity, specificity, and reproducibility of test methods employed by the firm shall be established and documented (**21 CFR 211.165(e)**).
- Drug products failing to meet established standards or specifications and any other relevant quality control criteria shall be rejected (**21 CFR 211.165(f)**).

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Table 3: Specification for Trademark™ Tablets (100 mg[1])				
Property Being Evaluated	**Representative Sample Number And Protocol (Individual {RI-N} or Homogeneous Composite [with testing of "n" aliquots] {HC-N-n})**	**Acceptance Criteria**	**Regulatory Analytical Procedure**	**Alternative Analytical Procedure**
Description	**RI – 800** (normal inspection) [RI – 125 (reduced inspection)]	White, biconvex, 11-mm diameter, 4-mm thick, film-coated tablet, with "identifier code XYZ" on one side.	**Visual**	
Appearance		0 [0] **Broken**; NMT[2] **5** [1] **Chipped**; NMT **7** [1] **Film holes/bubbles**; NMT **21** [5] **Other minor visual defects**	**ANSI Z 1.4 Normal Inspection: Single Level 0.015, 0.25 & 1.5 %**	**ANSI Z 1.4** Reduced: Inspection: Single Level Same %
Dimensions/Hardness		10.5 – 11.5 mm in diameter 3.9 – 4.5 mm thick	**AP[3] # DIM3A**	**AP # ADM09**
Core Weight and Core Hardness[4]	**RI – 9 or more sets of 23 tablets** (1 from each of 23 stations in tablet press used)	**Weight** / **Hardness** Setup Target: 443 mg / NLT[5] 9.5 KP[5] Setup Mean: NLT 442 mg / NLT 10.2 KP Setup Range: 440 – 446 mg / 8.7 – 12.5 KP Run Range: 437 – 449 mg / 7.5 – 14.0 KP Run Mean: NLT 440.5 mg / NLT 9.0 KP	**AP # WTS4B**	**AP #AWT11**
Identification Test #1	**HC-200-1**	Retention time of the major peak in the chromatogram of the assay preparation corresponds to that in the chromatogram of the standard preparation obtained as specified in the USP-based Assay.	**HPLC, AP # EFG2**	**AP # UVR19**
Identification Test #1	**HC-200-1**	Responds to the tests for sulfate	**USP <191>**	
Active Uniformity in the Tablets (AUT) - Content Uniformity (CU)	**RI – 200** (normal test) [RI – 75 (reduced test)]	**§§ 211.101(a) Compliance** (Release) **Mean ($\bar{x}$): NLT 100.2 LC[6] (200);** [NLT 100.0% (75)] **§§ 211.110 Compliance** (Release) **Range: 90 – 112 % LC; RSD: ≤ 3.7 %** [92 – 110 % LC; RSD: ≤ 4.0 % **§§ 211.165(d) Compliance** (Release) **SQC Acceptance Using ISO 3951** **The "s" method, n = 200, AQL 0.1 %** **Accept: ($\lvert 112 - \bar{x}\rvert/s$) & ($\lvert \bar{x} - 90\rvert/s$) ≥ 2.73** ."s" method, n = 75, AQL 0.1 % Accept: ($\lvert 112 - \bar{x}\rvert/s$) & ($\lvert \bar{x} - 90\rvert/s$) ≥ 2.55	**HPLC, AP # EFG2**	**AP # UVS29**
	Post-Release **USP Article 30**	**USP Compliance** (Lifetime) NONE outside of 75 – 125 % of LC, NMT 1 in 30 outside of 85 – 115 % of LC RSD NMT 7.8; Mean NLT 95 % LC	**HPLC, AP # EFG1**	

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Table 3: Specification for Trademark™ Tablets (100 mg[1]) [Continued]

Property Being Evaluated	Representative Sample Number And Protocol (Individual {RI-N} or Homogeneous Composite [with testing of "n" aliquots] {HC-N-n})	Acceptance Criteria	Regulatory Analytical Procedure	Alternative Analytical Procedure
Active Availability Stage 1[7]	**RI – 60** (correlated normal test) [RI – 42 (correlated reduced test)] (Release)	**§§ 211.110 Compliance** (Release) **Mean: NLT 85 % LC (60)** [NLT 85.5 % LC (42)] **Range: 78 – 97 % LC (60)** [80 – 95 % LC (42)] **§§ 211.165(d) Compliance** (Release) **SQC Acceptance Statistical Inference Using "s" Approach, n = 60, AQL 0.4 %** **Accept: (|97 – $\bar{x}$|/s) & (|$\bar{x}$ – 78|/s) ≥ 2.22** .Using "s" Approach, n = 42, AQL 0.4 % Accept: (|95 – $\bar{x}$|/s) & (|$\bar{x}$ – 80|/s) ≥ 2.04	**AP # BCD2**	**AP # UVS28**
	Post-Release **USP Article Dissolution on 6 units** (Lifetime))	**USP Compliance** (Lifetime) **None: LT[8] 80 % LC** (or MT[9] 100 % LC) **Mean NLT 85 % LC**	**AP # BCD1**	
Active Availability Stage 2	Post-Release **USP Article Dissolution on 12 units** (Lifetime)	**Release has NO intermediate Stage** **USP Compliance** (Lifetime) **None: LT 65 % LC** *(or MT 105 % LC)* **Mean NLT 80 % LC (corrected)**	**No Test Defined** **AP # BCD1**	**No Test** **AP # BCD1**
Active Availability Stage 3	**RI – 200** (correlated normal test) [RI – 75 (correlated reduced test)] (Release)	**§§ 211.110 Compliance** (Release) **Mean: NLT 85 % LC (200)** [NLT 85 % LC (75)] **Range: 75 – 100 % LC (200)** [77 – 98 % LC (75)] **§§ 211.165(d) Compliance** (Release) **SQC Acceptance Statistical Inference Using "s" Method, n = 200, AQL 0.4 %** **Accept: (|100 – $\bar{x}$|/s) & (|$\bar{x}$ – 75|/s) ≥ 2.33** .Using "s" Method, n = 75, AQL 0.4 % Accept: (|98 – $\bar{x}$|/s) & (|$\bar{x}$ – 77|/s) ≥ 2.12	**AP # BCD2**	**AP # UVS29**
	Post-Release **USP Article Dissolution on 24 units** (Lifetime)	**USP Compliance** (Lifetime) **None: LT[8] 55 % LC** *(or MT[9] 110 % LC)* NMT 2 LT 65 % LC Mean NLT 80 % LC (corrected)	**AP # BCD1**	
Tablet Strength (Assay)	**RI – 200**[75] (mean from **ADT** test) **or** **HC-200-8** (test NLT 8 aliquots ex. HC-200)	**§§ 211.101(a) Compliance** (Release) **Mean: NLT 100.2 LC (200);** [NLT 100.0 % (75)] – **or** – **Mean: NLT 100.0 LC** (8 aliquots)	**Result from "ADT" Test** **HPLC, AP # EFG2**	**AP # UVS29**
	Post-Release **USP Article – Assay 20** (homogenize and test duplicate aliquots)	**USP Compliance** (Lifetime) **Mean: 90 – 110 % LC** (2 aliquots) **RSD: NMT 2.0 %**	**HPLC, AP # EFG2**	

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Table 3: Specification for Trademark™ Tablets (100 mg[1]) [Continued]

Property Being Evaluated	Representative Sample Number And Protocol (Individual {RI-N} or Homogeneous Composite [with testing of "n" aliquots] {HC-N-n})	Acceptance Criteria		Regulatory Analytical Procedure	Alternative Analytical Procedure
Water Content	**HC-200-3** Post-Release **USP Article – grab 20 units** (homogenize and test single aliquots)	**NMT 0.7 % by weight – RSD NMT 1 %** (Release) **NMT 1.0%** (Lifetime)		**USP <921>; Method Ic**	**AP # PQR7**
Degradation Products **Specified Degradation Products** **Degradant A:** **Degradant B:** **Degradant at RRT[10] XX** **Unspecified Degradation Product** **Individual Unspecified** **Total Degradation Products:**	**Release** **HC-200-3** (Take 200 batch-representative units and homogenize them; then, test 3 unit-dose aliquots, average the results & compute the RSD values. Batch is acceptable when all impurities meet the release criteria set.) **Lifetime** Post-Release **USP Article – grab 20 units** (homogenize & test single aliquot)	**Release** **NMT 0.3 %; RSD <4 %** **NMT 0.4 %; RSD <3 %** **NMT 0.2%: RSD <5 %** **NMT 0.07%; RSD <8 %** **NMT 1.0%**	**Lifetime** **NMT 0.5 %** **NMT 0.6 %** **NMT 0.3%** **NMT 0.1%** **NMT 1.5%**	**HPLC; AP # EFG2**	
Residual Solvent A	**Release: HC-200-2** **Lifetime:** Post-Release **USP Article – grab 20 units** (homogenize & test single aliquot)	**Release** **NMT 100 ppm; RSD: NMT 2 %**	**Lifetime** **NMT 200 ppm**	**GC; AP # XYZ31**	

1 This product contains a 1 % formulation overage to ensure that the "**intent to provide not less than 100 % of the label claim or established amount**" requirement set forth in **21 CFR 211.101(a)** is met.

2 NMT = not more than

3 AP = Analytical Procedure

4 The Core Weight and Hardness tests are performed "in process" as the tablet cores are being produced.

5 NLT = not less than

6 LC = label claim

7 The process is designed to pass at "**Stage 1**." However, if a batch in release testing or a post-release **USP** article fails to meet the "**Stage-1**" criteria and all valid results are within the appropriate release range for the batch (60 % to 110 % of label claim) or the **USP**'s lifetime limits that, for this product, requires all tablets to have a dissolution value that is NLT 55 % of LC and no more than 2 in 6 tablets tested are less than 65 %, then the test plan should revert to full-sample testing (200 for the release test and any "12" [6 more] and "24" [18 more] for the post-release **USP** test).

8 LT = less than

9 MT = more than

10 RRT = relative retention time

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26 Page "35"

Lines "1250 – 1260," "If the analytical procedure used is in the current revision of an official compendium or another FDA-recognized standard reference (e.g., AOAC International Book of Methods) and the referenced analytical procedure is not modified, the analytical procedure need not be provided. A specific citation to the analytical procedure is sufficient.[32] When a general chapter or monograph included in an official compendium or other FDA recognized standard reference allows for the use of more than one analytical procedure for a test, the specific analytical procedure that will be used should be cited here (P.5.2) and in the specification (P.5.1). For example, when using USP <921> *Water Determination,* the method should be specified (e.g., Method Ia). If an analytical procedure is based on one of these sources but has been modified, the analytical procedure should be provided." **should be revised to read**:

If the *exact detailed written* analytical procedure used*: **a)** is available In, **b)** has been copied verbatim from, and **c)** uses the exact equipment specified in* the current revision of an official compendium or another FDA-recognized standard reference (e.g., AOAC International Book of Methods) and the referenced analytical procedure is not modified *in any manner*, the analytical procedure need not be provided. A specific citation to the analytical procedure is sufficient[32]. When a general chapter or monograph included in an official compendium or other FDA recognized standard reference allows for the use of more than one analytical procedure for a test, the specific analytical procedure that will be used should be cited here (P.5.2) and in the specification (P.5.1). For example, when using USP <921> *Water Determination,* the method should be specified (e.g., Method Ia). If an analytical procedure is based on one of these sources but has been modified *in any manner*, the *detailed written validated* analytical procedure *and its supporting validation report* must be provided.

27 Page "37"

Lines "1307 – 1309," "Test results should be expressed numerically or qualitatively (e.g., clear, colorless solution), as appropriate. Use of terms such as *conforms* or *meets specification* is discouraged." **should be revised to read**:

Test results should be expressed numerically or qualitatively (e.g., clear, colorless solution), as appropriate. Use of terms such as *"conforms"* or *"meets specification"* is *proscribed. In addition, where the value reported is the average of several individual results, either an ordered list of all of the individual results that were used to compute the average or, if the distribution of the results is at least pseudo-Gaussian, the range, number of values, standard deviation, mode, and median values should also be reported. In cases where the distribution is non-Gaussian and an average is reported, in addition to the reported average, either an ordered list of values found, or the number of values, a value frequency listing and the range, mode and median of the data set should also be reported.*

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28 Page "37"
Lines "1330 – 1334," "Presentation of results from all batches for a particular test in tabular and/or graphical format is often helpful in justifying the acceptance criteria. Collated batch analyses data are not warranted for all tests. However, collated data should be provided for assay and impurities (e.g., degradation products, residual solvents) and should be considered for other tests such as water content." **should be revised to read**:

Presentation of results from all batches for a particular test in tabular and/or graphical format is often helpful in justifying the acceptance criteria. Collated batch analyses data are not warranted for all tests. However, collated data should be provided for assay, impurities (e.g., degradation products, residual solvents), *active uniformity, and the uniformity of either the active-release or the active-release-rate* and *the reporting of collated data* should be considered for other tests such as water content.

29 Page "40"
Lines "1415 – 1427," "Justification for the proposed drug product specification should be provided. The justification should be based on relevant development data (P.2), standards in an official compendium, batch analyses (P.5.4), characterization of impurities (P.5.5), stability studies (P.8), toxicology data, and any other relevant data. The discussion in this section should unify data and information that are located in other sections of the application, either by reference or in summary. Data from the 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. If multiple manufacturing sites are planned, it can be valuable to consider data from these sites in establishing the tests and acceptance criteria. This is particularly true when there is limited initial experience with the manufacture of the drug product at any particular site. Justification for an in-process test that is used in lieu of a finished product test should be included in P.3.4." **should be revised to read**:

Justification for the proposed drug product specification should be provided. The justification should be based on

- *Relevant* development data (P.2),
- *The distributional properties in the dosage units in each batch required to ensure that each batch:* ***a)*** *meets the applicable CGMP requirements and* ***b)*** *will, if tested, be found to consist of articles having the property that every article in the batch will, with a high degree of certainty, meet the applicable* standards in an official compendium
- Batch analyses (P.5.4) *that demonstrate the uniformity of the batch with respect to its critical distributional quality properties,*
- *Characterization* of impurities (P.5.5),
- *Stability* studies (P.8),
- *Toxicology* data, and
- *Any* other relevant data.

The discussion in this section should unify data and information that are located in other sections of the application, either by reference or in summary.

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Data from the 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. If multiple manufacturing sites are planned, it can be valuable to consider data from these sites in establishing the tests and acceptance criteria. This is particularly true when there is limited initial experience with the manufacture of the drug product at any particular site. Justification, *including the rationale that clearly establishes that the proposed substitution complies with all of the applicable CGMP requirements set forth in* **21 CFR 211**, for *any proposed* in-process test that is *to be* used in lieu of a finished product test should be included in P.3.4.

30 Page "41"
Lines "1456 – 1459," "In these or similar circumstances, an applicant could propose a *sunset test protocol* for a test, which would provide for the test to be dropped from the specification after an agreed number of production batches have met certain criteria." **should be revised to read**:

In these or similar circumstances, an applicant could propose a *sunset test protocol* for a test, which would provide for the test to be dropped from the specification after an agreed number of production batches have met certain criteria *provided the applicable CGMP regulations do not explicitly require the test in question to be conducted on each batch.*[33]

31 Page "41"
Footnote "33," "[33] A proposal to drop a test, based on historical data, can also be submitted post approval in a prior approval supplement." **should be revised to read**:

[33] *Provided the test is not required by the CGMP for finished pharmaceuticals (***21 CRFR 211***) to be conducted on each batch,* a proposal to drop a test, based on historical data, can also be submitted post approval in a prior approval supplement.

32 Page "58"
Lines "2120 – 2122," After the definition of "**Acceptance Criteria**: Numerical limits, ranges, or other suitable measures for acceptance of results of analytical procedures (ICH Q6A). In these or similar circumstances, an applicant could propose a *sunset test protocol* for a test, which would provide for the test to be dropped from the specification after an agreed number of production batches have met certain criteria." **the draft should be revised to insert the definition of "Active Pharmaceutical Ingredient (API)" as follows:**

Active Pharmaceutical Ingredient (API): *The component containing the* ***drug substance*** *or* ***active ingredient*** *(***21 CFR 210.3(b)(7)***) that is available for inclusion into the formulation of a batch of drug product, or, the Agency's September 1996 definition,*
Active Pharmaceutical Ingredient (API): "any substance that is represented for use in a drug and that, when used in the manufacturing, processing, or packaging of a drug, becomes an active ingredient or a finished dosage form of the drug." (September 20, 1996, *Guidance for Industry Manufacture, Processing or Holding of Active Pharmaceutical Ingredients*, DISCUSSION DRAFT, pgs 2 - 3, at **D. 3**).

Concluding Remarks

The preceding comments and suggested changes in this "CMC" draft are intended to align it with the clear mandates of **21 CFR 211**.

Where I have suggested alternate wording, my proposed changes are in italicized text except where the regulations are referenced or quoted.

To ease the recognition of the different **textual** threads that compose this document, I have used different fonts.

Quotations from the original document are in a Times New Roman font; quotations from the CFR and other Agency documents are in a **Lydian** font; and my suggestions are in a News Gothic MT font with proposed wording changes in *italicized News Gothic MT* font.

Should there be any salient questions, please provide them to me in writing so that I may clearly understand and address the issues raised.

Paul G. King 16 May 2003