"Section XII.A. Executed Product Records (R.1.P)
Lines 1799-1800 require only one representative EPR to be submitted for an NDA. Please clarify lines 1803-1804 whether one representative EPR would be acceptable for submission of an ANDA also. One batch record clearly represents the product manufacture, multiple batch records in a submission contain very redundant information."

The commenters seem to have misread **Section XII.A.*1***.

The EPR discussed in **Lines 1799-1800** is but one of the EPRs required for NDAs as the narrative in **Lines 1802-1803** clearly indicates, "**Discussion of which EPRs should be included in the NDA can be a topic at pre-NDA meetings.**"

In the ANDA case, the batch records submitted serve: **a)** to establish that the batches listed were indeed produced in a controlled manner that is consistent with **CGMP** as well as: **b)** to provide details as to differences, if any, among the records.

In both cases, the EPRs are thus <u>not</u> at all redundant.

A REVIEW OF FORMAL COMMENTS TO PUBLIC DOCKET 02D-0526

J&J Pharmaceutical R&D's Submission Posted June 27, 2003 To Docket 02D-0526: "C-13"

[**Note:** The original comments are quoted in a condensed font (Perpetua), the quotes directly from the draft guidance are quoted in a stylized font (Lydian) and this reviewers comments are in a publishers font (News Gothic MT) to make it easier for the reader to differentiate the "speaker" in the various text passages that follow. When the commenters quote the draft guidance, the italicization that J&J introduced is preserved within J&J's quoting thereof.]

"Provided in the General Discussion Section are the general impressions of our scientists including comments on issues of greatest concern to our business. Other comments, as well as those discussed in the General Discussion Section, are presented in the Comments Section by section and line number. To assist you during the review, the draft guidance text appears in italics."

"General Discussion:

The following comments are intended to promote further discussion and ultimate creation of a scientifically-based, informative final guidance for Drug Product Chemistry, Manufacturing and Controls:"

While this reviewer generally agrees with the sentiment expressed, this statement would have been more meaningful if the phrase "scientifically-based, informative" had been "science-based, CGMP-compliant."

After all, one can scientifically structure a document without including any science or, for that matter, any text that demonstrates adherence to CGMP in it.

"This draft guidance appears to increase filing requirements in many areas and/or introduces requirements that have not been historically part of CDER filings. The collaborative work from CBER and CDER on this guidance may have precipitated these additional requirements. If so, intensive ongoing discussions between FDA and industry are recommended and non-essential requirements should be eliminated."

First of all, guidance cannot introduce requirements – it is only guidance.

Second, all that the current draft guidance seems to do is suggest means by which an applicant can incorporate into their application proofs that they understand and are intending to produce their candidate drug product in full compliance with the clear written requirements of the drug CGMP regulations as set forth in **21 CFR 210** and **21 CFR 211**.

Thus, this reviewer sees no reason for any "intensive ongoing discussions" and, having carefully reviewed the guidance suggested sees no instance where there is "non-essential" guidance that "should be eliminated."

That the Agency is finally upgrading its guidance to address all areas of the drug **CGMP**, a historical deficiency in the prior guidance, and provide guidance as to how an applicant can demonstrate compliance should be applauded.

"Where CDER and CBER filing approaches differ, scientific requirements can be met by noting in the guidance that certain requirements pertain to specific drug product categories. Greater use of cross-

referencing may be possible where new filing requirements duplicate information traditionally filed in IND Amendments. Similarly, it would be very beneficial if the draft guidance identified whether specific sections applied to NDAs, ANDAs or both. This would decrease potential confusion and filing requirements for industry. Finally, verification is requested that existing DMFs will not require reformatting into a CTD format. (Section: II.D. Line 216)"

Again the commenters confuse the general guidance being provided with "requirements."

In general, all sections in the guidance apply to both ANDAs and NDAs and, where differentiation is needed, the guidance clearly provides it.

Finally, the comment concerning the reformatting of existing DMFs is appropriate to "CDER's *Drug Master Files* guidance" – not to the current guidance

"Clarification is requested regarding FDA's position on Interim Acceptance Criteria. The draft guidance addresses the use of interim acceptance criteria when 'occasional' uncertainty due to limited data and experience with the product and scale-up of manufacturing process exists. (Section VI1.F. line 1480) Can FDA provide guidance on what is meant by 'limited'? Can FDA clarify whether the failure to meet the interim acceptable (acceptance?) criteria would result in batch failure on release?"

The commenters seem to be confused about what the guidance suggests and to have, by severely editing what was suggested, distorted the guidance being offered.

The guidance states (emphases added):

"• Acceptance Criteria

...

Occasionally, an applicant may wish to propose *interim acceptance criteria* for a specific test because there is some uncertainty whether the same type of results will continue to be observed for production batches. This uncertainty often occurs when (1) there are limited data available at the time the application is submitted and/or (2) the manufacturing process for production batches will be different (e.g., scale, equipment, site) from that used to produce the batches used to support the application and the effect, if any, of the differences has yet to be characterized. The proposal should include the (1) reason why the interim acceptance criteria are being proposed, (2) number of consecutive production batches that will be produced and tested and/or the time frame before the acceptance criteria will be finalized, (3) data analysis plan, and (4) proposed reporting mechanisms for finalizing the acceptance criteria when the proposed final acceptance criteria are tighter, broader, or the same as the interim acceptance criteria. An applicant should not propose using interim acceptance criteria as a substitute for providing recommended or agreed upon (e.g., at pre-NDA meetings) information in an application. For example, proposing interim acceptance criteria would not be appropriate when the stability data package recommended in the ICH guidance *Q1A: Stability Testing of New Drug Substances and Products* has not been provided.[34] For NDAs, finalization of interim acceptance criteria will be a Phase 4 commitment.

[34] For those applications that fall within the scope of Q1A."

Since the guidance in this area begins by stating, "Occasionally, an applicant may wish to propose *interim acceptance criteria*," the use of interim acceptance criteria should only be proposed when the applicant cannot (not has not bothered to)

acquire sufficient data for the test in question to project definite acceptance criteria that the batches drug product will meet that are appropriately inside of those criteria permitted for the drug product in commerce.

Thus, it is obvious that the term "limited data" applies to the scope of the data and not to the number of values. For example, an ANDA or NDA applicant isw orking with an API that hasn ot been manufactured for a period of time sufficient to establish valid process ranges for the critical property the test is designed to measure. In such cases, the applicant may, based on the availability of only one or two lots of the API, be forced to propose interim particle distribution specification acceptance limits when particle size distribution is a key (critical) API property.

However, the applicant is in a better position than the Agency to determine whether, or not, the available data is "limited" to the extent that the "**interim acceptance criteria**" approach presented should be used.

Given its inherent complexity, the Agency rightly concludes that most of the time applicants can set definite acceptance criteria that, as they gain experience in producing the drug product, they may revise based on the results of their "annual review" of the drug product.

[**Note:** For example, based on the observed batch uniformity of the final blends from the initial production, the firm may set a "tablet weight" acceptance specification from **a)** the batch target weight (200 mg) to **b)** the batch target weight + 10 mg (210 mg). Subsequently, a review of the prior year's data finds that the final blends for the batches, though within thea pproved production limits, are not quite as uniform as originally projected. The firm can then change its weight range from "200 mg to 210 mg" to "202 mg to 206 mg" to reduce content variability and file the change with its annual report.]

Thus, the Agency rightly leaves it up to the applicant to determine when they have a "**limited data**" case.

The drug **CGMP** regulations explicitly require a drug product batch to meet all of its batch acceptance criteria including statistical quality control criteria (**21 CFR 211.165(d)**) as a condition of the release of that batch from one stage to the next and for release for distribution.

Thus, there is no need for the **FDA** to comment in this regard.

"The draft guidance statement regarding inconsistencies between procedures published in the European, Japanese and United States Pharmacopoeias is incomplete. As stated in the draft guidance, "... where the texts differ or where there is a dispute, the result obtained from the USP procedure is conclusive." (Section V.I.A. line 1045) The use of the USP procedure however, may be inappropriate for any number of scientifically justified reasons. A requirement that justification be given for non-use should be added to the draft guidance statement. The statement should be revised to read "... where the texts differ or where there is a dispute, the result obtained from the USP procedure is conclusive. If the USP procedure can not be used, scientific justification should be provided."

The **FDA** cannot ignore the explicit requirements written into the law (the **FDC Act**) governing the manufacture of drugs.

That law makes the requirements of the applicable ***USP***, ***NF***, or ***Homeopathic Pharmacopeia of the United States*** ("**HP-US**") the sole final arbitrators ONLY for components in commerce.

From the point of view of science, there is no time that an approved **USP** procedure for an excipient cannot be used.

The reality is that excipients from certain sources may not meet the requirements set forth in the **USP**, **NF** or the **HP-US** even though they may meet the requirements established in the **EP** or the **JP** and *vice versa*.

If a compendial componentd oes not meet the requirements set forth in an official compendium, it cannot, by law, be used in the production of an **FDA**-approved drug product for which there is an official **USP** monograph.

Moreover, the use of such in a new drug product will require the applicant to work with the **USP** to have the official component monograph (**USP** or **NF**) modified or a new monograph issued before the **USP** issues a monograph of the new drug product or risk having to cease manufacturing the new drug product when the USP monograph for the new drug product becomes official.

Therefore, the Agency should not make the change proposed.

"If multiple manufacturing sites are planned, it can be valuable to consider data from these sites in establishing the tests and acceptance criteria." (Section V.1I.F. line 1423) The statement regarding the use of data from planned manufacturing sites to establish tests and acceptance criteria is confusing. This statement appears to be inconsistent with FDA's position that site-specific stability data is not necessary. Further clarification would be appreciated."

The guidance provided is for establishing "acceptance criteria" for the tests that an applicant is proposing.

Rightly, the Agency recommends including test data from samples from multiple sites when the use of multiple manufacturing sites is planned so that the confounding effects, if any, that are site specific will be properly recognized and incorporated into the acceptance specifications being proposed.

No where does this guidance propose that the data being incorporated into the setting of the acceptance criteria for the production of the drug product are to be from stability data – rather it simply recommends that, in such instances, the applicant would do well to generate data from multiple sites or risk, post approval, finding that batches produced in a given site fail to meet the acceptance criteria established in the firm's approved filing.

Thus, the Agency's guidance recommends a *scientifically sound* and prudent course of action for those who contemplate manufacture in multiple sites.

"Clarification is requested on the level of testing suggested for non-novel excipients by the sponsor. The statement '*A certificate of analysis (COA) from the manufacturer and the test results from the same batch from the drug product manufacturer should be provided for the components described in P. 4*' is confusing. The guidance seems to suggest that the drug product manufacturer may not utilize vendor COAs after the vendor has been qualified. Will additional testing (beyond Appearance and Identification) by the drug product manufacturer be required? (Section V1.D. line 1089). The inclusion of a complete listing of 'FDA-recognized standard references (e.g. AOAC International Book of Methods...)' in the guidance would be extremely useful."

There is no contradiction between what the guidance requests and the routine, post-approval practices available to the applicant.

The guidance simply requests that, for the lots used in the application, the applicant provide both the **"certificate of analysis (COA) from the manufacturer"** of the component and **"the test results from the same batch from the drug product manufacturer."**

Currently, the drug **CGMP** requires "additional testing (beyond Appearance and Identification) by the drug product manufacturer."

Unless the manufacturer develops, validates, and uses **specific identity tests** (and, in general, the **"Identification"** tests in the **USP** and **NF** areN OT specific), the drug product manufacturer is currently required to do full compendial testing on **"representative samples from each lot of each shipment of each component."**

In addition, when other tests (such as, flow, affinity, compressibility, surface roughness, bulk density, tapped density, and intrinsic dissolution) are critical to the differentiation between lots that should produce acceptable batches of the drug product and lotst hat will not, the drug manufacturer is required to develop and perform such testing on appropriate lot-shipment-representative samples from each shipment of each lot of each component.

Because the listing for FDA-recognized standard references would be required to be updated annually and readily available from the FDA's web site, it would be inappropriate to include them in this guidance.

However, a reference to said document list and its on-line web address could be included in the guidance to address this issue.

Therefore, this reviewer again recommends that such a list be developed and a reference to it be provided in the guidance (**see** reviewer's review of PhRMA's formal docket submission).

"Our scientists are concerned that this draft guidance greatly expands the requirement for identification of impurities in excipients. The draft guidance states, 'All expected drug impurities (e.g., degradation products of the active ingredient, residual solvents, enantiomeric impurities, excipient degradants, leachables from the container/closure system) should be listed in this section of the application whether or not the impurities are included in the drug product specification." (Section VII.E.*1* line 1343) This statement appears to imply that stability indicating methods should be developed by either the vendor or sponsor for vast numbers of potential excipient impurities and degradation products. Limits of detection and quantitation would potentially need to be set on a product-by-product basis. The enormous effort is scientifically difficult to justify (especially for oral or topical drug products) and is extremely burdensome for non-novel excipients. Clarification from FDA would be greatly appreciated.

First, the draft guidance simply requires the applicant to **list** the items – not to develop stability indicating methods, set limits of detection, set limits of quantitation, and test for all such.

Obviously, the Agency expects the component manufacturer to know the compositional make-up and stability of the components that it manufactures for use in the manufacture of drug products.

However, as stated initially, this section only asks the applicant to list all such.

The real impact of an applicant's doing what is suggested would be to eliminate those vendors that cannot supply the requisite data from the applicant's approved vendors list.

"Additional clarification is needed for the following statement: 'All analytical procedures for excipients should be validated.' (Section KC. line 1062) Compendial procedures are well characterized, validated methods and generally should not require additional validation. Manufacturers however should ensure that these methods are appropriate for specific drug products. We propose that 'All' be deleted and 'appropriate' be added to the statement. The statement should be revised to read 'Analytical procedures for excipients should be validated, where appropriate.'"

Given the text which follows the quoted portion of **Line 1062**, "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," the definition of term "validated" used here includes "verified" when the analytical procedures are from recognized sources, it would be inappropriate to make the change suggested.

If alternate wording is needed, perhaps the Agency should consider the use of the phrase "*qualified under the actual conditions of use*" in place of the word "validated" with the understanding that the requirements for compendial and recognized procedures are less than for applicant-developed procedures.

"Comments Section:
Part III
IIIC - Line 265
Please change the following statement to read '*In some instances, the composition of distinct subformulations (e.g., cores, coating) of the drug product* may *be listed separately in the composition statement.*'"
"IIIC - Line 269
'In these cases, the composition of the immediate release and extended release portions of the drug product **may** *be listed separately.'* These changes are suggested to provide flexibility in the presentation of information. In some instances it may be more illustrative to include both subformulations in the same table."

Since this guidance presents suggestions and not requirements, there is no need and the commenters present no rationale to justify the change suggested.

Moreover, the text as proposed in the draft is rational and should facilitate the reviewer's assessment of the applicants' submissions.

Finally, provided they are listed separately, the guidance as written, does not specify separate tables, and the examples provided do not show the information in separate tables.

For all of the preceding reasons, this reviewer cannot support the changes recommended.

"IIIC - Line 358 (footnote 1)
'*Equivalent to 50, 100 and 150 mg, respectively on the anhydrous basis.*' Does this suggest that potency should be reported on an anhydrous basis? We request guidance regarding how potency should be reported, as free base/acid or salt form."

Lines 341 – 345 clearly address the reporting issue and, thus, no additional guidance is needed. .

"Part IV
IVA.1a - Line 394
'For example, if particle size is expected to influence the dissolution rate, drug product testing should be conducted to support the appropriateness of the test and acceptance criteria for the drug substance particle size distribution.' We recommend the following be added to the statement above 'Dose Volume term > 250 mL (BCS Category 2 and 4).' The statement should be revised to read '*For example, if particle size is expected to influence the dissolution rate* (Dose Volume term > 250 mL (BCS Category 2 and 4), *drug product testing should be conducted to support the appropriateness of the test and acceptance criteria for the drug substance particle size distribution.*'"

Knowing that particle size distribution, as well as other critical variable factors, may both directly and indirectly affect dissolution, this reviewer's inclination would be to suggest that particle-size distribution effects be established and documented for the particle size distribution's effect on batch-representative samples evaluated for drug-product uniformity and stability with respect to the observed sample, and projected batch, distribution of: **a)** the dosage unit's weights; **b)** the contents and specific contents of each active; **c)** the availability and rates of release of each active; **d)** the key impurities; and **e)**, in some cases, manufacturability.

"IVA.1b - Line 409
'The compatibility of the drug substance with the excipients used in the drug product should be discussed' if formulation stability data suggest potential incompatibility. The statement implies that formal excipient compatibility studies are required. Because excipient compatibility is often carried out as part of formulation selection studies, compatibility studies on drug substance and individual excipient should not be performed separately."

Contrary to the suggested wording change, the draft language is what should be suggested.

The applicant should discuss the compatibility of the drug substance even when the data clearly show that they are compatible.

Obviously, such discussions must be supported by appropriate studies.

Moreover, as written **"compatibility of the drug substances with the excipients"** (collectively), the guidance suggests for them to be studied together and <u>not</u> as inferred individually.

If the intent were to suggest individual testing, the language would have stated **"compatibility of the drug substances with"** each of **"the excipients used."**

"IVA.2 - Line 451
'An applicant **may wish** *to discuss the use of noncompendial-non-novel excipients with the appropriate review division prior to submitting its application to ascertain the level of information that would be warranted to support the use of the excipient.'*"

Given the Agency's goal of reducing the length of time between application submission and application approval, the **"is encouraged to"** language in the draft is more appropriate than the alternative proposed.

If any change is warranted, the phrase "**is encouraged to**" could be simply changed to "should" in keeping with the guidance's overriding goal of presenting the Agency's best thinking on how an applicant "**should**" go about preparing the Chemistry, Manufacturing, and Controls sections of an application.

"IVA.2 - Line 456
'See sections VI and XI C for additional guidance on the information that should be submitted to support the use of this type of excipient.' Please define the term non-novel (e.g. used in EU, listed in Inactive Ingredient Guide, etc.)."

The term "non-novel," as it applies to excipients used in drug product formulations, means *any excipient that has been previously used in one or more approved submissions for a drug product of the same type as the applicant is proposing.*

Obviously the complete set of terminology pairs for excipients is: **a)** compendial—non-novel, **b)** compendial—novel, **c)** noncompendial—non-novel and **d)** noncompendial—novel.

"IVC - Line 580
'A table should be provided that compares the equipment used to produce clinical batches that support efficacy or bioequivalence and primary stability batches to the equipment proposed for production batches.' The FDA has sought to simplify equipment comparisons and has issued guidance (e.g. SUPAC Equipment Addendum) to assist industry in describing smaller scale and production equipment in a manner that allows for rapid review and approval. Clarification is requested regarding whether a list of equipment, using the table format and terminology recommended in the SUPAC guidance is satisfactory."

Only in cases where the drug product proposed is covered by the "SUPAC Equipment Addendum" would it be appropriate to use the format and terminology recommended, provided that information provides all the information being requested.

"IVC - Line 580
Please change the statement to read, 'For equipment of different operating design or principle, *a table should be provided that compares the equipment used to produce clinical batches that support efficacy or bioequivalence and primary stability batches to the equipment proposed for production batches.*'"

Regardless of the apparent differences or lack thereof, the applicant should submit a table that compares the equipment used in the key submission batches specified to the equipment proposed for the production batches.

Notwithstanding the permissions conveyed by SUPAC, the applicant bears the burden of proving what they are proposing to do is similar enough to what has been done to ensure that there is little or no risk of significant drug-product uniformity changes between the equipment and scale that has been used and the equipment and scale that the applicant proposes to use for full-scale production.

This reviewer (having some experience with formulations ranging in scale from 0.75 cu. ft. [0.02 cu. m] to 175 cu. ft. [5 cu. m]) has been in several situations where a firm failed to recognize the negative impacts of scale on

materials and found that simply scaling up the production process, while "permitted," produced drug-product materials that failed to meet the drug product's in-process and/or release specification.

For all of the preceding reasons, this reviewer opposes the change proposed.

"IV.C. - Line 584

'*The table should identify (1) the identity (e.g., batch number) and use of the batches produced using the specified equipment (e.g., bioequivalence study batch # 1234), and (4) any significant equipment differences (e.g., different design, operating principle, size).*' Please include in this guidance a representative table of equipment similar to that provided in SUPAC Equipment Addendum. Alternatively, a cross reference should be provided."

Agree with the commenters that a detailed example table would be useful to include in the guidance.

Because it might mislead those whose products fall outside of SUPAC, the guidance should <u>not</u> cross reference the "SUPAC Equipment Addendum."

"IVD - Line 589

'*D. Container Closure System (P.2.4')* We recommend that the container-closure section be clarified and generalized into a broad outline of the information contained in FDA Guidance: Container-Closure Systems for Packaging Human Drugs and Biologics, followed by a reference to the FDA Guidance: Container-Closure Systems for Packaging Human Drugs and Biologics for more specific information."

"IVD - Line 596

For clarity, the following sentence should be revised to read, '*A brief description of the container closure systems listed in P. 7*' should be provided. Any special storage and transportation container closure systems that may be necessary for proteins or other environmentally sensitive drug products should also be provided."

"Part V

VA - Line 695

'*Addresses for foreign sites should be provided in comparable detail, and the name, address, and phone number of the U.S. agent for each foreign drug establishment, as required under 21 CFR 207.40(c), should be included.*' Maintaining accurate and current information in the NDA can be problematic. Please provide guidance whether Form FDA-2857 (Drug Listing Requirement) may be used alternately to provide the detailed information requested."

Maintaining accurate and current information in compliance with **21 CFR 207.40(c)** in any "CMC" document being prepared for submission can be problematic.

However, because: **a)** the applicant has more "control" (influence) over and interaction with the foreign firms it is proposing to reference in an application than the **FDA**; **b)** there is no assurance that the Form FDA-2857 data is up to date; and **c)** the applicant has the responsibility for submitting accurate

information, it would inappropriate to suggest that an applicant can rely on the information in the Form FDA-2857 database.

Of course, an applicant is free to use this approach when the firm is certain that the foreign site maintains an accurate and up-to-date Form FDA-2857 that provides all of the information requested by the Agency.

"VA-Line710

'*To facilitate pre-approval inspection related activities, it is recommended that the name, telephone, fax number and e-mail address of a contact person be provided for each site listed in the application.*' See comment to Line 695."

Please see this reviewer's comments to the prior entry.

"VB - Line 748

The section '*Reference to Quality Standards*' is redundant as this information is already provided in lines 304 through 315 of the draft guidance."

The commenters are correct, but no point is made as to what action, if any, the commenters' think should be taken to address this redundancy.

Perhaps, the commenters' concerns could be addressed by replacing the wording in the second instance with a reference to the first instance such as:

"The suggested information for reporting in this section is the same as the guidance provided in the corresponding text in Section III. C. under the same heading, '• Reference to Quality Standards.'"

"VC - Line 824

'*A statement should be provided that ruminant-derived materials from bovine spongiform encephalopathy (BSE) countries as defined by the U.S. Department of Agriculture (9 CFR 94.1 I) are not used or manipulated in the same facility.*' This information should be provided in Section XII, Regional Information."

This reviewer thinks that the inclusion of the simple statement quoted is appropriate where it is.

However, the guidance should be modified to provide a section in Section XII that spells out, for each referenced site, exactly how the site ensures compliance with the commitment made in Section V. C.

VC.2 - Line 849

"*Steps in the process should have the appropriate process controls identified. Associated numeric values can be presented as an expected range. All* **critical** *process controls should be included in the description of the manufacturing process (MPR or narrative).*"

The revision in the language suggested would place the guidance at odds with the requirements for process controls set forth in 21 CFR 211.110 and 211.160, and the other areas of 21 CFR 210 and 211 that mandate controls.

Therefore, the guidance should remain as drafted, **"All process controls, critical or otherwise, should be included in the description of the manufacturing process (MPR or narrative)."**

"Part VI

VI - Line 9136

'The P.4.1 to P.4.4 information for each individual excipient should be grouped together in the application.' For greater document clarity, we propose a flexible approach that minimizes information redundancy by permitting information common to excipients to be grouped together."

Since the guidance is only that – guidance, each firm is free to follow an alternative provided it implementation satisfies all of the applicable **CGMP** requirements.

However, for the comment to have meaning, the commenters need to have spelled out their approach in some detail.

On that basis, this undefined alternative "flexible approach" should not be substituted for the one spelled out in the draft.

"VIA - Line 1022

'In addition to listing all the tests for an excipient, the specification should identify the tests that the drug product manufacturer will routinely perform and the test results that will be accepted from the excipient manufacturer s certificate of analysis (CofA).' We would greatly appreciate clarification regarding the impact of this statement on reduced testing/vendor qualification. Would the filing of a Supplement be required to change testing agreements between the excipient manufacturer and the drug product manufacturer?"

Some type of notification is required in all cases (minimally, as a "changes effected" section in the firm's next "annual review" report for the drug product).

In cases where the drug product manufacturer is implementing a major reduction in the level of routine testing performed, a "changes effective" supplement might be needed.

For "narrow therapeutic range" and sterile drugs, the drug-product manufacture may, in some cases, need to file a "pre-approval" supplement and wait for the Agency to approve it.

In all cases, a call to the local district should clarify what the approved application holder needs to do.

"VIC - Line: 1062

'All analytical procedures for excipients should be validated.' Please note that most compendia1 methods are well characterized and consequently do not require validation. We request that the statement be clarified to reemphasize this fact."

As stated in the review of the General Comments that brought up this very point, the statement is what should be said since the guidance provided clearly indicates that "complete validation" is not needed for analytical procedures methods that are from those published by bodies recognized by the FDA provided the recognized analytical procedure is used without any modification – such "**only require verification under actual conditions of use.**"

"VID - Line: 1089

'A certificate of analysis (COA) from the manufacturer and the test results for the same batch from the drug product manufacturer should be provided for the components described in P.4. The information should be for the materials used to produce the batch described in the executed production record (R.1.P).' We request that the last sentence be changed to 'The information should be for a representative batch of the material showing conformance to

the specification (P.4.1).' Results of tests on the components of EPRs will be included in section R.I.P, as stated in the draft guideline."

This reviewer sees the logic in suggesting the information provided here **"should be for the materials used to produce the batch described in the executed production record"** and NOT just from some "representative batch of the material" as the commenters propose.

The rational goal of this guidance is to ensure that the manufacturer fully characterizes the materials used in the key batches submitted in support of an application.

Therefore, this reviewer sees compelling reasons for retaining the language in the draft guidance.

"VID - Line 1093

'*Use of terms such as conforms or meets specification is discouraged.*' We suggest that this paragraph be removed as it is stated in R.I.P Part VII."

Rather than removing it, this reviewer continues to recommend changing it to **"Use of terms such as conforms or meets specification is proscribed,"** but accepts that the current language is probably adequate.

"VIIA - Line 1147

The following sentence should be revised to include "and/or". The sentence should read as follows: '*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/or** *tests with sunset...*'"

"VIIA -Line 1167

'*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 and justification.*' Please provide further information regarding what FDA would consider sufficient data and justification to support a periodic quality indicator test."

"VII A- Line 1194

'*For example, justification for a PQIT would be* **more** *likely for the oral dosage form then for a biological or biotechnology-derived parenteral drug product.*'"

The proposed change improves the grammatical correctness of the statement being made and should be adopted.

"VIID -Line 1288

'*Batch analysis data should be provided for all batches used for clinical efficacy and safety, bioavailability, bioequivalence, and primary stability studies.*' This requirement may be redundant if certificates of analysis are provided in other sections of the NDA. The sentence should be revised to read "Batch analysis data should be provided (or cross reference provided to this data in another NDA section) for all batches used for clinical efficacy and safety, bioavailability, bioequivalence, and primary stability studies."

While this reviewer agrees with the need to revise this sentence along the lines presented, the review suggests the revised language should be:

"**Batch analysis data should be provided** here (or a cross reference should be provided to this data when all of it has already been reported in another part of the CMC section of an application) **for all batches used for clinical efficacy and safety, bioavailability, bioequivalence, and primary stability studies.**"

"VIID -Line 1289
'*Batch analysis data should also be provided for any other batches that are being used to establish or justify specification and/or evaluate consistency in manufacturing.*' We feel that this statement is also redundant as this is provided in Control of Drug Product, Specifications (VII. A.)"

If the commenters' statement is true, then the proper course is to change this sentence in a manner similar to that used in the previous comment.

Therefore, this reviewer would suggest the following:

"**Batch analysis data should be provided** here (or a cross reference should be provided to this data when it has already been reported in another part of the CMC section of an application) **for any other batches that are being used to establish or justify specification and/or evaluate consistency in manufacturing.**"

"VIID - Line 1288
'Batch analysis data **may** be provided for all batches used for clinical efficacy and safety, bioavailability, bioequivalence, and primary stability studies.'"

The reviewer disagrees with this substitution of "may" for "should" in the guidance and supports the use of the draft language as originally drafted.

The application reviewer needs the batch analysis data from all batches used for clinical efficacy and safety, bioavailability, bioequivalence, and primary stability studies to judge whether or not the drug product meets the expected standards of safety and efficacy as well as whether or not, the production process and controls conform to all of the requirements of applicable **CGMP** regulations.

"VIID -Line 1291
'The batch analysis reports (e.g., COAs) and collated batch analyses data should include a description of the batches.' This should not be necessary if the data is tabulated. Does this mean that COAs are required for all of the aforementioned batches?"

Given the nature of the information that the Agency expects to find in the "description of the batch" (**Lines 1294-1305**), the provision of this information is necessary regardless of whether or not the data is collated.

Contrary to the commenters' inference of a requirement for "COAs," the need is for the listed information that identifies the batch; COAs are only suggested as an example ("e.g.") not as what is meant ("i.e.").

On this basis, the requested information should be provided and the language in the draft for this part of the guidance should be kept as it is.

VIID.1 -Line 1311
'*Batch Analysis*' We recommend that the requirements in this section be deleted. The information requested is extensive and would typically be included in IND amendments. Only information required to support the NDA specification should be included in the NDA.

Again the commenters mistake the scope of the proposed guidance and acts as if it only addresses NDA applications.

Since it addresses both NDA and ANDA applications, and there is a justified need for the reporting of the requested information in the application (if nothing else, it facilitates the application's review), the requirements of this section need to be kept as they are.

The little additional effort required by today's NDA filer to transfer the information from electronic files in an IND to the NDA application is more than offset by the decrease in review time that the application reviewer must expend in searching through disparate documents to find the information that he or she is seeking.

"VIID.1 -Line 1317
'*A summary of any change in the analytical procedures should be provided if the analytical procedure (1) change over the course of generating the batch analysis data and/or (2) are different from the analytical procedure included in P.5.2.*' We believe this is also redundant as the historical information about the analytical procedures is captured in the stability section (X.C.). We feel that the requirement of a summary of changes is unduly burdensome. If the principle of the assay changes (titration versus HPLC) then this should be included, but minor changes (mobile phase and chromatographic conditions) need not be reported."

Contrary to what the commenters assert, not all of the historical information about all test procedures is captured in X. C.

Moreover, the generation and inclusion of a summary of the changes, if any, in this section of the CMC again facilitates the review process.

Since the applicant's method history section of SOP or Work Instruction for each method used should contain this information, incorporating the requested information into the application is not "unduly burdensome."

For all of the preceding reasons, this reviewer recommends that the draft language be retained.

"VIID.2 - Line 1332

'However, collated data should be provided for **at least** assay and impurities *(e.g., degradation products, residual solvents) and should be considered for other tests* ~~such as water content~~ **dependent on the dosage form**. "

This reviewer sees no need for the addition of the phrase "**at least**" and frankly does not understand what is the intended meaning of the phrase "**dependent** (, depending?) **on the dosage form**" in the context that it appears.

This reviewer therefore recommends that the draft's language be retained.

"VIIF -Line 1371

'Attempts should be made to identify all degradation products found at significant levels in the drug product.' Please provide clarification regarding what is meant by *'significant levels.'*"

While this reviewer supports the need for a definition of the term "significant levels," he believes that this is a complex issue that should be addressed by the applicant in his or her discussions with the Agency.

The answer will obviously be influenced by the nature of the drug product and its route of administration as well as by the toxicity (acute and short-term chronic) of the degradants in question.

For example if administering 0.1 micrograms/kg of a given degradants' fraction to the mouse in an acute toxicity study kills all of the test subjects, knowing what the degradants are and controlling them become critical issues – in such cases, the appropriate "significant level" may be 0.0001 % by weight or less.

This is the case because the degradants fraction is very toxic.

On the other hand, if a 1 mg/kg 30-day chronic toxicity study in the mouse and the hamster shows no evidence of adverse effect, the degradants information is less crucial and the ICH API guidance limit of 0.1 % by weight may be an appropriate "significant level" threshold

"IX Line - 1539

'If an NDA is submitted for a new plastic that will be used for blood component storage, adequate information on the plastic should be submitted, including the composition of the plastic.' We recommend that specifications also be included for blood component container-closures."

This reviewer believes that the commenters' concerns can be addressed by revising the language beginning at **Line 1539** to read:

> "If an NDA is submitted for a new" material "that will be used" in a "blood component storage" system, "adequate information on the" material "should be submitted, including the composition of the" material.

After all, though new plastics head today's concerns in the blood component area, in the future some other material or material class may be introduced that would raise similar concerns.

"XIIIA. 1 - Line 1799

'*For NDA submissions, an EPR for a batch manufactured on at least a pilot scale should be submitted.*' We recommend that "In cases of multiple strengths, one batch per strength should be sufficient for submission" be added to the above statement. The statement should be revised to read, "For NDA submissions, an EPR for a batch manufactured on at least a pilot scale should be submitted. In cases of multiple strengths, one batch per strength should be sufficient for submission."

This reviewer does not object to the suggested addition but feels that is not crucial because of the language (in **Lines 1800 – 1803**) that follows the line the commenters addressed, **"In cases where clinical batches used in Phase III trials were less than pilot scale, submission of the EPR for the largest scale clinical batch is also recommended. Discussion of which EPRs should be included in the NDA can be a topic at pre-NDA meetings,"** clearly indicates that applicant and the Agency should agree on the nature and number of EPRs that an applicant should submit before the application is submitted.

A REVIEW OF FORMAL COMMENTS TO PUBLIC DOCKET 02D-0526

GlaxoSmithKline's Submission Posted June 26, 2003
To Docket 02D-0526: "C-12"

[**Note:** The original comments are quoted in a condensed font (Perpetua), the quotes directly from the draft guidance are quoted in a stylized font (Lydian) and this reviewers comments are in a publishers font (News Gothic MT) to make it easier for the reader to differentiate the "speaker" in the various text passages that follow.]

The overall impression that these comments convey is that the commenters are reacting in a combative manner to the guidance proposed.

Time and time again the word "escalation" is used.

Repeatedly, demands are made for the Agency to provide additional guidance or information or lists.

The commenters also frequently cast their remarks in terms of what the commenters will do – not in terms of what the commenters think should be required of applicants in general.

On the positive side, the commenters provide considerable impetus to a restructuring of certain sections to make them more compatible with the formats mandated in a CTD format that has been adopted by the EU.

With the preceding in mind, let us consider the specific comments provided by the commenters.

"III. DESCRIPTION AND COMPOSITION OF THE DRUG PRODUCT (P.1)
A. Description of Dosage Form
We recommend a standardized list of dosage forms be provided by FDA. The list should be aligned with European Pharmacopoeia1 Standard terms. (Lines 244-245)"

While this reviewer is all for the use of standardized terms, the industry and not the **FDA** should develop the list and, as in the **EU**, the **USP** is the appropriate place where such should be established.

Since the **EP** has such a list it should be easy to get the **USP** and the **JP** to **a)** use the **EP** list as the basis and **b)** agree upon common language definitions of such.

In the interim, an applicant is certainly free to use the **EP** text as a part of its description of the dosage form.

"C. Composition Statement
By first intent, the Drug Master File (DMF) and qualitative information should be referenced. If it is not available, quantitative information will be provided. (Lines 289-296)"

Though the comment is somewhat cryptic, the commenters seem to be saying that the DMF option should have been presented first.

However, the commenters do agree that when "it is not available, quantitative information" should "be provided."

If this is the case, then there is no need to change the draft text because it presents both options.

"IV. PHARMACEUTICAL DEVELOPMENT (P.2)

A.2. Excipients (P.2.1.2)
An updated list of known excipients from FDA is needed, because a company would only have information on its own products. The inactive ingredient list (published by the FDA) should be updated on a regular basis. (Lines 460-466)"

Though the FDA may need to update its excipient list more frequently, the Agency could assist applicants if it were to include the maximum approved level for each excipient in each drug-product type in which that excipient has been used.

"An updated list of known agents that impart pharmacological activity is needed from FDA. (Lines 468-483)"

While an updated list may be needed, this reviewer thinks that the pharmaceutical industry and academia are better equipped to generate the needed list than the **FDA**.

If an updated list is needed, then the industry should submit all instances where they have observed such to the **USP** for publication in an informational monograph therein.

However, *no matter what the list states*, the applicants should still test their formulations for this effect because the formulation may be using: **a)** an ingredient not on the list that imparts pharmacological activity in the formulation they have developed or **b)** an ingredient on the list in a "novel" manner such that ingredient may have a previously unrecognized pharmacological effect.

"B.1. Formulation Development (P.2.2.1)
Clarity is needed about the special features of drug product discussed. (Lines 507-5 12)"

Again, the comment is too cryptic to convey what specifically are the concerns that the commenters have about the special features guidance.

"B.1. Overages (P.2.2.2)
The last sentence is too constraining. It should be changed to 'Use of an overage to compensate for degradation must be justified by data on the basic stability of the drug substance and data on drug product manufacture and stability. Information must also be provided demonstrating that the excess active ingredient added to compensate for instability does not compromise safety nor efficacy of the medication and that the level of degradation products associated with the need for an overage do not pose safety nor tolerability issues.' (Lines 537-539)"

This reviewer agrees with the commenters' suggestion and supports the language proposed.

This is the case because: **a)** permits overages of actives to compensate for degradation losses and **b)** spells out what an applicant needs to provide to in the application whenever the applicant proposes to add an overage to offset degradation of the active in production of the drug product and/or over the drug product's proposed expiration dating period.

"B.3. Physicochemical and Biological Properties (P.2.2.3)

More clarity is needed relative to establishing a relationship between biobatches and in vitro release (dissolution) testing. (Lines 543-550)"

What the commenters seem to be requesting here is for the Agency to include in the guidance some explicit suggestion that the applicant should link the performance of the biobatches to the in vitro release testing obtained for the test used.

Given that bioequivalence batches are associated with ANDA applications where the in vitro release testing (Dissolution or Drug Release) has long been established in an official compendial monograph, the applicant usually has little flexibility in adjusting the in vitro release test.

Since this link is often tenuous, this reviewer sees no need to suggest that, in general, the data for such be interpreted by some esoteric comparison to the performance of the biobatches tested.

"We agree, as these seem scientifically reasonable, that 1) the drug substance concentration in the drug product should be compared to the solubility of the least soluble solid state form and 2) when the drug load is close to saturation, the solid state forms of the drug substance that can crystallize from the drug product vehicle should be discussed. (Lines 552-556)"

"C. Manufacturing Process Development (P.2.3)
Only equipment specified as part of critical step(s) should be defined by its basic operating principle. The additional level of detail should be handled during a pre-approval inspection (PAI) or a Good Manufacturing Practices (GMP) inspection. (Lines 580-587)"

This reviewer disagrees and thinks that all design differences should be provided to the application's reviewer in the submission.

The guidance only requests that the "operating principle" differences be reported not that the operating principle be reported for all.

In general, submissions in an application can be used to evaluate **a)** the applicant's understanding of the **CGMP** requirements requested for equipment and **b)** the applicant's approach to compliance.

The inspectional process (PAI and GMP) is designed how well the applicant's performance in manufacturing complies with CGMP.

Moreover, the **FDA** inspectorate uses a copy of the CMC section of an application to plan its PAI inspection.

The less clear the CMC section is the more likely it is that **a)** the length of the inspection will increase and/or **b)** Agency resources will be less than optimally deployed.

This reviewer knows that the requested information should be provided and that providing it should speed up the overall application review process.

"F. Compatability (P.2.6)
Clarity is needed for which dosage forms to which this should be applied. This needs to be tied to label use; not off-label use of the drug product. (Lines 655-666)"

Since all dosage forms have compatibility issues that should be addressed, this reviewer does not know what facets of the guidance provided that the commenters think need to be clarified.

The commenters' remark, "not to off-label use of the drug product," seems to tie to the draft guidance's suggestion that the applicant should supply compatibility information for the drug product proposed in the application "with likely coadministered drug products."

Given the language in the draft guidance, this reviewer see no need to add verbiage to deal with compatibility studies with a coadministered drug product being used in an off-label manner.

Based on the preceding, there is no compelling reason to modify the referenced language in the draft guidance.

"V. MANUFACTURE (P.3)
A. Manufacturer(s) (P.3.1)
This information should be put in the Establishment Information (in Module 1). As is, this reduces the reusability of this module for Common Technical Document (CTD) submissions. (Lines 685-708)

The information requested should be provided as requested because it is needed by the Office of Compliance (which usually only receives a copy of the CMC section of an application) for identifying the sites and the inspections needed for the sites specified in the application.

For that reason alone, the draft text in this area should remain as it is.

"Batch Formula (P.3.2)
Clarity is needed as to how this relates to the ± 10% range that is assumed is acceptable variability following GMP. The concern is that this may apply to film coating quantities that are specified as ranges (since an exact quantity is not practical). The agency should clarify how this guidance on ranges applies to processing agents/solvents that may change during granulation, for example. (Lines 745-746)"

Nowhere in the CGMP regulations is there any permission for any given level of variability much less a 10 % range.

Each applicant is supposed to develop a formulation and justify the variability that is allowed about the target value in the formulation.

For example, applicants have and can easily justify film coat limits that range from the target minus 20 % up to target plus 50 % for a film "seal" coat (containing no a) color, b) active or c) release control ingredient) that is used to seal the surface for inking.

As with other guidance, how it applies depends upon the exact instance and, in general, an applicant can establish whatever ranges the science, practical limitations of the production process used, and the controls permit provided the tolerances set are set based on sound science and produce CGMP-compliant batches.

Since no manufacturing process produces units with "0" tolerances, practically, all have ranges.

From the point of view of quality and CGMP compliance, the ranges established should be as narrow as production limitations permit when the factor can adversely affect the critical variable properties of the drug product.

In any case, the applicant must establish the ranges allowed and justify the ranges set in the application.

"C. Description of Manufacturing Process and Process Controls (P.3.3)
Replace the phrase 'the material might be held for a period of time prior to the next step' with 'including holding times as appropriate for the product and manufacturing process.' (Lines 787-796)."

Given that CGMP requires the holding of in-process batches (21 CFR 211.110(c) **In-process materials shall be tested for identity, strength, quality, and purity as appropriate, and approved or rejected by the quality control unit, during the production process, e.g., at commencement or completion of significant phases or after storage for long periods**) until approved for further processing by the quality control unit (QCU), most process are non-continuous.

What seems to be meant is, therefore, "might be held an extended period of time prior to the next step."

Similarly, the word "noncontinuous" should be replaced with the word "discontinuous."

With all of the preceding in mind, this reviewer would suggest that **Lines 790 – 793** be revised to:

- **each manufacturing step with identification of the critical steps and any manufacturing step where, once the step is completed, the material might be held for an extended period of time (i.e., discontinuous process) before the next processing step is performed**

"Comments related to the statement in the guidance "A statement should be provided that ruminant-derived materials from bovine spongiform encephalopathy (BSE) countries as defined by the US Department of Agriculture (9CFR 94.11) are not used or manipulated in the same facility." follow: (Lines 824 -830)

1) This appears to be an issue that would more typically be addressed through GMP inspection rather than within the NDA as it relates to site quality practices and procedures, which are not product specific.

2) If FDA insists that such information be presented in the NDA, further clarity, is needed regarding the typical expectations for new chemical entity (NCE) products as compared to biologics and biotech products.

3) If FDA insist on provision of this information for NCE products, they must qualify their requirements with suitable exemptions for low risk materials such as milk derivatives, tallow derivatives, gelatin, etc., as reflected in the CDER guidance on sourcing and processing of gelatin, provided certain measures are taken, it is acceptable to use animals that have resided in BSE countries in the production of gelatin. Similar guidance is required for other such low risk materials i.e. tallow derivatives, milk derivatives, etc.

The commenters raise some issues that the Agency may need to address as it revises the initial draft and, where indicated, deal with the issues raised.

However, the information requested is a simple declaration and, as such, seems to be a reasonable compromise given the lack of detailed guidance that the commenters think is needed.

"D. Controls of Critical Steps and Intermediates (P.3.4)
The company should have flexibility to determine which batches are included for giving data that support the process. These would not necessarily have to be batches for which full batch analysis data according to specification are given, or for items that would be more appropriate in P.5.4, e.g., (a) portion(s) of a batch may be used to establish mixing times. (Lines 927-929)"

Since the FDA is only providing guidance, the company does maintain the "flexibility to determine which batches are included for giving data that support the process."

In cases where a firm wants to provide analysis data from different batches than those in the guidance, the firm should discuss their decision with their local FDA office and work out an acceptable set to supply and submit that set along with the justification that establishes that the set submitted is as informative as the suggested set.

Finally, since the commenters did <u>not</u> suggest alternative wording, the current language should be retained.

"VI. CONTROL OF EXCIPIENTS (P.4)
For non-novel, non-critical excipients (i.e. excipients which do not have a major impact on the quality or safety of the finished product), this escalation is unwarranted. FDA will have ample opportunity to review the rationale and justification for reduced testing and/or substitution of analytical methods during a PAI or a routine GMP inspection. (Lines 977-1004)

Clarification of information on pharmaceutical proprietary mixtures (filmcoats and flavors) is needed.
A. Specifications (P.4.1)
For non-novel, non-critical excipients (i.e. excipients which do not have a major impact on the quality or safety of the finished product), this escalation is unwarranted. FDA will have ample opportunity to review the rationale and justification for reduced testing and/or substitution of analytical methods during a PA1 or a routine GMP inspection.

It is unclear why information on the quality control (specification, analytical methods, validation and justification of specifications) of novel excipients should not be presented in sections P.4.1 -P.4.4 along with other excipients. Other manufacturing and controls information logically resides in P4.6 and A.3, but it would seem sensible to keep all excipient specs and methods etc in one place.

It is assumed that composition and DMF references etc. for proprietary mixtures should be given in P.4.1 with methods in P.4.2 etc. Clarity would be helpful."

Other than to suggest that the requested information should be reported in different sections and/or to complain that there is no need for the additional information requested, the commenters do <u>not</u> suggest an alternative.

Based on this, the guidance should continue to include these requests <u>with</u> some consideration for relocating the text as the commenters suggest.

"B. Analytical Procedures (P.4.2)
For non-novel, non-critical excipients (i.e. excipients which do not have a major impact on the quality or safety of the finished product), this escalation is unwarranted. FDA will have ample opportunity to

review the rationale and justification for reduced testing and/or substitution of analytical methods during a PAI or a routine GMP inspection.

It is unclear why information on the quality control (specification, analytical methods, validation and justification of specifications) of novel excipients should not be presented in sections P.4.1-P.4.4 along with other excipients. Other manufacturing and controls information logically resides in P.4.6 and A.3, but it would seem sensible to keep all excipient specifications and methods etc in one place.

It is assumed that composition and DMF references etc. for proprietary mixtures should be given in P4.1 with methods in P4.2 etc. Clarity would be helpful."

Again, other than to suggest that the requested information should be reported in different sections and/or to complain that there is no need for the additional information requested, the commenters do not suggest alternatives or present a regulation or science-based rationale for the commenters' position.

Based on the preceding and the observations made in the prior reviews, the language in the guidance should be kept as it is in the draft guidance with some consideration for relocation as the commenters suggest.

"C. Validation of Analytical Procedures (P.4.3)

For non-novel, non-critical excipients (i.e. excipients which do not have a major impact on the quality or safety of the finished product), this escalation is unwarranted. FDA will have ample opportunity to review the rationale and justification for reduced testing and/or substitution of analytical methods during a PA1 or a routine GMP inspection.

It is unclear why information on the quality control (specification, analytical methods, validation and justification of specifications) of novel excipients should not be presented in sections P.4.1-P.4.4 along with other excipients. Other manufacturing and controls information logically resides in P.4.6 and A.3, but it would seem sensible to keep all excipient specifications and methods etc in one place.

It is assumed that composition and DMF references etc. for proprietary mixtures should be given in P.4.1 with methods in P.4.2 etc. Clarity would be helpful.

As was the case in the prior two sections, other than to suggest that the requested information should be reported in different sections and to complain that there is no need for the additional information requested, the commenters do not suggest alternatives or present a regulation- or science- based rationale for the commenter's position.

Based on the preceding and the observations made in the prior reviews, the language in the guidance should be kept as it is in this draft guidance with some consideration for the relocation that the commenters request.

"D. Justification of Specifications (P.4.4)
As stated above, the requirement to provide information to justify the use of reduced testing regimes for standard excipients is excessive. (Lines 1089- 1094)

Without providing any science-based or regulation-based rationale to omit the requested information, the commenters again object to the request for information that demonstrates that the CMC section demonstrates compliance with clear requirements of the CGMP regulations governing drugs.

Based on the preceding and observations made in the prior reviews, the language in the guidance should be kept as it is in this draft guidance

"E. Excipients of Human or Animal Origin (P.4.5)
Further clarity is required from FDA as to the extent of information that must be presented for NCE products as compared to biologics and biotech products. (Lines 1102-1104)"

This reviewer sees no such need to clarify a simple request for a declaration concerning the source of said excipients.

"Should FDA require information regarding the risk of transmission of TSE agents via the use of ruminant derived materials in the manufacture of NCE products, further guidance is required from FDA regarding appropriate sourcing and processing criteria. Currently, guidance is only available for gelatin for pharmaceutical use and is not available for other low risk materials such as milk and tallow derivatives etc."

Lines 1108 — 1111 state: **"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. Details of the control strategy and the rationale for the controls should be provided in A.2."**

Clearly, the FDA has limited its requests to information on: a) the identity of potential adventitious agents; b) the practices used to control for the potential adventitious agents identified.

Recognizing that information on the risk of transmission of any adventitious is difficult to generate, the Agency has focused upon ensuring that the applicant has recognized the potential adventitious agents and adopted scientifically sound and appropriate controls to reduce the risk of transmission and identify when transmission has occurred.

"F. Novel Excipients (P.4.6)
Instead of US only, consideration should be given to those excipients with approval in well-regulated markets. (Lines 1118-1 119)

The rationale for including the specification for novel excipients in this section and all other details, including analytical methods, validation of analytical methods and justification of specification in Appendix A.3 is unclear. Rather than fragment basic information (specification, methods etc) regarding quality control of excipients over three sections, it is suggested that such details be presented in sections P.4.1 - P.4.4 for all classes of excipients."

Because of the restrictions placed on the FDA by the FDC Act, the FDA can only consider excipients from the point of their first use in the United States.

Therefore, the FDA rightly treats any excipient that has not been previously used in any FDA-approved application or in an FDA-approved application for the route of administration proposed in an application as a novel excipient.

If such novel excipients have been used that have "approval in well-regulated markets, then much of the requested data to be submitted may be derived from scientifically sound and appropriate studies done in those countries provided the meet FDA standards.

Again, consideration should be given to restructuring the guidance in the manner suggested by the commenters.

"VII. CONTROL OF DRUG PRODUCT (P.5)
A. Specification(s) (P.5.1)
We recommend that method numbers are listed in a separate table so as to support CTD (Lines 1144-1146)"

"The acceptance criteria for the description should not be as prescriptive to give exact measurements (of the tablet). (Line 1174)"

Again, the commenters object to the example provided for the information requested, but the commenters do not provide any detailed alternative.

Remembering that this is guidance, nothing prevents an applicant for incorporating ranges into the tables.

For an example, the commenters are directed to the alternative proposed in formal comments submitted to this docket in May of 2003 ("C-01").

• "Periodic Quality Indicator Tests
Clarification is needed, as PQIT is not well defined. In creating a number of different analytical information sheets/tables, the information supplied makes the submission more complex. This information seems to "muddy" the issue of what is needed for a 'non-routine' test (recommend an option to footnote the specification) and why. The justification of these non-routine tests should be provided in the justification of specification section. Inclusion of this information will make the module not usable in other regions. (Lines 1178- 1235)

A. Batch Analyses (P.5.4)
The batch information for tests performed that are not a part of the specification (content uniformity, microbiological testing, etc.) should be presented in a more relevant section (manufacturing process development or validation), but not here because not directly relevant to the proposed specification. (Lines 1313- 13 15)"

The commenters' remarks on guidance organization should be considered by the Agency as it proceeds from draft to final guidance.

"The text should be changed to the following. "A detailed summary of any changes (when the change occurred, differences between old and new methods, impact of significant differences between methods on the data) may be provided, as appropriate" (Lines 13 17-1322).

This reviewer thinks that the existing language, "A summary of any changes in the analytical procedures should be provided if the analytical procedures (1) changed over the course of generating the batch analyses data and/or (2) are different from the analytical procedure included in P.5.2," should be retained.

There is no compelling need and the commenters have not presented any rationale for reducing a request for needed information to less than a request.

The FDA's guidance is only asking for information that it needs to ensure that the application provides evidence of CGMP compliance in all areas governed thereby.

2. Collated Batch Analyses Data 1328
1329
Presentation of results from all batches for a particular test in tabular and/or graphical
1330 format is often helpful in justifying the acceptance criteria.

"Clarification of the text is needed. The text states that judgement is allowed for inclusion of data then contradicts itself by stating specific data to be included. (Lines 1330- 1334)"

Contrary to the commenters' statement, the cited text range (Lines 1330 – 1334):

> "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."

does not contradict itself.

It does not mention judgment, it talks of test data that the agency needs in all cases and others that should be considered for inclusion in the application.

"Collated data in this section is excessive as the information for relevant information can be found in the batch analysis tables. (Lines 1332-1334)"

While the commenters are correct that the "relevant information can be found in the batch analysis tables," the commenters ignore the reality that tabulating the data facilitates the review process and properly collating the data should further facilitate the review process.

Because it eliminates the time that the application reviewer would spend in collating the data in the manner suggested, this is one of the suggestions in the guidance that will directly benefit those firms who submit applications that comply with this request.

"B. Characterization of Impurities (P.5.5)
The information that is needed is not clear; therefore clarify what is needed. This section needs to address typical and/or identified formulation related (i.e. product specific) impurities that may not be covered by cross-reference to the drug substance section.

However, discussion on qualified levels is best placed in the product justification of specifications section. (Lines 1343- 135 1)

Cross-reference should ONLY be to non-clinical sections (at a high level). This section should be in the justification of specification section, where reference to qualification of impurities and relevant studies are discussed. (Lines 1349- 135 1 and 1379- 1382)

Change opening sentence of paragraph to 'Summary information on the characterization. .' (Lines 1362-1363)"

The commenters' suggested clarifications for "typical and/or identified formulation related (i.e. product specific) impurities that may not be covered by cross-reference to the drug substance section," are well taken.

The Agency may also want to consider placing the requested information as the commenters suggest.

However, this reviewer thinks that the requested cross reference should be as suggested in the draft – to the study and study number.

"F. Justification of Specification(s) (P.5.6)
Use of jargon terminology (sunset test) should be avoided. Replace with definitive text or provide a definition of the term. (Lines 1456-1465)

This reviewer agrees with the commenters and suggests that the **FDA** define the phrase "**sunset test.**"

1X. CONTAINER CLOSURE SYSTEM (P.7)
This information needs to be located ONLY in Section.P.2.4, not here. (Lines 1536-1537)

This reviewer is all for non-duplicative submissions unless the duplication facilitates the review of the application.

The Agency should consider the commenters' remark in that light and proceed based on the Agency's assessment of the possible facilitation of the application review process that this comment present.

"XI. APPENDICES (A)
A. Facilities and Equipment (A.l)
The guidance on facilities and equipment requires extensive clarification, especially with regard to the requirements related to the potential for cross-contamination with viral and non-viral adventitious agents. The original M4Q guidance stated clearly that facilities and equipment information was required for biologic and biotech products only and the FDA guidance appears to have ignored this distinction. While materials of human or animal origin are used in the manufacture of NCE products, the risks associated with their use are generally accepted to be low, by virtue of the types of materials typically used, the processing, applied to them, and the eventual route of administration. While it is not suggested that companies should ignore the possibility of direct or indirect (via cross-contamination) transmission of viral

and non-viral agents via NCE products, it is suggested that the level of risk is such that this may be managed through GMP rather than registration activity. (Lines 1638-1678)"

As the commenters correctly point out, the **FDA** has correctly chosen to ignore the guidance in M4Q because materials of human and animal origin are currently used in the manufacture of NCEs.

Moreover, the increasing ease with which animals and plants can be genetically manipulated to make NCEs, this problem will only increase.

Though the risks may be low, the applicants for drug products that made from such should provide the information requested.

Based on the preceding it is clear that the requested information is needed by the applicant reviewer to assess drug-product safety.

As with many Agency activities, registration has a CGMP component that needs to be both clearly recognized and appropriately addressed.

"B. Adventitious Agents Safety Evaluation (A.2)
As with A. 1, the guidance in this section requires extensive clarification, as there is no clear distinction made between the requirements for NCE and biotech/biologics. (Lines 1682- 1742)"

This reviewer doesn_ot think that this guidance should make, what the commenters admit in their previous remarks, are artificial distinctions between NCEs and biotech/biologics.

"C. Excipients

- Novel Excipients

For non-novel, non-critical excipients (i.e. excipients which do not have a major impact on the quality or safety of the finished product), this escalation is unwarranted. FDA will have ample opportunity to review the rationale and justification for reduced testing and/or substitution of analytical methods during a PAI or a routine GMP inspection. (Lines 1753-1755)"

As this reviewer has stated in previous reviews, the CGMP regulations cover all and the FDA needs to collect supporting data on all in order to gather sufficient information and (via appropriate PIA inspections) documented evidence to indicate that the applicant's application demonstrates that the applicant probably does fully comply with the CGMP requirements BEFORE approving the firm's application.

Thus, requesting this information is definitely warranted.

"XII. REGIONAL INFORMATION (R)
A. Executed Production Records (R.1.P)
The amount of information requested is excessive. This information can be addressed during PA1 or GMP inspections. (Lines 18 17- 18 19)"

Again (see the preceding comment), this reviewer disagrees with the assertion that the requested information is excessive and would again remind the commenters that this information is needed by the Agency if it is to plan effective PAI inspections in support of an application that is under review.

"ATTACHMENT 1
Rheology
Add the end of the section add this statement. 'If rheological measurements are inappropriate for control of consistency or viscosity, the reasons for lack of such control should be listed.' (Line 1900)"

A Review of Formal Comments To Public Docket 02D-0526

Novartis Pharmaceutical Corporation's Submission Posted June 26, 2003 To Docket 02D-0526: "C-11"

[**Note:** The original comments are quoted in a condensed font (Perpetua), the quotes directly from the draft guidance are quoted in a stylized font (Lydian) and this reviewers comments are in a publishers font (News Gothic MT) or, to conserve space in the tables, in Times New Roman to make it easier for the reader to differentiate the "speaker" in the various text passages that follow.]

The commenters start their submission by stating:

"Novartis Pharmaceuticals Corporation is a world leader in the research and development of products to protect and improve health and well-being.

Novartis researches, develops, manufacturers and markets leading innovative prescription drugs used to treat a number of diseases and conditions, including central nervous system disorders, organ transplantation, cardiovascular diseases, dermatological diseases, respiratory disorders, cancer and arthritis.

The company's mission is to improve people's lives by pioneering novel healthcare solutions.

As a global pharmaceutical corporation, Novartis is supportive of efforts to improve and to harmonize the technical requirements for registration of pharmaceutical products.

We appreciate the opportunity to comment on this guidance in accordance with FDA's Good Guidance practices.

Novartis understands the need to update the Guidance for Drug Products to incorporate change necessitated by the Common Technical Document (CTD) and International Conference on Harmonization (ICH) global initiatives supported by the FDA.

As a global pharmaceutical corporation, Novartis supports those efforts which lead to greater consistency and quality in global registrations.

Novartis is also aware of several ambitious initiatives currently undertaken at FDA to improve drug quality in the 21st century.

However, Novartis has some concern that the magnitude of the proposed Guidance revisions as compared with the 1987 FDA Drug Product Guidance, when considered in sum, could be more transparently portrayed to ease evaluation of the proposed changes.

These points are elaborated and additional comments are provided in the attached tabular format, for ease of FDA use."

The commenters' introductory remarks are both interesting and instructive.

However, the tabular format provided, no matter the intent, makes difficult, to say the least, for anyone to review the electronic version posted to the dockets database.

"**General Comments**

This draft Drug Product Guidance represents a comprehensive rewrite of the 1987 NDA Drug Product Guideline and as such warrants a critical review. Critical review is hampered by several factors, including:

1. The open status of several significant draft documents such as the 1997 draft Stability Guidance
2. The harmonization efforts of CDER and CBER requirements in one DP Guidance
3. The introduction of additional regulatory content requirements through the CTD format changes and ICH references

4. The lack of a current Drug Substance baseline due to the planned revision of the Drug Substance and BACPAC II Guidances under development."

This reviewer doesn_ot feel that a critical review of this document was hampered by any of the preceding.

While these do tangentially impact the draft guidance, they, in no way, directly affect what it suggests should currently be provided in the a drug product application

As evidence of the validity of this reviewer's remarks, the commenters need only consult the formal submission to the docket posted on May 20, 2003 "(C-01)."

"The logical flow of regulatory requirements and scientific criteria beginning with drug substance starting materials and culminating with the final drug product would result in a more unified NDA Guidance set for submission and review purposes."

This reviewer agrees that the suggested restructuring could enhance the "logical flow of the regulatory requirements and scientific criteria."

However, the reviewer knows that a "controls structured" "incoming, in-process, drug product"-ordered approach that incorporates references to the appropriate CGMP requirement or requirements that the requested information serves to verify cognizance and probable compliance format would result in a more CGMP-compliant **Chemistry, Manufacturing and Controls** guidance set for submission and review purposes.

"Changing DP requirements' before establishing new DS requirements may require amendment of the proposed DP Guidance."

Though the comment cannot be argued with, this reviewer finds it both unpersuasive and not relevant.

"Revision in multiple areas concurrently, although ambitious, may result in unintended contradictory regulatory requirements, with respect to:

- GMP review and revision
- Finalization of planned or open draft FDA Guidances
- Ongoing harmonization efforts
- Electronic submissions standards, and maintenance of electronic dossiers as submissions are updated."

Again, given the language used, the comment cannot be refuted.

However, having repeatedly read the draft guidance proposed and submitted formal comments to its docket, and having a thorough understanding of the requirements of the drug CGMP, this reviewer is persuaded that the items raised by the commenters are red herrings designed to needlessly delay or sidetrack this much-needed and long-delayed revision of the CMC guidance provided.

A REVIEW OF FORMAL COMMENTS TO PUBLIC DOCKET 02D-0526

Guidance Reference [CTD section]	Line Range	Major Comments	Rationale
General	N/A	Overall, this seems to increase filing information requirements for NDAs and ANDAs while the CTD structure was meant only as a formatting tool and was not intended to identify additional requirements above and beyond those currently required for drugs. *Instances throughout the document identify requirements not previously listed in regulations or current guidances for drugs.* **(1)** Cross-reference to other Guidance documents is very useful! However, the reference to Guidances that remain in the draft or development stage increases the difficulty in reviewing this draft.	This Guidance is intended to be applicable to NDAs and ANDAs. *In cases where specific sections would not be required for an ANDA, or would require amplification for a biological, it should be stated as such in that section.* **(2)**
Review Comments [to *italized* text]		**(1) Contrary to what is asserted, the requirements <u>not</u> in current guidances are requirements in the CGMP regulations for drugs [21 CFR 210 and 21 CFR 211].** **(2) Having read this guidance more than once, this reviewer has failed to find any section that he or the other commenters found did <u>not</u> apply to some degree to all applications – therefore this reviewer finds no such need**	
General	N/A	*This document places a great focus on development activities and the need for comparative historical data to support and justify the information in the "for market" application for the intended commercial product.* **(3)** For examples, please see: lines 495-505; lines 580-587; lines 777-780; lines 1317-1326; lines 1469-1472; lines 1573-1593.	*These requests for historical information are excessive. Novartis believes much of this information would have been exchanged with the Agency during product development (for example at end-of-Phase meetings), rather than at the time of the original NDA, and is therefore redundant.* **(4)** *This information should be consolidated in the Development Pharmaceutics part of the application, and its purpose and use in Application review of the historical information clarified for both industry and FDA staff.* **(5)**
Review Comments [to *italicized* text]		**(3) This reviewer agrees that this draft requires the applicant to provide a body of evidence derived from historical information to support the implicit claim that the proposed drug product and its production process complies with CGMP – in this regard, the proposed guidance is a significant improvement over the existing guidance.** **(4) This review does <u>not</u> find that the requests for information are excessive. Moreover, the issue is <u>not</u> whether or not the information has, in some form been exchanged, the issue is that the requested information needed to be provided in the format requested to facilitate a) the review of the application by an assigned reviewer (who may never have attended any Agency/firm meetings prior to being assigned to review a submitted application) and b) the determination that the information submitted establishes (proves) i), if approved, the drug product will be safe and effective, and ii) the manufacture of the drug product and the drug product will comply with ALL of the applicable CGMP regulations. Finally, the commenters ignore that this guidance is for both ANDA and NDA applications** **(5) Contrary to the commenter's position, it is crucial that this information be provided in the "CMC" section of an application because a) that is the section that the Office of Compliance receives and uses to plan its PAI inspectional plan after the application is submitted and b) the reviewer needs the information to ensure that the goals enunciated in Point (4) can be met.**	

Guidance Reference [CTD section]	Line Range	Major Comments	Rationale
General	N/A	*This draft cites the GMPs on a regular basis. This is not appropriate.* (6) These citations are most prominent in the analytical sections, in which acceptance of results on protocol are discussed. *These lines should be removed from the Guidance as being under GMP regulations:* *Lines 1022-1025;* *Lines 1035-1038;* *Line 1089;* *Lines 1607-1609;* *Lines 1817-1819.* (7)	*GMP requirements are covered in separate regulations. Although we are aware of recent FDA initiatives in updating GMPs, it may be premature to integrate specific GMP requirements into the Drug Product dossier requirements prior to the completion of these ongoing initiatives.* (8)
Review Comments [to *italicized* text]		**(6) First of all, the commenters incorrectly assert that the "*draft cites GMPs on a regular basis*" when they cite CGMP. Moreover, because the FDC Act requires that all drugs and drug products be produced in compliance with CGMP or it is adulterated and cannot be sold. Therefore it is important for any guidance to request all the information from the applicant that is required to establish that this is the case BEFORE approving or licensing the drug product and its manufacture under the conditions proposed in the application.** **(7) As per (6),t hese lines should NOT be removed.** **(8) Again, the commenters ignore the CGMP requirement in the FDC Act and its requirements. Moreover, though the CGMP regulations for drugs and drug products are covered in other sections, any application for a drug product must demonstrate that the processes and controls used and the materials (incoming and in-process) and the drug product meet or exceed the requirements et forth in said regulations. Therefore, to the extent that the requirements of the CGMP regulations bear directly or indirectly on the need for the requested information to support the application's information conformance to said CGMP, it is very appropriate to cite the applicable regulations.**	
IV.C [P.2.3]	580 - 588	*The guidance is very specific on what information should be in the equipment comparison table; however, this amount of detail is typically not required.* (9) *Change to:* ***For equipment of different operating design or principle,** a table should be provided that compares equipment used to produce the clinical batches that support efficacy or bioequivalence and primary stability batches to the equipment proposed for production batches.* *The table should identify (1) the identity (e.g., batch number) and use of the batches produced using the specified equipment (e.g., bioequivalence study batch # 1234), and (4) any significant equipment differences (e.g., different design, operating principle, size).* (10) **Please provide a representative table of equipment similar to that provided in the SUPAC Equipment Addendum**	*This section is an example of information considered this excessive for conventional dosage forms.* (11) We also suggest that the agency and industry develop standardized terms for operating equipment, including those for transdermal and other unconventional products, to make the comparison process more consistent and meaningful. Equipment comparisons should be based on existing SUPAC Guidances, where possible.

Guidance Reference [CTD section]	Line Range	Major Comments	Rationale
Review Comment [to *italized* text]		**(9) This reviewer agrees that the guidance is very specific but thinks that, forgetting history, the amount of detail is simply that required to provide the needed evidence that the applicant is proposing a CGMP-compliant process and product.** **(10) This reviewer does <u>not</u> support the changes proposed by the commenters because, for the reasons previously stated, it is <u>not</u> appropriate. Moreover, the reviewer can help but notice that the commenters have truncated the list of items from (1) though (4) to (1) and (4).** **(11) While the commenters may consider this information excessive for conventional dosage forms, this reviewer sees the request as being both reasonable and appropriate**	
V.C. [P.3.3]	790-796	*Change to:* • *each manufacturing step, with identification of the **critical process controls** and any manufacturing step where, once the step is completed, the material might be held for a period of time (i.e. noncontinuous process) before the next processing step is performed.* **(12)** • *the material being processed* • ***critical in-process material tests** and the points at which they are conducted* **(13)** • *the type of equipment used (equipment vendor model and model number is not needed)*	For clarification purposes, it is recommended to revise "critical steps" to "critical process controls" in the first bullet and "critical process controls" to "critical in-process material tests" in the third bullet. It is also recommended to reduce the level of equipment detail. The section should be revised from: • each manufacturing step with identification of the critical steps and any manufacturing step where, once the step is completed, the material might be held for a period of time (i.e. noncontinuous process) before the next processing step is performed. • the material being processed • critical process controls and the points at which they are conducted • the type of equipment used (equipment model number is not needed)
Review Comments [to *italicized* text]		**(12) Do <u>not</u> agree with the change proposed by the commenters – the applicant needs to identify which <u>steps</u> the firm considers "critical" and which have "significant hold times"** **(13) Do <u>not</u> agree with the change proposed by the commenters. The CGMP regulations require the identification of the process controls and control points – tests are but one type of control – examinations and active regulation systems are other types of controls**	
v.c.2 [P.3.3]	824-826	BSE statement currently required only for biologics? *Please clarify the extent of effort to be expended concerning ruminant-derived materials "used or manipulated" at a facility, with respect to pharmaceutical materials.* **(14)** *The cited **9 CFR 94.11** concerns importation of meat and animal products from specified regions.* **(15)**	Regulatory requirement clarification
Review Comments [to *italicized* text]		**(14) The commenters should consult the previous review to see that NCE are sometimes and, in the future, may be increasingly produced by genetically manipulated animals** **(15) The regulation is cited only with respect to the identification of countries of concern for BSE now that its risk to human health has been realized**	

Guidance Reference [CTD section]	Line Range	Major Comments	Rationale
	849-852	*Add word "critical":* *Steps in the process should have the appropriate process controls identified. Associated numeric values can be presented as an expected range. All* ***critical*** *process controls should be included in the description of the manufacturing process (MPR or narrative).* **(16)**	*"All process controls" are considered too inclusive. Frequently, there are processing controls that have no effect on the quality attributes of the product. These controls may be in place to monitor process yields or efficiencies. These may be added or deleted during routine Production and should not require regulatory action to change.* **(17)**
Review Comments [to *italicized* text]		**(16) This reviewer objects to this change because it would allow the applicant to "inadvertently," or "erroneously" classify a control as "non-critical' when, in fact, it is a critical control. By requiring all controls to be included in the description, the Agency eliminates the possibility that a critical control will be overlooked.** **(17) First of all the calculation of yields and the establishment of yield limits are CGMP requirements and are therefore required to demonstrate compliance. However, a non-CGMP mandated monitoring of the process for efficiency is <u>not</u>, in and of itself, a control and, <u>provided</u> no conditions are attached to the efficiencies measured that may negatively impact product quality, such are <u>not</u> controls. Such "pure" unfettered monitoring activities need <u>not</u> be listed. However, if the firm sets goals, provides performance efficiency incentives, and/or pressures its manufacturing personnel to perform at higher efficiencies than some target level – then such become controls that usually have negative impacts on product quality and they should be reported as such. If a procedure is purely a performance monitoring activity of any kind that is <u>not</u> required by the CGMP regulations, then this reviewer would agree that a firm may add or delete such with impunity. However, this reviewer's experience has been that most such activities encompass more than monitoring – when that is the case, that activity is a control that should be reported if its has been used to characterize the process and/or the firm plans to use it post-approval.**	
V.E. [P.3.5]	956-958	Please provide examples of where validation documentation is "appropriate" for submission, as this information is not typically submitted to the FDA, with the exception of sterilization validation.	*It should be made clear that for US submissions the only process validation data needed is for sterile drug products. Further, the level of documentation typically provided in non-US applications is much less than that typically provided in the US for sterile product validation. Clarification of the expected level of detail in light of the CTD harmonization efforts is requested. Process validation is the responsibility of the field inspectors for all other types of dosage forms.* **(18)**
Review Comments [to *italicized* text]		**(18) If the commenters read the entire section (Lines 956 – 963), then the commenters would see that, besides sterilization processes, the Agency only request validation documentation be submitted in the application when the "process is used to control adventitious agents." Moreover, contrary to the statement made, field inspectors are only responsible for verifying that the firm has performed and is performing the CGMP-mandated validation activities – Process Validation is the responsibility of the drug-product manufacturer.**	

Guidance Reference [CTD section]	Line Range	Major Comments	Rationale
VLA [P.4.1]	1022	We request that the agency clarify the impact the following statement has on reduced testing: In addition to listing all the tests for an excipient, the specification should identify the tests that the drug product manufacturer will routinely perform and the test results that will be accepted from the excipient manufacturer's certificate of analysis (CofA).	*Does this approach indicate that a supplement will be required if the reduced testing arrangements stated in the NDA are subsequently changed? As a GMP issue, it may be appropriate to remove this point from the draft Guidance (see General point 3).* **(19)**
Review Comments [to *italicized* text]		**(19) If the firm makes any change in its approved inspection plans (including, but <u>not</u> limited to, reduced sampling, increased sampling, repositioning of sampling points, change in the amount of sample taken, any change in any testing plan, any change in examination plan, any change in the test, etc.), then the firm needs to take some action to notify the Agency. At a minimum, the change must be included in the firm's next "annual review" report for the drug product affected. In some cases, like a significant reduction in the number of batch-representative samples routinely tested, the approved application holder or licensee may need to file a prior-approval supplement. The local district office of the FDA should be consulted and agreement obtained on the type of filing that is appropriate for the change proposed. CGMP compliance is product salability issue – batches that don't meet CGMP cannot legally be even shipped much less sold as they are adulterated.**	
	1024-1026	Specifications - ID Testing	*A CMC guidance should not be citing the GMPs.* **(20) & (21)**

Review Comments [to *italicized* text]	**(20) For the reasons stated in this reviewer's response to the commenter's general remarks on this point clearly established that incorporating CGMP requirements into the CMC guidance is <u>not</u> only permissible but that such: a) provide the justification for the information requested and b) assist the applicant in developing and submitting a process and drug product that is CGMP-compliant –a clear requirement in the FDC Act with serious consequences when a process or drug product is <u>not</u> CGMP-compliant.** **(21) With the preceding in mind, let us review a) what the guidance says: "At a minimum, the drug product manufacturer must perform an appropriate identification test (21 CFR 211.84(d)(1)). However, when there are specific safety concerns relating to an excipient, testing in addition to an identity test would be warranted. For example, diethylene glycol contamination of polyols such as glycerin and propylene glycol has caused numerous fatalities, and the specification should include testing for potential impurities and contaminants for each batch received by the drug product manufacturer," and b) what it should have said to fully conform to the requirements set forth in the CGMP regulations cited. The controlling regulation for component testing is set forth in 21 CFR 211.84(d) (1) and (d)(2) which state (emphasis added):** 21 CFR 211.84(d) Samples shall be examined and tested as follows: (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. (2) Each component shall be tested for conformity with all appropriate written specifications for purity, strength, and quality. In lieu of such testing by the manufacturer, a report of analysis may be accepted from the supplier of a component, provided that at least one specific identity test is conducted on such component by the manufacturer, and provided that the manufacturer establishes the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals. **Based on the preceding, the minimum testing that a firm can do for component testing is <u>NOT</u> "an appropriate identity test," BUT "a specific identity test."** **Thus, the guidance should be changed to read at Line 1024 and following:** "At a minimum, the drug product manufacturer must perform **a specific** identification test (21 CFR 211.84(d)(1)(2)) **on a representative set of samples (21 CFR 211.84(b)) from each shipment of each lot (21 CFR 211.160(b)(1).** However, when there are specific safety concerns relating to an excipient, testing in addition to an identity test would be warranted. For example, diethylene glycol contamination of polyols such as glycerin and propylene glycol has caused numerous fatalities, and the specification **for these and any other such** should include testing for **potential toxic and hazardous** impurities and contaminants for each batch received by the drug product manufacturer."

Guidance Reference [CTD section]	Line Range	Major Comments	Rationale
	1034	*Full monograph testing need not be performed in house by the sponsor on every batch. Acceptance of data from the vendor can be done if the vendor's data has been confirmed to be comparable to the data generated internally.* (22) & (23)	Established as part of vendor certification requirements.
Review Comments [to *italicized* text]		**(22) This reviewer must object to the out-of-context and inappropriately placed change from the draft. First the text is only intended to provide guidance as to when more than the citation of the compendial method needs to be done. The text being modified starts at Line 1032 and reads (Lines 1032 – 1034) as follows: "Only a citation to the appropriate official compendium need be provided when the excipient specification is identical to the compendial monograph and full monograph testing will be performed on each batch of excipient." The text does <u>not</u> indicate or imply that a firm should do fullco mpendial testing on each lot. It is intended to address the issue of whether or not more than the citation of the compendial method is required.** **(23) Further the commenter's inappropriately placed language does <u>not</u> meet the clear requirements set forth in 21 CFR 211.84 and 21 CFR 211.160(b)(1). [See Review Comment (21).]**	
VI.C. [P.4.3]	1062	Change to: Analytical procedures for excipients should be validated as appropriate.	We prefer not to state all analytical procedures. For example, compendia1 methods are well characterized and thus need not be validated additionally. (24)
Review Comments [to *italicized* text]		**(24) This reviewer again thinks that the proposed change is inappropriate. This is the case because: a) it is clear, when the next sentence is read, that the guidance is using the word "validated" in its broadest sense – one that encompasses "verified" and b) the paragraph as written correctly states the requirements for qualifying methods that are compendial or from other sources that the FDA recognizes – "verified to be suitable under actual conditions of use."**	
VI.D. [P.4.4]	1089	A certificate of analysis (COA) from the manufacturer and the test results for the same batch from the drug product manufacturer should be provided for the components described in P.4. The information should be for the materials used to produce the batch described in the executed production record (R. 1. P)	*The comparative analytical information request need not be submitted in the NDA and the statement should be removed from the draft Guidance. This is part of the qualification process for suppliers (GMP process which should be held internally).* (25) *Alternatively, Results of tests on the components of EPRs will be included in section R. 1 .P, as stated in the draft guidance.* (26)
Review Comments [to *italicized* text]		**(25) If nothing else, the information requested needs to be submitted to support the applicant's adoption of the "accept COA" approach in lieu of full monograph testing. Therefore, the rationale for objecting to reporting the information requested escapes me.** **(26) Since the guidance is just that – guidance, the alternative the commenters propose to use may be acceptable PROVIDED the requested COAs are also provided.**	
VI.F. [P 4.6]	Section	Unable to comment as Guidance unavailable	
Review Comments [to *italicized* text]			

Guidance Reference [CTD section]	Line Range	Major Comments	Rationale
VII.A. [P.5.1]	1174 (Table 3)	*Release Specifications should not be included.* **(27)** *We trust that IPCs such as "core weight" was provided for example purposes only, and not as an indicator that tablet weight should be part of product release testing.* **(28)**	*A true "regulatory" specification is a "control" (stability) specification.* **(29)** *Non-functional tests such as dosage unit weight are of limited value as accept/reject criteria; tests such as assay or dissolution provide more useful data. Further, the IPC example again brings up the question if the testing needs to be carried out in the Quality Unit.* **(30)**
Review Comments [to *italicized* text]		**(27) Contrary to the commenter's statement, detailed, CGMP-compliant batch release should be provided because they are crucial to establishing the requisite CGMP compliance of the drug product. This reviewer suggests that you carefully read the comments posted to this docket on 20 May 2003.** **(28) Technically in-process core (IPC) weight testing on a batch representative set of cores should be an integral part of the critical controls for release of the cores for further processing. However, for most film coated tablet drug products, the final tablet weights should be included in the batch release controls so that the specific content and the specific drug availability values may be assessed to conform the uniformity of the final blend that was formed into the dosage units and, as was the case for the IPCs, a batch representative set is needed for each critical variable that is evaluated to determine (based on SQC) whether or nott he batch (<u>not</u> just the samples tested) is acceptable for release.** **(29) The commenters seem to have left out the phrase "post-release." Thus, had the commenters said, "Post release, the "regulatory" specification set forth in the USP or established by the FDA as a part of the approval process is the in-commerce "control" (stability) specification, this reviewer would have concurred. However, prior to release of the batch into commerce, the pre-release specifications established in the CGMP are the "control" specifications for the batch.** **(30) Contrary to what the commenters state, scientifically sound non-functional tests are of great value as in-process controls (accept/reject criteria) and most firms use them for tests such as appearance, dimension, imperfections, hardness, friability, dose weight or dose volume, deliverable volume, defects, and the like. Since the CGMP regulations do <u>not</u> specify WHERE such non-functional tests must be conducted, this reviewer sees no such location issue.**	
	1176	*PQIT Testing-why not use the ICH Q6A term "periodic" or "skip" testing, instead of introducing another term?* **(31)**	All testing which is critical to product quality should be listed in the filed control procedure and specifications. *Discussions concerning product failure investigations (GMP) are not appropriate for this document.* **(32)** Sponsors should have the option of including periodic frequency testing in the filed control procedure and specifications, or, in a separate document. Consistency of terminology with ICH would be helpful to reduce potential confusion.
Review Comments [to *italicized* text]		**(31) The reason that the term was chosen seems to be a desire by the Agency to emphasize a) these are tests that <u>augment</u> the specification tests, b) these are to be quality tests – they do <u>NOT</u>, like the other terms carry the connotation of a reduction in testing from the baseline specification level.**	

Guidance Reference [CTD section]	Line Range	Major Comments	Rationale
Review Comments [to *italicized* text] (Continued)		**(32) Contrary to the commenter's position, the inclusion of appropriate information from batches that failed should be included whenever such serve to support the progression in the applicant's understanding of and degree of control over the process and the quality of the drug product. This is especially true when the basis for a subsequent successful trial is the prior failure itself.**	
VII.D.1. [P.5.4]	1311 (section); 1317 — 1326	Batch Analysis – History A summary of any change in the analytical procedures should be provided if the analytical procedure (1) change over the course of generating the batch analysis data and/or (2) are different from the analytical procedure included in P.5.2.	*Batch Analysis Reports (DELETE THIS SECTION - We fail to see the value of including such extensive information in the NDA since this would have already been included in IND amendments. (Only information required to support justification of the proposed NDA specification is relevant).* **(33)** *We feel that this is also redundant as the historical information about the analytical procedures is captured in the stability section (X.C.). We feel that the requirement of a summary of changes is unduly burdensome. If the principle of the assay changes (titration versus HPLC) then this should be included, but minor changes (mobile phase and chromatographic conditions) need not be reported.* **(34)**
Review Comments [to *italicized* text]		**(33) First, the value is to collect the requested information from diverse resources and present the collection as an aid to the review process for the application reviewer who, lacking this collected information would need to search for it in a collection of disparate documents – an obvious waste for the reviewer's time. Second, because the guidance applies to both ANDAs and NDAs, modst applications (ANDAs) are <u>not</u> based on INDs. For both reasons the Agency has rightly requested that the applicant present the requested information in the manner requested and the request does <u>not</u> seem unduly burdensome.** **(34) <u>Not</u> all firms capture ALL of the historical information about the ALL of the changes in the analytical procedures. Moreover, what one firm may consider a minor change may, in fact, be a major change in the method. Lacking assurance that all changes have been reported that the summaries provide, the application reviewer would be compelled to review all of the analytical procedures' documentation to establish what were the changes – again, <u>not</u> a good use of the reviewers time. Thus, if nothing else, a firm would want to provide what has been requested because it will assist the application reviewer's being satisfied that the analytical procedures are scientifically sound and have been properly developed and controlled.**	
VII.E.1 [P.5.5]	1344,1399	All expected drug product impurities (e.g., degradation products of the active ingredient, residual solvents, enantiomeric impurities, excipient degradants, leachables from the container closure system) should be listed in this section of the application whether or not the impurities are included in the drug product specification.	*This implies the potential need for analytical methods that are stability indicating for selected excipients.* **(35)** *Under what circumstances are these excipient-related impurities quantified and qualified?* **(36)**
Review Comments [to *italicized* text]		**(35) First of all, the request is for a listing and nothing more. As such it implies that the applicant must know what the excipient degradants are in the formulation that the applicant is proposing. In most cases, the manufacturer of the ingredient should be able to provide that information.** **(36) Whenever such are significantly toxic to the population that will consume them.**	

Guidance Reference	Line Range	Major Comments	Rationale

[CTD section]			
X.C [P.8.3]	1607-1609	*Stability data to support holding in-process materials for longer than 30 days is not usually provided in the NDA. The data is available internally as per GMPs.* (37)	Reference to GMPs
Review Comments [to *italicized* text]		**(37) Lacking the data requested, an application reviewer cannot know that the holding times proposed in an application are scientifically sound and appropriate – a CGMP requirement. If these holding times are <u>not</u> substantiated by the data provided, then the prudent application reviewer could place the application on hold and request the applicant provide said data. Most firms claim they do <u>not</u> want to delay their applications. If this is the case, prudent firms will report the stability data that support any and all hold times <u>not</u> just those longer than 30 days. Finally, because this document is guidance, a firm may choose to follow the course that the commenters have proposed. For all of the preceding reasons, the draft text in this location should remain as it is.**	

Guidance reference	Line reference	Minor Comments	Rationale
General	N/A	*Define the terms "critical process" or "critical step" and "PQIT" in the glossary. Use the ICH Q6A term instead of introducing a new acronym (PQIT).* **(38)** Discuss the concept of PQIT's in a separate document that addresses both pre- and post-approval concerns. **(39)**	Clarity of concepts
Review Comments [to *italicized* text]		**(38) This reviewer agrees that these terms should be formally defined in the glossary and recommends using the appropriate text in 21 CFR 211 to define "critical process" and critical step." When defining the term "PQIT," this reviewer suggests defining it as those periodic quality tests beyond those required for each batch by 21 CFR 211 that are added to assess the degree that the quality standards of the manufacturer exceed the SQC (statistical quality control) level requirements of CGMP. For the obvious, previously stated reasons, the ICH Q6A terminology is NOT appropriate.** **(39) If the term "PQIT" is defined as this reviewer proposes, there would be no need to discuss the concept thereof in a separate document because the use of a PQIT would be in addition to the CGMP minimums and could, therefore, be omitted or changed without any need to address "*pre- and post-approval concerns.*" It would only impact post-approval concerns if the application holder decided to upgrade its quality standards by incorporating a given PQIT into its approved routine "each batch" drug-product controls and specification.**	
III.C [P-11]	265 269	*Change to:* *In some instances, the composition of distinct subformulations (e.g., cores, coating) of the drug product may be listed separately in the composition statement.* **(40)** *In these cases, the composition of the immediate release and extended release portions of the drug product may be listed separately.* **(40)**	*These changes are suggested to provide flexibility for the presentation. In some instances it may be more illustrative to include both subformulations in the same table. This should be left to the discretion of the applicant in particular if drug substance is not portioned between the parts of the subformulation.* **(40)**
Review Comments [to *italicized* text]		**(40) The commenters seem to confuse a request "to list separately" with one "to list in separate tables." Since the request is the former, the draft should be left as it is:** 265-66 "In some instances, the composition of distinct subformulations (e.g., cores, coating) of the drug product should be listed separately in the composition statement." 269-71 "In these cases, the composition of the immediate release and extended release portions of the drug product should be listed separately."	
	304, (footnote 10)	Efforts to accept compendia in addition to USP/NF(for example, EP or JP) should be accelerated to provide global consistency. **(41)**	Global consistency
Review Comments [to *italicized* text]		**(41) Until the FDC Act is changed to recognize other official compendia, the footnote should be left as it is: "[10] A compendial component is a component that has a monograph in an official compendium as defined in section 201(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321(j))." – Reality should NOT be ignored. Moreover, the language proposed is particularly inappropriate because, as we all know, the industry and not the FDA has more leverage with Congress – the only "agency" that can effect the change that the commenters are espousing.**	

Guidance Reference [CTD section]	Line Range	Minor Comments	Rationale
IV.A.2 [P.2.1.2]	**451-454**	*Change to:* *An applicant **may wish** to discuss the use of noncompendial-non-novel excipients with the appropriate review division prior to submitting its application to ascertain the level of information that would be warranted to support the use of the excipient.* **(42)**	Define non-novel (e.g. used in EU, listed in Inactive Ingredient Guide, etc.) at this point in Guidance. **(43)**
Review Comments [to *italicized* text]		**(42) This reviewer does <u>not</u> see any compelling need to change the language from "is encouraged" to "may wish." If any change is warranted, it should be from "is encouraged to" to "should" to be consistent with the tenor of the guidance.** **(43) This reviewer agrees that the term "non-novel excipient" should be defined**	
V.A. [P.3.1]	692	Building #s	*Building numbers need not be registered (with the exception of sterile products)* **(44)**
Review Comments [to *italicized* text]		**(44) This reviewer fails to see what a request for the applicant to provide "building numbers or other specific identifying information" has to do with the registration thereof. The request is obviously made in an attempt to facilitate the required PAI when the site is a "multifacility campus" and should be honored. If providing building numbers is a problem, then the applicant can provide other specific identifying information in such cases. Moreover, because this document is guidance and <u>not</u> regulation, an applicant can simply choose to ignore this request.**	
	695-697; 710 (with respect to PAI)	Clarify: Addresses for foreign sites should be provided in comparable detail, and the name, address, and phone number of the U.S. agent for each foreign drug establishment, as required under 21 CFR 207.40(c), should be included. US agents – The reference to 21 CFR 207.40(c) is for registering drug establishments. The FDA needs a contact or responsible person at the site in question for the purposes of scheduling an inspection as noted on line 710.	Format (placement in CTD Module 1?) and regulatory requirement question to clarify the number of individuals the FDA would like named in the Application, and whether a change in Agent would necessitate an update to the NDA.
Review Comments [to *italicized* text]			
V.C. [P.3.3]	832	It appears redundant to the sterile validation information already required for inclusion in the "US Regional" part of a CTD.	Clarification of format for US CTD.
VI [P-4]	1003	Please clarify why the "patch" would be different from the drug product.	
Review Comments [to *italicized* text]			
VII.E.1 [P.5.5]	1344	What is the intention of including excipient degradants as a miscellaneous drug product impurity? How should it be quantified? **(45)**	
Review Comments [to *italicized* text]		**(45) As a % of the unit's weight for solids and as a % of the volume for liquids and gasses.**	
IX [P.7.]	1536	Secondary Packaging	Information on non-functional secondary packaging should not be needed in the file.
Review Comments [to *italicized* text]			

A REVIEW OF FORMAL COMMENTS TO PUBLIC DOCKET 02D-0526

AstraZeneca's Submission Posted June 26, 2003
To Docket 02D-0526: "C-10"

[**Note:** The original comments are quoted in a condensed font (Perpetua), the quotes directly from the draft guidance are quoted in a stylized font (Lydian) and this reviewers comments are in a publishers font (News Gothic MT) to make it easier for the reader to differentiate the "speaker" in the various text passages that follow.]

The commenters begins by stating: "In accordance with the Notice of Availability in Vol. 68, No. 18 of the Federal Register, AstraZeneca wishes to provide the Food and Drug Administration Dockets Management Branch with the following written comments on Federal Register Docket No. 02D-0526 (Draft Guidance for Industry on Drug Product: Chemistry, Manufacturing, and Controls Information)."

Overall, this reviewer finds that the commenters present issues in terms of the commenting firm's beliefs without providing any valid science-based or regulation-based rationale to support what is recommended.

Thus, this reviewer would classify the commenters' positions as faith based – they seem to expect the Agency to accept their positions on faith.

That having been said let us review the commenters' posting to the docket.

"Lines 26-28: Please clarify if this draft guidance applies to biotechnology products."

To the extent that the biotechnology product is a drug product or the Agency regulates it as a drug product, this guidance should apply.

"Lines 79-81: The use of alphanumeric designations in parentheses is confusing. AstraZeneca recommends that the draft guidance document adopt Common Technical Document (CTD) heading numbers, heading names, and sub-headings to reduce confusion and improve ease of use."

"Lines 91-93: The draft guidance recommends that Sponsors discuss cross-referencing of drug product quality information with appropriate review divisions. AstraZeneca believes this stipulation is unnecessary and that cross-referencing of quality information on file with the Agency should not ordinarily be a matter that requires discussion with review divisions."

"Lines 243-245: AstraZeneca requests that the Agency clarify that, by default, United States Pharmacopeia (USP) nomenclature ~~are~~ **is** the standard for descriptions of dosage forms."

"Line 358: AstraZeneca requests that the Agency clarify that it is sufficient to delineate the specific sections and page numbers of the Drug Master File (DMF) that are pertinent to the application in the DMF holder's Letter of Authorization."

To facilitate the application's CMC-section reviewers, it is better to provide the requested information in the form requested in the table because this will facilitate the reviewer's accessing the requisite information should there be a need to.

"Lines 450-454: AstraZeneca believes the recommendation for additional information, up to and including the level of information for novel excipients, for noncompendial, non-novel excipients is

not warranted. The use of noncompendial, non-novel excipients should not routinely trigger the recommended stringent submissions requirements or the need for prior discussions with review div is ion staff."

This reviewer sees the need for the information that the Agency is requesting and finds that, while the information requested is more than in the prior guidance, it is that information that is required to demonstrate that the applicant is and/or intends to operate in compliance with the applicable drug CGMP.

"Lines 514-524 and 531-539: AstraZeneca requests that the Agency clarify the differences between 'overfill' and 'overage.'

Perhaps this humble reviewer can assist in this regard.

An **overage** is *any additional amount of a component that increases the CONCENTRATION (amount/unit) of that component.*

For example, adding additional active (with a concomitant reduction in some other ingredient to maintain a constant total) beyond that needed to meet the "per dose" label claim.

An **overfill** is the amount a material beyond the nominal (label) or target level that is added to or found in the finished unit.

For tablets, making tablet cores with a minimum weight that is 10 mg larger than the approved core target weight is an example of a tablet overfill.

For liquids, the examples are obvious, filling a nominal 150-mL claimed product container capable of holding up to 200 mL with 160 mL to ensure that the deliverable volume label claim of 30, 5-mL doses is met.

Hopefully, the preceding are both clear and sufficient to

"Lines 580-587: AstraZeneca believes that it is sufficient to provide summarized results from a bioequivalence study, linking the tablets used in pivotal clinical studies to the proposed commercial formulation. Alternatively, if a bioequivalence study has not been conducted, then a table should be provided that compares the equipment used to produce the clinical batches that support efficacy or bioequivalence and primary stability batches to the equipment proposed for manufacture of the production batches. The information should be presented in a way that facilitates comparison of the processes and the corresponding batch analyses information (P.5.4). The table should identify (1) the identity (e.g. batch number) and use of the batches produced using the specified equipment; (2) the manufacturing site; (3) the batch size; (4) any significant equipment differences (e.g. different design, operating principle, and size)."

This reviewer does not understand how the summarized results from a bioequivalence study (which does not even report all of the data) link the tablets used in a pivotal clinical study (not the bioequivalence study) to the proposed commercial formulation from which there are no data because no tablets have been made?

This reviewer thinks that the draft language is language that should be incorporated into the final CMC guidance.

This is the case because it facilitates the application reviewer's understanding that the proposed production process does not differ significantly

from that used for the key batches, or, if it does, ascertain, by reviewing the appropriate supporting studies, that, though different, the proposed production process will produce drug product that meets the applicable CGMP uniformity requirements in all respects.

"Line 692: AstraZeneca believes that this level of detail is not needed for products which are not aseptically produced and requests that the Agency clarify what is meant by the terms multi-facility and multifunctional."

As a site auditor, this reviewer understands the reasons for the Agency's requests and knows that, for "**multifacility campuses**," having a layout that identifies the buildings and their association with the drug product manufacturing process helps the audit team to schedule the audit in a manner that minimizes the time wasted in commuting between facilities.

Since the Office of Compliance receives and uses the CMC section of each application to support its pre-inspection planning, inspection scheduling and inspection activities, it is clearly needed.

Therefore, this reviewer would recommend keeping the text for this request as it is.

[Suggested definitions: A **multifacility campus** is a *campus on which there are multiple discrete facilities in which different operations are performed and/or different products are produced.* A **multifunctional campus** is a *campus on which multiple functions are performed in a single integrated facility ("under one roof").*]

"Lines 693-695: The draft guidance recommends that for sites processing sterile drug substances, products, or packaging components, the sterile processing area (e.g. filling room) is included in the list of manufacturers (Section P.3.1). AstraZeneca suggests that this information is not needed here since it will be contained in the sterilization process validation document."

Since providing the information here is no undue burden and doing so should facilitate the review process, this reviewer sees no need to omit this request from this section of the guidance.

"Line 696: AstraZeneca believes that the information for the US agent should not be required in this section since this information is already provided in Module 1 of the Common Technical Document (CTD)."

The issue isn_ot whether the information an FDA reviewer needs exists somewhere but whether it is readily available in the CMC section of the application to those that will be needing it for their review activities (including the on-site PAI inspectorate).

For this reason, the information requested should be provided in the CMC section and the guidance should retain this text.

"Line 710: AstraZeneca believes that this information should not be required in this section since this information is already provided in Module 1 of the Common Technical Document (CTD)."

Again, the issue isn_ot whether the information an FDA reviewer needs exists somewhere but whether it is readily available in the CMC section of the

application to those that will be needing it for their review activities (including the on-site PAI inspectorate).

For this reason, the information requested should be provided in the CMC section and the guidance should also retain this text.

"Lines 717-718: AstraZeneca requests that the Agency clarify if overfills are to be included in the proposed batch formula that includes a list of all components used in the manufacturing process."

Since the guidance does not ask the applicant to specify the exact number of finished units to be made from the batch, there is, per se, no need to report proposed "overfill" information – one need only report the theoretical yield.

However, if the applicant intends to deliberate fill the tablets with an extra 2 % of the final blend, then, that applicant is free to add text indicating that while the theoretical yield is 2,000,000 tablets, the expected yield is 1,960,000 tablets, and, to allow for losses, a portion at the end that cannot tableted and actual weight variation, the allowable yield range is from 1,900,000 tablets to 1,970,000 tablets.

"Lines 720-722: AstraZeneca believes that cross-reference to the quality standards contained in Section P.1 should be permitted."

While this reviewer thinks that the redundancy is *de minimus* and repeating the information will facilitate application review, this reviewer would not oppose permitting simply because the information is duplicative.

Thus, for the example presented, the table would contain a column for the standard that would be filled with a bunch of "See Table n, line m" entries.

Obviously reviewing information provided in this manner would be less efficient than in the manner suggested by the draft guidance.

For the economic reasons associated with the cost of lost revenue per day of review delay to the applicant, this reviewer would favor all such duplications.

"Line 748: AstraZeneca believes that cross-reference to the quality standards contained in Section P. 1 should be permitted to eliminate redundancy."

See this reviewer's previous answer.

"Line 800: AstraZeneca recommends that packaging steps should be described in the manufacturing process only when packaging is an integral part of the dosage form manufacture, such as in liquid fills, dry powder fills, and sterile packaging operations. Oral tablet packaging is typically a separate and distinct process that should not be included as part of the dosage form manufacture."

Because each reviewer of an application, *not just the inspectorate*, is charged with assuring that the application provides documented evidence that both the production process being proposed and the proposed drug product are "CGMP compliant," the packaging information should be included in all applications.

This is the case because the applicable CGMP regulations, 21 CFR 211, explicitly address, in **"Subpart G -- Packaging and Labeling Control."**

Therefore, this information should be provided in all cases.

"Line 824: AstraZeneca believes this information is relevant only to inspection and cGMP compliance and should not be required for inclusion in a filing. AstraZeneca recommends that this information be made available for review during an Agency inspection to demonstrate that a Sponsor has appropriate controls in place for the potential of cross-contamination. In addition, AstraZeneca requests that the Agency provide additional guidance and clarification regarding the use of same and separate facilities when formulating products containing materials of possible animal origin, such as magnesium stearate, lactose and gelatin capsules."

The commenters are asked to reread the first sentence of the previous response and then read the first portion of their first sentence as it applies to CGMP, "AstraZeneca believes this information is relevant ... to ... cGMP compliance ..."

Since the commenters recognize that this information is relevant to CGMP compliance, this reviewer trusts that the commenters really have no objection to providing documented evidence that establishes their compliance with CGMP.

On this bases, this reviewer recommends that this language be retained in the guidance.

Of course the commenters and any other applicant are free to choose an alternate approach, provided it also provides the requisite documentation of the CGMP compliance to all reviewers, because such is the nature of guidance

"Lines 965-970: AstraZeneca requests that the Agency provide additional guidance and clarification, since the information in this section appears to be in conflict with information presented on line 885. AstraZeneca believes that it is generally accepted practice to not include validation data in an original application, and thus questions the need for these data for reprocessing operations. AstraZeneca believes that this information is relevant only to inspection and cGMP compliance and should not be required for inclusion in a filing. AstraZeneca recommends that this information be made available for review during an Agency inspection."

This reviewer finds that a careful reading of **all** of "3. Reprocessing and Reworking," Lines 885 through 916, and "E. Process Validation and/or Evaluation (P.3.5)," Lines 954 through 973, should resolve this commenter's perception of unspecified conflicts between the two sections.

As written, the comment speaks of an unspecified, apparent conflict between a section title "3. Reprocessing and Reworking" (Line 885) and a section of the text (Lines 965-970), "**Submission of validation information for reprocessing and reworking operations usually is not warranted. However, it can be warranted when the reprocessing or reworking operation is of the type for which process validation information is submitted when routinely performed or when the reprocessing or reworking operations have a significant potential to affect the identity, strength, quality, purity, or potency of the product (e.g., protein drug products).**

Since the commenters again recognize that the requested information is related to CGMP compliance, the commenters should, *after reading the preceding comments*, recognize the need for including the requested information in the application.

Finally, the "generally accepted practice to not include validation data in an original application" applies to data from the full-scale validation batches that are allowed to be made after approval has been obtained in some cases.

Moreover, as with any general practice, the Agency's experience has provided ample evidence where this "generally accepted practice" should be discontinued.

Based on all of the preceding, this reviewer continues to recommend that this section of the guidance remain as it is.

"Line 981 (Footnote 26): AstraZeneca believes that this statement implies that if an excipient is compendial but also "novel" then the same level of documentation required for a drug substance may be required for the use of such an excipient. AstraZeneca requests that the Agency clarify this interpretation. AstraZeneca believes that requiring such a stringent level of documentation for compendial materials represents a new regulatory standard that is not justified."

This reviewer does not understand exactly how the footnote in question which states, "**A compendial excipient is an excipient that has a monograph in an official compendium as defined in the Federal Food, Drug, and Cosmetic Act. Inclusion of an excipient in an official compendium does not ensure that the excipient has ever been used in an FDA-approved human drug product. Therefore, a compendial excipient can be a novel excipient,**" translates *per se* into any documentation requirement.

Moreover, the documentation requested in this section can be found in Lines 996 which simply states, "**• Novel Excipients: Information on novel excipients should be included in P.4.6 and A.3.**"

Given the preceding the commenter's beliefs are not supported by the plain language of the text.

In addition, if compendial, the requisite information on the excipient, outside of any special requirements imposed by the applicant (such as manufacturer-specified limits on particle size distribution, flow, intrinsic dissolution, viscosity, color, odor, etc.), should be readily available from the manufacturer thereof.

For all of the preceding reasons, this reviewer recommends retaining the text without change.

"Lines 981-986: AstraZeneca does not believe that the amount of test detail in an application depends on whether or not the applicant intends to perform full testing on each batch of excipient received versus vendor qualification and acceptance by Certificate of Analysis. AstraZeneca believes that full testing is not required by the Sponsor if a vendor has been certified, and that the testing documentation maintained by a certified vendor is a cGMP compliance issue and not a filing and review issue."

First of all, Lines 981 – **987** state, "**• Compendial-Non-novel Excipients:[26] When a compendial excipient is tested according to the monograph standard with no additional testing and the applicant intends to perform full testing on each batch received, 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. In any other circumstance, information should be included in P.4.1 through P.4.4 of the application. The P.4.1 to P.4.4 information for each individual excipient should be grouped together in the application.**"

Thus, if an applicant does all of the testing required in this case in a manner that complies with the applicable CGMP requirements, all that the applicant need do is list it.

If the applicant wants to partition the testing between itself and the manufacturer of the excipient or to do additional testing that is not in the compendium, as often the case, then the applicant needs to provide the requested information (P.4.1 through P.4.4).

By providing this information, the applicant provides documented evidence of what it is doing and the values it is observing and thus assists the applicant reviewer in determining whether or not the materials being used are adequately controlled in a manner that is CGMP compliant and ensures that the drug product will meet its specifications.

For the preceding reasons and all of the reasons stated in the previous responses to AstraZeneca's comments that, among other things, "believe" that anything to do with CGMP is automatically NOT an application issue, this reviewer again dismisses this comment and supports keeping the draft text without change.

"Lines 1022-1024: The draft guidance recommends that the excipient specifications should indicate which tests will be performed by the manufacturer and which tests will be accepted by Certificate of Analysis. AstraZeneca believes this is a cGMP compliance issue and not a filing and review issue. AstraZeneca recommends that this proposed requirement be deleted from the draft guidance document."

Again the commenters attempt to artificially separate the reviewers into two groups those responsible for reviewing the application and those responsible for auditing the manufacturer.

They overlook the realities that: **a)** both groups are charged with ensuring that the production processes and the drug products approved are CGMP compliant and **b)** both are not only reviewers but also both recommend ether the granting or the withholding of the approval that the applicant is seeking.

Factually, both groups need the information requested to properly discharge their responsibilities.

Therefore, this reviewer recommends that the text in the draft be incorporated into the final guidance.

"Line 1062-1067: AstraZeneca requests that the Agency clarify that validation of excipient methods is not required for compendial methods. AstraZeneca further requests that the Agency clarify what is meant by 'verification' of analytical methods."

First of all, this reviewer was surprised to read that the commenters do not understand "what is meant by 'verification' of analytical methods."

In the drug CGMP, 21 CFR 211.194(a)(2) states: **"The suitability of all testing methods used shall be verified under actual conditions of use."**

Since this has been a CGMP requirement since 1979, this reviewer has a hard time "believing" that the commenters do not know that this "what is meant by 'verification' of analytical methods."

Hopefully, after they read this review comment, they will.

This reviewer would suggest that the commenters carefully read the lines cited.

The text clearly indicates that, ***if used without modification***, compendial and methods from any other FDA-recognized source need only be "verified to be suitable under actual conditions of use."

Thus, in this context, having "verified" such an excipient method "to be suitable under actual conditions of use" results in a "validated" analytical procedure for excipient.

Therefore, the text is valid as written and should be retained.

"Lines 1081-1082: The draft guidance recommends that the same degree of justification is necessary for noncompendial excipient specifications as for drug substance specifications. AstraZeneca believes that this level of detail is not necessary, particularly for non-novel excipients."

Apparently, the commenters have failed to read the sections of the drug CGMP regulations governing the components especially those contained in **21 CFR 211.84** and **21 CFR 211.160(b)(2).**

Since 1979, the legal regulations governing the manufacture of drug products have required the active and inactive (excipients are, by definition, inactive) components to be treated in the same manner.

Therefore, this reviewer is surprised that the commenters would raise this as an issue.

Based on the preceding, and the application reviewers' need for documented evidence to establish that the applicant is submitting an application that establishes that the proposed process and drug product conforms to CGMP, this reviewer understands that the requested information is needed.

Thus, this reviewer recommends that the draft text be adopted in the final guidance.

"Lines 1089-1091: AstraZeneca believes that only test data used to release a batch of excipient should be included in an application. Comparison of vendor data to drug product manufacturer data for an excipient is a cGMP compliance issue and not a review issue. AstraZeneca does not believe it is appropriate to include this information in an application and that these data should be made available during inspection."

For all of the reasons stated in the previous answers to comments that attempt to remove proof of CGMP compliance from the application review process, this reviewer again finds the commenter's remarks to be unsupportable based on the reality of the requirements of CGMP as expressed in the **FDC Act** and reiterated in **21 CFR 210** which, though some seem to forget, applies to drugs and drug products.

This reviewer strongly recommends that the commenters read the referenced sections of both.

To aid the commenters, the applicable cites in **21 CFR 210** are:

Sec. 210.1—Status of current good manufacturing practice regulations.

(a) **The regulations set forth in this part and in parts 211 through 226 of this chapter contain the minimum current good manufacturing practice for methods to be used in, and the facilities or controls to be used for, the manufacture, processing, packing, or holding of a drug to assure**

that such drug meets the requirements of the act as to safety, and has the identity and strength and meets the quality and purity characteristics that it purports or is represented to possess.

(b) The failure to comply with any regulation set forth in this part and in parts 211 through 226 of this chapter in the manufacture, processing, packing, or holding of a drug shall render such drug to be adulterated under section 501(a)(2)(B) of the act and such drug, as well as the person who is responsible for the failure to comply, shall be subject to regulatory action.

Sec. 210.2—Applicability ofcurrent good manufacturing practice regulations.

(a) The regulations in this part and in parts 211 through 226 of this chapter as they may pertain to a drug and in parts 600 through 680 of this chapter as they may pertain to a biological product for human use, shall be considered to supplement, not supersede, each other, unless the regulations explicitly provide otherwise. In the event that it is impossible to comply with all applicable regulations in these parts, the regulations specifically applicable to the drug in question shall supersede the more general.

(b) If a person engages in only some operations subject to the regulations in this part and in parts 211 through 226 and parts 600 through 680 of this chapter, and not in others, that person need only comply with those regulations applicable to the operations in which he or she is engaged.

For all of the preceding reasons, this reviewer recommends that the draft text be incorporated into the final guidance.

"Line 1115: AstraZeneca requests that the Agency clarify if a new or different route of administration qualifies excipients as novel. The draft guidance recommends that the same degree of justification is necessary for novel excipient specifications as for drug substance specifications. AstraZeneca believes that this proposed requirement is unnecessary, particularly for compendial excipients that are considered 'novel.'"

Though this reviewer would consider both to qualify an excipient as novel – his "two cents" opinion, this reviewer will defer to the FDA – "its their nickel."

Again, the commenters have failed to consider the sections of the drug CGMP regulations governing the components especially those contained in **21 CFR 211.84** and **21 CFR 211.160.**

Since 1979, the legal regulations governing the manufacture of drug products have required the active and inactive (excipients are, by definition, inactive) components to be treated in the same manner.

Therefore, this reviewer is surprised that the commenters would raise this as an issue.

Based on the preceding, and the application reviewers' need for documented evidence to establish that the applicant is submitting an application that establishes that the proposed process and drug product conforms to CGMP, this reviewer understands that the requested justifications are needed.

Moreover, for all of the reasons stated in the previous answers to comments that attempt to remove proof of CGMP compliance from the application review process, this reviewer again finds the commenter's remarks to be unsupportable based on the reality of the requirements of CGMP as

expressed in the FDC Act and reiterated in **21 CFR 210** which, though some seem to forget, applies to drugs and drug products.

Thus, this reviewer recommends that the draft text be adopted in the final guidance.

> "Line 1162: The draft guidance recommends that both release and shelf-life specifications for drug product be filed. AstraZeneca believes this recommendation represents new regulatory policy. AstraZeneca requests that the Agency clarify this proposed recommendation and provide clear guidance on whether the Agency intends to require Sponsors to register in-house release limits."

Again, this reviewer would recommend that the commenters carefully read the CGMP requirements for drug product release set forth in **21 CFR 211.160**, **165**, and **167** and the General Notices section of the USP that clearly states the USP's "in commerce" sampling plans are "not statistical sampling plans," its lifetime post-release specifications may, or may not, be appropriate for release, and each firm should develop appropriate release specifications.

In doing so, the commenters should focus on the requirements of **21 CFR 211.165(d)**, "**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.**"

Since to comply with **21 CFR 211.165**, one must a valid statistical sampling plan and the **USP**'s sampling plans are not statistical sampling plans, the release specifications cannot validly be based on any aspect of the **USP**'s sampling plan.

Thus, since 1979, the CGMP regulations have required release specifications that are scientifically sound and based on, among other things statistical quality control (SQC) and the FDC Act has required, post-release compliance to the non-statistical **USP** "article in commerce complies when tested" requirements

Therefore, since 1979, if a firm has operated in compliance with CGMP (*as the FDC Act requires*), they have had two specifications for their product,

1. **A statistically based specification** that complies with all the applicable requirements of **21 CFR 211.160, Sec. 211.165, Sec. 211.166**, and **211.167** including the specific requirements set forth in **21 CFR 211.160(b)(3) and 21 CFR 211.165(d)**, and
2. **A USP-based *post-release* specification** for articles in commerce.

Thus, the guidance's request is not new regulatory policy.

It is a request for the firm to prove that its applications comply with CGMP.

What is clear is that the FDA's guidance is requesting that a firm provide proof of compliance with the batch-release requirements of drug CGMP.

Nothing that a firm has not been required to comply with for more than two decades is being requested.

Hopefully, the FDA intends to require Sponsors to provide proof that their applications comply with the law and therefore no guidance, clear or otherwise, is needed concerning "in-house release limits."

Therefore, this reviewer recognizes that this information is key to the application reviewers' ability to determine that the production process and the drug product comply with CGMP.

This text should therefore be incorporated without change into the final CMC guidance.

"Line 1176: AstraZeneca believes that the implementation of the proposed PQIT is in direct conflict with the Agency's Process Analytical Technologies (PAT) initiative and has the potential to inhibit the effective development and application of PAT."

Obviously, the commenters apparently do not understand either PQIT or PAT.

One has nothing *per se* to do with the other.

PAT is designed to apply in-process dynamic analysis to shorten the delay time between the various "phases" in the manufacture of a drug product.

21 CFR 211.110(c) requires (*emphasis* added): "***In-process materials shall be tested*** for identity, strength, quality, and purity as appropriate, ***and approved or rejected by the quality control unit, during the production process***, e.g., at commencement or completion of significant phases or after storage for long periods."

21 CFR 211.160(b)(2) requires: "***Determination of conformance to written specifications*** and a description of sampling and testing procedures ***for in-process materials.*** Such ***samples shall be representative*** and properly identified.

21 CFR 211.160(a) requires: "The establishment of any specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms required by this subpart, including any change in such specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms, shall be drafted by the appropriate organizational unit and reviewed and approved by the quality control unit. ***The requirements in this subpart*** (Subpart I—Laboratory Controls) ***shall be followed and shall be documented at the time of performance.*** Any deviation from the written specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms shall be recorded and justified."

PAT is designed to apply on-line automation to dynamically measure a set of samples that is collectively batch-representative as the manufacturing phase progresses rather than, what is typically the case, a) sample the representative samples (dynamically across the phase or at the end), b) transport them to the lab, c) have the lab prepare the samples for evaluation, d) test the sample preparations, e) generate results, f) verify that the results are valid and g) then have the quality control unit (QCU) decide whether or not the batch can be released to the next phase.

The goal of PAT is to eliminate steps a) through d) by directly testing the material and controls materials to verify instrumentation validity without physically removing any sample from the batch.

Then, using validated computerized systems evaluate the batch results and the control results to verify the batch is releasable to the next step just after the current step has been completed.

The QCU would then only need to review the data for the samples and controls and the system's findings and electronically either release the batch for further processing or reject it.

Since a periodic quality indicator test (PQIT) is, by definition, an additional quality indicator (quality assessment) test that is performed periodically to assess the quality of whatever that the test is designed to monitor.

Thus, PAT is an initiative addressing the required routine sampling, testing, evaluation and release controls and PQIT is a test outside the normal testing envelope.

Therefore the commenter's remarks: a) are, at best, based on a misunderstanding of both PAT and PQIT and b) should therefore be disregarded.

Since there is no conflict, this reviewer applauds the Agency for seeking to advance the goals of quality by suggesting this option to the industry and would hope that it is incorporated into the final guidance in its present form.

"Lines 1219-1221: The draft guidance recommends that a Changes Being Effected Supplemental New Drug Application (CBE) be submitted to the Agency to include a PQIT test in the drug product release specifications in the event of a batch failure. AstraZeneca believes that submission of a CBE should not be required, and recommends that a commitment to include the test in the release specification, if a failure occurs, be made in the original application."

Obviously, the Agency needs to be informed whenever a firm's routine quality system is found to have failed.

Provided the commitment in the application includes a commitment to immediately notify the Agency in writing whenever a failure occurs in the release area (a Field Alert is the only other appropriate mechanism besides the CBE that this reviewer), this reviewer has no problem with the commenter's suggestion.

"Lines 1277-1278: The draft guidance recommends that stability data be used to support validation of analytical methods. AstraZeneca requests that the Agency clarify if this is a new regulatory requirement and further clarify why this recommendation is needed, since it is expected that stability data will be generated using validated analytical methods."

The Agency is requesting that the applicant provide data to support the validity of the analytical test procedures used.

Again this is just asking that the firm provide proof that the analytical procedures are valid.

Having been involved in more than one instance where the analytical test procedure was less than valid (scientifically sound), this reviewer understands all to well the need for this data. [In the worst case, the method submitted in the approved application seemed to be deliberately designed not to work – the method proposed dissolving a softgel capsule by dropping it into 25 mL of cold water in an open Erlenmeyer flask, stirring it in an ultrasconic bath until the softgel capsule dissolves, and then injecting an aliquot into a GC to measure the level of residual solvent in the capsule. The "stirring step" heated the water up until it was hot enough to dissolve the softgel and, because the flask was open, allowed most of the residual solvent to be carried away with the water vapor that escaped the flask.]

Obviously the Agency has found more instances of this than this reviewer has and now knows that it needs to critically evaluate the analytical test data that establishes the validity of the analytical procedures.

Since this document is guidance, this reviewer does not see how the commenters can classify it as a new regulatory requirement – only a change in the regulations or the FDC Act can establish a new regulatory requirement.

Based on the obvious need for the information requested, this reviewer again finds that the draft text should be kept and incorporated "as is" into the final guidance.

"Line 1286: AstraZeneca recommends that this section should include results for all specification tests on appropriate batches and may also include additional tests which do not form part of the product specification as data to support justification for skip testing."

This reviewer finds that the draft guidance provided is what the Agency needs for a proper review of the application and that the commenter's proposed alternative does not ensure that the applicant will provide the needed results.

Lines 1288-1289: AstraZeneca requests that the Agency clarify if all safety and clinical batches used throughout all development phases need to be included in the batch analysis documentation, AstraZeneca recommends the use of commercial formulation batches.

This reviewer agrees that the Agency should clarify the draft guidance as the commenters suggest.

This can be easily accomplished by appropriately incorporating the suggested phase, "throughout all development phases" into the first sentence.

This reviewer does not agree with limiting the guidance's request to "commercial formulation batches."

Therefore, this reviewer recommends that the introductory portion (Lines 1288 – 1292) of this section of the final guidance should read:

"Batch analysis data should be provided for all batches, from all phases of development, that were used for clinical efficacy and safety, bioavailability, bioequivalence, and primary stability studies. Batch analysis data should also be provided for any other batches that are being used to establish or justify specifications and/or evaluate consistency in manufacturing. The batch analysis reports (e.g., COAs) and collated batch analyses data should include a description of the batches."

Lines 1332-1334: AstraZeneca requests that the Agency clarify if "collated data" means, for example, that assay data for all batches be included in the same table. If so, AstraZeneca believes this represents a new regulatory requirement.

First, given the meaning of the verb "collate" in this context, the Agency is requesting that each type of test be tabulated in a database in a manner that permits a viewer thereof to compare the data across all batches.

This request is being made to facilitate the Agency's review of the key data supporting the application by asking the applicant to provide the data in the format specified that, if not provided by the applicant, the reviewer would be compelled to compile the data.

Since collating unstructured data is a time consuming task, the applicant's question should be is it better for the firm if we supply the data in the requested format that permits easy comparisons or in a format that would compel the reviewer to collate it?

Again, because this is guidance it cannot be a regulatory requirement.

However, this reviewer does not think that the text goes far enough because it does not call for the tabulation of the most useful of all data – data that supports the uniformity of each batch with respect to its critical variable factors (such as, for solids, active content, and active release (Dissolution or Drug Release); for liquids, ointments and creams, average content, deliverable volume, and, in some cases, Dissolution, pH and preservative level; and, for metered products, delivered dose, number of doses per container and, in some cases, particle size distribution.

Therefore, this reviewer suggests the following:

"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), and, to assess batch uniformity:

a) For solids and unit-dose drug products in any form: active content, and the appropriate active availability test (Dissolution, Drug Release or, rarely, Disintegration
b) For multiple-dose liquids, ointments, creams and the like: average content, deliverable volume, and, in some cases, Dissolution, pH and preservative level.
c) For metered products, delivered dose, number of doses per container and, in some cases, particle size distribution.

The reporting of collated data should be considered for other tests such as water content."

Line 1386-1409: AstraZeneca recommends that if residual solvent and miscellaneous impurities are discussed and controlled in other parts of the application, there is no need to repeat that information here. AstraZeneca further believes that if residual solvents are not used in the drug product and compendial excipients are used in the formulation, there is no need for this section. Residual solvents and miscellaneous impurities are not required when these are controlled by component specifications.

The commenters should reread the predicate lines (Lines 1360 to 1365) to the Lines (1386—1409) that the comment provided is addressing.

The predicate lines state (emphasis added):

"2. Identification of Impurities

Information on the characterization (i.e., structural characterization) of impurities should be provided if not previously provided in S.3.2. An applicant is encouraged to discuss any questions about the identification of impurities with the appropriate review divisions.

Clearly, "Residual Solvents" and "Miscellaneous Drug Product Impurities" only need to be reported here when they have not been reported previously in S.3.2.

Therefore, this section is needed to ensure that, ifn ot reported in Section "S.3.2," these get reported t the Agency.

Given the overall wording, this reviewer thinks that the wording provided in the draft should be incorporated into the final CMC guidance.

"Lines: 1533- 1534: AstraZeneca requests that the Agency provide clarification and further guidance for the level of detail required for functional secondary packaging."

Lines 1534-1536: The draft guidance recommends that a brief description be provided for nonfunctional secondary packaging components. AstraZeneca believes that this recommendation is unnecessary because these components do not provide an additional measure of protection to the drug product.

If the application review personnel are to truly understand the drug-product production process, then applicant should provide the descriptions being requested by the Agency.

Line 1560: AstraZeneca requests that the Agency clarify if the recommendation to provide a post-approval stability protocol includes a stability protocol for annual stability batches.

Line 1607: AstraZeneca recommends that stability data for holding in-process materials less than 30 days is a cGMP compliance issue and is not a filing and review issue. Supportive data should be maintained on file with the Sponsor and available for review during an Agency inspection, and should not be required for inclusion in a filing.

This reviewer continues to oppose attempts to exclude information that is needed by the application reviewers from being incorporated into the application simply because the information is required by CGMP.

For the reasons stated repeatedly in this reviewer's comments, all of the application reviewers, not just those who perform the requisite PAIs, are charged with ensuring the application establishes that both the drug

manufacturing process and the drug product adhere to all of the CGMP requirements.

Both this reviewer and the commenters agree that determining stability is needed to justify hold times and that it is a CGMP requirement.

Therefore, the original text in the draft should be included in the final guidance.

Lines 1644-1739: AstraZeneca requests that the Agency clarify that this information is in agreement with current guidance from the International Conference on Harmonization (ICH) and is only required in applications for biotechnology-derived products.

This reviewer disagrees with the commenters and thinks that the requested information should be gathered and reported in the application for any facility where there is an identifiable potential safety risk to the drug product and/or the public.

Lines 1840-1843: AstraZeneca requests that the Agency clarify that this section can contain hypertext links to appropriate analytical methods and validation reports that permit the Agency reference laboratories to produce hardcopies.

This reviewer cannot agree with the commenter's proposal because: a) the regulations require that the requested information be submitted to the Agency and b0 there is no way the Agency can ensure that the methods in the links are exactly the same as the methods certified for use by the applicant.

If an applicantd oes not wish to bear the burden of providing the required number of paper copies, then the applicant can submit an electronic application.

Either way the required documentation packages (21 CFR 314.50(e)(2)(i) and 314.94(a)(10)) MUST be submitted.

A REVIEW OF FORMAL COMMENTS TO PUBLIC DOCKET 02D-0526

IPEC America's Submission Dated June 26, 2003
To Docket 02D-0526: "C-09"

[**Note:** The original INTRODUCTORY and GENERAL comments are quoted in a condensed font (**Perpetua**), the quotes directly from the draft guidance are quoted in a stylized font (**Lydian**) and this reviewers comments are in a publisher's font (**News Gothic MT**) to make it easier for the reader to differentiate the "speaker" in the various text passages that follow. When this reviewer is only addressing a portion of the commenter's remarks, the commenter's text will be **bolded**]

The commenters begin by stating: "The following comments are submitted on behalf of the International Pharmaceutical Excipients Council of the Americas (IPEC-Americas). IPEC-Americas is a regional pharmaceutical industry trade association headquartered in Arlington, Virginia. Many of its member companies are U.S. based and manufacture either finished drug products or components used in such products for various purposes, and therefore are affected by the subject guidance. IPEC-Americas appreciates the opportunity to provide these comments. Individual member companies may also elect to do so separately."

"General Comments

1. IPEC-Americas applauds and generally supports the agency's effort to produce and publish this important guidance. This guidance is parallel to the efforts of IPEC-Americas to ensure the safety of excipients used in pharmaceutical products. It is the culmination of work begun years ago by Ralph Shangraw and others that has led to a greater understanding of the different roles excipients can play in the pharmaceutical manufacturing process and in drug delivery itself"

"2. We believe it is important to note that in addition to agency reviewers and industry drug formulators, this guidance will also be important to excipient producers. Many such companies are engaged in the development of new materials for use in pharmaceuticals, as well as for new uses of older materials. As the agency is aware, this innovation has become more frequent in recent years and has resulted in a number of significant therapeutic advances."

"3. **Our major comments concern the need for explicit registration of methods used for testing pharmacopoeial excipients.** We, of course, agree that the specifications applied to excipients must be consistent with those of the pharmacopoeia, and that methods used must be appropriate to demonstrate compliance. **The question we wish the Food and Drug Administration (FDA) to consider more carefully is the amount of paperwork necessary to ensure appropriate control of those excipients.** Excipients are an important part of most formulations, and in many cases the quantity of excipients is much greater than the active substance. Clearly, excipients must be controlled to ensure the quality of the pharmaceutical product and patient safety. **However, excipients differ from most active substances and finished products in that excipients are often used in multiple products.** Because of this fundamental characteristic, testing of a single excipient has a potential to impact many New Drug Applications (NDA) and Abbreviated New Drug Applications (ANDA). **Moreover, once initial product submissions are made, maintenance of excipient commitments in multiple NDAs/ANDAs becomes a significant burden for both manufacturers and the FDA."**

The commenter's remarks concerning the records maintenance burden are, at best, ad hominem.

Provided the manufacturers have carefully specified the excipients used, the only times the manufacturers will need to update their specifications are when: i) they change source materials; ii), if compendial tests are used, the compendial method changes; or iii) the manufacturer elects to change them.

Moreover, the monographs for compendial excipients do not, as a rule, change *frequently*.

Therefore, in most cases, the majority of the change burden is self-imposed.

In addition, though excipients that are compendially the same are used in multiple filings, often the grade (specific physiochemical properties within the permitted compendial envelope) of the excipients differ from product to product.

In many cases, *the grade of excipient is unique to* a particular manufacturer's formulation for, as narrow as, *a single strength of one product.*

Based on this reviewer's experience, the major portion of the records' updating "burden" arises from the non-compendial specifications that manufacturers are forced to adopt to ensure that each ACCEPTED lot of each excipient is the same as the lots initially used to obtain and support the approval of the manufacturing process.

For all of the preceding reasons, the commenter's observation, while true, is made in a way that distorts the impact of the Agency's proposed draft on the paperwork burden after the manufacturer receives approval.

Moreover, as written, *the draft guidance*, contrary to the implications of the commenter's remarks, *should have little*, if any, *real impact on the current post-approval paperwork burden*, provided the manufacturers are currently operating in compliance with CGMP.

This is the case because manufacturers are currently compelled by the CGMP regulations to update, at least annually, any changes in their specifications, standards, sampling plans, testing procedures and any other control mechanisms they employ.

"4. **The language used in sections P.4 through P.4.4 would require manufacturers to specify each method used for routine testing of excipients, unless the method is exactly that of the pharmacopoeia.** Two situations commonly occur which are impacted by this requirement: **First, methods are used which have been demonstrated to be equivalent or superior to those in the pharmacopoeia.** Often a manufacturer has methods used internally that are shown to produce equivalent results to those in the pharmacopoeia. Also, many manufacturers must meet global requirements and seek to eliminate redundant testing of the same property (e.g., European Pharmacopoeia (PhEur), United States Pharmacopeia -National Formulary (USP-NF), and Japanese Pharmacopoeia (JP) Heavy Metals tests) by selecting a single method shown to be capable of ensuring compliance with all the requirements. **Second, excipient testing is performed by the supplier and accepted on Certificate Of Analysis (COA). Suppliers are generally expected to perform testing to demonstrate compliance with pharmacopoeia requirements, and pharmaceutical manufacturers often accept the supplier results on COA. With proper auditing of supplier processes and lab capability, this practice ensures compliance. In each of the cases above, the pharmaceutical manufacturer must have systems in place to ensure compliance.**

However, even with appropriate internal controls, the regulatory hurdles in implementing and maintaining such systems are significant."

a. Contrary to the commenter's remarks, because the CMC guidance is just that guidance, the "**language used in sections P.4 through P.4.4**" *only requests* that the applicant provide information on the methods that they propose to use for the routine testing of the excipients.

b. When the method is an unmodified official compendial method (the commenter's "**the method is exactly that of the pharmacopoeia**"), the information request is limited to the official name of the method. In all other cases, more information is requested because more is required for the applicant reviewer to be able to judge whether or not **i)** the information provided meets CGMP strictures and **ii)** will ensure that the lots of each listed component will be the same as those used to obtain FDA approval when they meet the specifications established by the applicant.

c. Even the commenters recognize that "**the pharmaceutical manufacturer must have systems in place to ensure compliance**" – notice "must have" indicates that this is a recognized present requirement.

d. Moreover, when the commenters state "**the regulatory hurdles in implementing and maintaining such systems are significant,**" the commenters recognize that the systems in question are currently in existence and not, as the commenter's remarks would seem to imply, needing to be developed and implemented if the Agency's proposed draft guidance were to be issued in its present form as official CMC guidance.

e. Thus, the information request in P.4 through P.4.4 is: **i)** reasonable and proper and **ii)** asks the applicant for nothing, other than a copy of the information requested, that the CGMP regulations do not *already* require the applicant to establish and maintain.

5. **Because a particular excipient may be used in many products, submissions of the routine excipient-testing program would be required in many product registrations.** If the testing program were to be changed, for example, to reflect acceptance on supplier COAs or adoption of tests shown to meet multiple pharmacopoeias, each of these product registrations would have to be changed. **Also note that pharmacopoeia change frequently, so that testing regimes must also be amended to conform.**

a. The commenters begin by misstating the obvious – *applicants wishing to conform to the guidance's requests* would need to submit their routine excipient-testing programs (*which, **since 1979**, the CGMP regulations have required manufacturers to have*) for each new drug-product in the application (ANDA and NDA) that they submit.

b. However, as stated in the previous commentary, many of the manufacturer's requirements (specifications) are for tests that: **i)** are not in

the compendia or **ii)**, if in the compendia, have the ranges inside of those permitted in their compendial monographs. [**Note:** Examples include tests for physical properties such as bulk density, compressibility, flow, intrinsic solubility, isomeric distribution, oligomeric distribution, particle-size distribution, permeability, refractive index, surface roughness, tapped density, and viscosity; and chemical tests such as the CGMP-required one, "as is" purity," and uncommon ones such as ICP trace-metal fingerprinting and solid-state NMR.]

c. While the official compendial change frequently, **i)** most of the changes are to add new component monographs and general chapters to the compendium being updated, **ii)** the monographs for most excipients change much less frequently, and **iii)** increasingly the excipient monographs in the USP and NF are being harmonized with those in the EP and the JP.

6. In summary, this guidance would drive industry to adopt full monograph testing for each excipient using the exact methods specified in the USP-NF or Homeopathic Pharmacopoeia. The draft guidance presents barriers for companies utilizing alternative methods (e.g. PhEur, or JP), or vendor qualification strategies using audits or reduced testing protocols that eliminate redundant excipient tests. As written, the draft guidance creates a paperwork burden that would eliminate existing vendor qualification programs.

a. Given the CGMP requirement (**21 CFR 211.160(b)**) that a **manufacturer: i) must have and use** "***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***" and **ii) must ensure** that these are adequate to ensure that **each lot is the "same" as the lots upon which the drug product's approval rests**, the reality is that both the suppliers of excipients and the manufacturers of the drug products are increasingly developing and using product-specific tests and or specifications for excipients. The result is that, in some cases, each manufacturer has several "unique" proprietary grades of each of the excipients that it uses for the drug products it manufacturers. This is being done both to improve the manufacturer's control on the sameness of the lots of excipients used and, for new NDA and, in some cases, the first filed ANDA to thwart those who would copy the formulation.

b. Contrary to the commenter's unsubstantiated claim, this draft guidance presents no barrier to the use of methods in the EP (PhEUR) and the JP – *as the commenters should know*, the FDC Act is the source of the barriers that exist to the use of these pharmacopeias. Moreover, nothing is the draft guidance is a barrier, *per se*, to "**vendor qualification strategies using audits or reduced testing protocols that eliminate redundant excipient tests.**"

c. Finally, *nothing in the draft guidance*, which only requests that an applicant file some of the information that substantives its proposed processes, controls and drug product will comply with the applicable CGMP, *will create*

a significant paperwork burden beyond the current one much less one "**that would eliminate existing vendor qualification programs.**" The only things that might eliminate some of the existing vendor qualification programs is the Agency's finding: **i)** that the information provided by an applicant clearly indicates that the existing vendor qualification programs do not comply with the requirements of CGMP – mainly because the Agency may find, *as this reviewer often has*, the identity test (or tests) that the manufacturers are currentlyd oing are not the CGMP-required **specific** identity tests and/or the manufacturer'ss ampling plans and test proceduresd o not take and test lot shipment representative samples, **ii)** the vendor does not provide COAs that include the "as is" wt-% purity of the excipient when providing such should be required, or **iii)** the FDA audits the vendor's manufacturing site and finds that the testing done is not representative of the batch or not from the testing of all of the lots released for drug use ("pharmaceutical grade").

d. Given the increasing number of cases where drug product problems have been traced to problems with the quality of one or more of the components that the commenters classify as excipients, the science-based approach to compliance, and the attempt to use a scientifically sound risk-based strategy to ensure process and drug product compliance, the Agency's draft guidance actually requests less than it could, and perhaps should, have requested.

e. Based on all of the preceding, this commenter's remarks are not supported by: **i)** the existing CGMP requirements, **ii)** any scientifically sound or regulation-based counter proposal, or **iii)** a dispassionate review of the commenter's own words.

Having addressed the commenter's "General Requirements," this reviewer will now evaluate the commenter's "Specific Comments."

[**Note:** To minimize reformatting, ***within the tables that follow***, the commenter's original SPECIFIC comments are quoted in the **Arial** font used by the commenters and, the quotes directly from the draft guidance are in a **Times New Roman** font. This reviewer's comments are in a **News Gothic MT** font, and **Lydian** will be used as the font for citations from the **USP** or any legally binding US statute (**FDA Act**) or regulation (for example, **21 CFR 210** and **21 CFR 211**). The font differences should make it easier for the reader to differentiate the "speaker" within the tables that follow.]

"Specific Comments

(Guidance Citations are in Times New Roman font, and comments are in Arial)"

Line #s, page #	Guidance Citations with comments
Lines 981 - 987, page 27	"Compendial-Non-novel Excipients: When a compendial excipient is tested according to the monograph standard with no additional testing and the applicant intends to perform full testing on each batch received, the excipient (e.g. Sodium Chloride, USP) can be listed under P.4 with no detailed information provided in P.4.1 to P.4.4." The implication is that the applicant will not be able to use vendor qualification to accept excipients via COA without providing additional information in the application. On the other hand, the USP General Notices state that application of every analytical procedure is not needed to meet compendial requirements. In addition, 21 CFR 211 states "In lieu of such testing by the manufacturer, a report of analysis may be accepted from the supplier of a component, provided that at least one identity test is conducted by the manufacturer." In such cases, the manufacturer establishes the reliability of the suppliers test results through validation at appropriate intervals. It is not reasonable to require the pharmaceutical manufacturer to commit to fully test all excipient lots. 1. The commenter's first observation is correct but the extra information required is information that the firm is required to have. To comply with **21 CFR 211** (the drug products) CGMP. 2. In this instance, the commenters have **a)** taken what the **USP General Notices** say out of context and **b)** misquoted it. In context, the **USP**, *discussing tests for the **RELEASE** of a compendial item into commerce **by the manufacturer thereof***, states: "However, it is not to be inferred that the application of every analytical procedure in the monograph to samples from every production batch is necessarily a prerequisite for assuring compliance with Pharmacopeial standards before the batch is released for distribution. Data derived from *process validation* studies and from in-process controls may provide greater assurance that a batch meets a particular monograph requirement than analytical data derived from an examination of finished units drawn from that batch." Thus, this reviewer fails to see how the **USP**'s guidance to the compendial item's manufacturer applies in this instance other than to point out that the excipient manufacturer may not be performing the compendial tests. 3. By omitting the word "specific," the commenters misconstrue **21 CFR 211** in a manner that is critical to the understanding of what is required. Correctly, **21 CFR 211.84(d)(2)** states (emphases added): "... In lieu of such testing by the manufacturer, a report of analysis may be accepted from the supplier of a component, provided that at least one specific identity test is conducted on such component by the manufacturer, and provided that the manufacturer establishes the reliability of the supplier's analyses through appropriate validation *of the supplier's test results* at appropriate intervals." The reason that the word **specific** is crucial is that the **USP monograph**'s **IDENTIFICATION** tests are, as written, NOT truly specific (in analytical testing, a specific test has to differentiate the material being tested from *all other similar* and dissimilar *materials* – a requirement that few tests meet and a requirement that the **USP IDENTIFICATION** tests rarely meet). 4. As written, the draft guidance does not "require the pharmaceutical manufacturer to commit to fully test all excipient lots." 5. Based on **Points 1** through **4**, the draft text should be incorporated "as is" into the final guidance.

Line #s, page #	Guidance Citations with comments
Lines 1022 - 1024 and Footnote 27, page 28	"In addition to listing all the tests for an excipient, the specification should, identify the tests that the drug product manufacturer will routinely perform and the test results that will be accepted from the excipient manufacturer's COA." The drug manufacturer does not normally know at the time a submission is filed which tests will be accepted from the vendor's COA. At submission, the manufacturer may have limited experience with some of the excipients or suppliers. Because there is limited experience with new excipients, or new suppliers, an excipient from supplier 1 might be accepted on a COA, but the same excipient from supplier 2 might require full testing. Therefore, a reduced testing program by the drug product manufacturer would only be implemented well after submission of the NDA. Deletion of the requirement and footnote is requested. 1. The applicable CGMP requires the drug product manufacturer to have established the firm's specifications, standards, sampling plans, test procedures, and other laboratory control mechanisms prior to engaging in the manufacture of any drug product for introduction into commerce (21 CFR 211.160(a). Moreover, to be incompliance with the requirements of the FDC Act's CGMP strictures, set forth in section 501(a)(2)(B) of the act, the applicant must submit an application that demonstrates that the processes and control and drug products are in conformance with CGMP. Since a firm cannot know what its scientifically sound and appropriate specifications, sampling plans and test procedures are for a material unless it knows which tests it will be performing on that material, it is required for the manufacturer to know, at the time of submission, which tests it will perform. Therefore, a CGMP-complaint application cannot be submitted until the inspection plans that the firm proposes to use have been established and approved by the quality control unit. 2. Based on **Point 1**, while the manufacturer's experience may be limited, CGMP requires it to be sufficient to establish "**scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that**" each component conforms "**to appropriate standards of identity, strength, quality, and purity**" (**21 CFR 211.160(b)**). To be CGMP compliant, the applicant must have these BEFORE submitting an application or the application is violative (does not conform to the FDC Act's expectations for CGMP). 3. Moreover, for the example given, the manufacturer's inspection plans would simply be required to be material source specific or hierarchical (have scientifically sound a) defined criteria for various levels of inspection and b) switching rules governing the progression from level to level – not a big deal really. *In fact, a quality proactive company understands the utility of such plans and would probably have such for all control areas (incoming, in-process, release, and post release).* 4. To address the issue of reduced plans at later points, the firm need only submit a valid hierarchical plan like that discussed in **Point 3**. Based on **Points 1** through **4**, this reviewer **a)** finds the commenters have submitted no valid justification for deleting this text from the CMC guidance; **b)** understand, based on the commenters' own words why the Agency, committed to a science-based approach to establishing CGMP compliance that is capable of assessing risk, is requesting that this information be provided; and **c)** supports its inclusion in the final guidance (**see PhRMA section**).

Line #s, page #	Guidance Citations with comments
Lines 1026 – 130, page 28	"However when there are specific concerns relating to an excipient, testing in addition to an identity test would be warranted." Revise the statement to read "... testing in addition to an identity test may be warranted." 1. In suggesting this, the commenters disregard the implication of the phrase "specific concerns." When there are concerns, the FDA and CGMP expect that those concerns will be addressed – not that they may be addressed. For example, if a manufacturer of an inhaler has concerns that some lot of metered-dose containers contain no active, that firm is supposed to do additional testing to either confirm or ally its concern. 2. Given the nature of these concerns, they can only truly be addressed by performing testing appropriate to the concern (i.e., if it is a microbial contamination concern then the firm must do microbiological testing and not assay testing 3. Based on **Points 1** and **2**, the text in question is proper as written and the alternative wording is NOT – concerns are NOT permitted to go unadressed and, in this context additional testing "would be warranted." Therefore, this comment is invalid and should be ignored.. And "For example, diethylene glycol contamination of polyols such as glycerin and propylene glycol has caused numerous fatalities.. . " This is an example where basic GMPs were not used. The impact of this tragedy is great and cannot be ignored, but other tools are available to ensure excipient and excipient supply chain safety. When excipient suppliers and users apply appropriate GMPs the excipient supply chain is made reliable. For glycerol, the USP monograph includes specific testing for diethylene glycol, so the reference to this specific 'additional testing' is unnecessary. The comments made are non-sequiturs, unsubstantiated self-serving generalizations, and information that is not relevant to the issue that the example presents. What difference does it make if the tests exist ***when they are not used***? It makes no difference. Thus, as the Agency points out, when there is a known danger that may be present in a given excipient (a specific mandated "safety" concern that drug manufacturers must address under CGMP), then the manufacturer must do the tests that address that concern or risk the civil and criminal penalties that may accrue when a concern is ignored and public harm results (500 plus billion dollars and counting for the most recent instance in the US).

Line #s, page #	Guidance Citations with comments
Lines 1032 - 1035, page 28	"Only a citation to the appropriate official compendium need be provided when the excipient specification is identical to the compendial monograph and full monograph testing will be performed on each batch of excipient" Excipient Quality is not improved by full monograph testing. If other internal testing and audits have confirmed excipient supplier data, then supplier data can be accepted. See Lines 981 - 987 for similar comments. 1. Do not understand the direct relevance of the commenter's remarks to the text cited. 2. Though excipient quality is not improved by full monograph or, for that matter, any other testing, *the testing firm's understanding of* what *the quality of the lot* being tested truly is *certainly improves* when additional relevant testing is performed. 3. Even when a supplier's data may properly be accepted, certain tests are required, including, but not limited to, those that determine the specific identity of the excipient or other component and those that address concerns that are associated with said excipient or component. 4. The cited text does not suggest that other approaches may not be used. 5. Based on **Points 1 though 4**, the commenter's remarks are not relevant to the guidance being suggested – yes, guidance not regulation. As such, the comments should therefore be ignored.

Line #s, page #	Guidance Citations with comments
Lines 1035 - 1038, page 28	"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) or test results will be accepted from the excipient manufacturer's COA, the in-house specification should be provided. " See Lines 981 - 987 for similar comments. Please read the review comments made to this commenter's remarks concerning this draft guidance.

Line #s, page #	Guidance Citations with comments
Lines 1038 - 1041, page 28	"If the specification for an excipient is based on a compendium other than an official compendium, the excipient should still conform to the monograph in an official compendium, if there is such a monograph" The "official compendium" should clearly state USP-NF and Homeopathic Pharmacopoeia. This section should refer to PhEur and JP, specifically because there is much current effort to bring USP, PhEur and JP into a greater degree of agreement. There is a difference between conforming to a monograph and to a compendia. Focus on the monograph eliminates General Chapters, and GMPs that are in place to ensure excipient safety. 1. This reviewer agrees with the commenter's first statement that it would be clearer if the guidance text were to spell out in the text the official compendia and would propose modifying the text to read: If the specification for an excipient is based on a compendium other than the United States Pharmacopeia, the National Formulary or the Homeopathic Pharmacopeia of the United States (the ONLY official compendia recognized by the FDC Act), the excipient should still conform to the monograph in one of these official compendia. if there is such a monograph." 2. Since, by law (FDC Act), only the listed compendia may be referenced, the FDA should not reference other compendia by name in its guidance. 3. Contrary to what the commenters assert, if one asserts that one conforms to a monograph contained in the USP, then one is also asserting conformance to that compendium because one cannot conform to the first without also conforming to the second – would suggest that the commenter read the **General Notices** section of the **USP** to confirm the validity of this statement. 4. The commenters' last sentence is, at best, confused and patently untrue with respect to the relationship between the monograph in a compendium and its **General Chapters**. Moreover, its syntax is difficult to interpret. Do the commenters mean: "Focus on the monograph eliminates **General Chapters**" and "GMPs ~~that~~ are in place to ensure excipient safety"? Or is the remark intended to be read: "Focus on the monograph eliminates": **a)** "**General Chapters**, and" **b)** "GMPs that are in place to ensure excipient safety." The former reading is partly factual; while the latter reading seems to be Freudian. 5. Based on **Points 1** through **4**, this comment should be ignored and the proposed text incorporated in to the final CMC guidance.

Line #s, page #	Guidance Citations with comments
Lines 1043 -1046, page 29	"However, where a difference appears, or in the event of dispute, the result obtained from the USP procedure is conclusive." Sentence deletion is requested, because the phrase is duplication of compendia requirements. Contrary to the commenter's remarks, the text cited expresses the legal status of the official compendia as set forth in the Food, Drug, and Cosmetic Act as amended (FDC Act). Given the commenter's demonstrated lack of understanding in this regard, it is obvious that this text needs to be included in the final CMC guidance perhaps with the citing of the FDC Act section.

A REVIEW OF FORMAL COMMENTS TO PUBLIC DOCKET 02D-0526

Line #s, page #	Guidance Citations with comments
Lines 1089 - 1092, page 30	"A COA from the manufacturer and the test results for the same batch from the drug product manufacturer should be provided for the components described in P.4." This requirement duplicates GMP requirements for confirmatory testing. Please delete the sentence. 1. Factually, this request is: **a)** not a requirement and **b)** duplicates nothing in the CGMP for any testing – it is simply a request for information. 2. Because the Agency needs evidence in the application to establish that the filed production processes, including incoming component receipt, handling, and release, and the drug product controls meet all applicable CGMP requirements, the Agency's request for this information is appropriate. 3. Based on Points 1 and 2, the commenter's request should be denied and the text in question incorporated "as is" into the final CMC guidance.

Line #s, page #	Guidance Citations with comments
Lines 1092 - 1094, page 30	"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." If the material must pass the compendia test, then there is little point in putting in different qualitative text such as "does not form precipitate" or "violet-blue color" from the method onto the COA. For this type of compendial requirement, it either meets the specification or it doesn't. Therefore, on the COA, for compendial tests, it is sufficient to report the test result as "pass". For non-compendial methods, there may be value to reporting the results numerically or qualitatively since the expected results of non-compendial tests may not be obvious to a reader. Please delete "Use of terms such as conforms or meets specification is discouraged." 1. The commenters begin by ignoring the purpose of any report or certificate of analysis – to report: a) the samples tested, b) the tests performed and c) the resultsf ound. The assessment of passing, or not, is what the evaluatory remarks and the signature attesting thereto are supposed to convey. 2. Contrary to what is asserted, even when a material does not pass, a certificate of analysis is required to so that the concurrence of the controlling authority (signature) supports the evaluation of the results found. 3. In today's world, where the test is qualitative, the format for the "Is Approved for Release" COA contains boilerplate wording so that the Agency's request presents no significant report generation burden beyond initial set up. 4. This reviewer's own inclination (as stated in the reviewer's response to the docket) is to prohibit the use of "conforms" or "meets specification" because they obscure what the test result was. 5. In light of **Points 1** though **4**, and this commenters rationale, this reviewer has seem that the Agency's position represents a reasonable compromise and, in light of this commenter's remarks about non-compendial tests, would suggest that the draft text, as a compromise, be revised to read: "Test results should be expressed numerically or qualitatively (e.g. clear, colorless solution), as appropriate. Moreover, for non-compendial tests, the use of terms such as 'conforms' or 'meets specification' is proscribed."

A Review of Formal Comments To Public Docket 02D-0526

Amersham Health's Submission Posted June 26, 2003 To Docket 02D-0526: "C-08"

Note: The original INTRODUCTORY and GENERAL comments are quoted in a condensed font (Perpetua), the quotes directly from the draft guidance are quoted in a stylized font (Lydian) and this reviewers comments are in a publishers font (News Gothic MT) to make it easier for the reader to differentiate the "speaker" in the various text passages that follow.]

The commenters made no introductory comments about the firm other than to state how it had responded to the docket.

That having been said let us get right to the comments.

"General Comments:"

"1. Where appropriate, provide a correlation table matching the old NDA format to the new CID format. This helps to place the information in the old format into the correct section in the CTD format."

This reviewer agrees – this is an excellent suggestion!

"2. Delete section classifications III, IV, V, VI, VII, VIII, IX, X, XI, XII, XIII and replace with P1, P2, P3, P4, P5, P6, P7, P8, A, and R, respectively. For example, use "P.2 PHARMACEUTICAL DEVELOPMENT" instead of "IV PHARMACEUTICAL DEVELOPMENT (P.2)" This will allow the document to be consistent with CTD section names and numbers."

This too is a good suggestion.

"Specific Comments:"

"1. Section IV-C (P.2.3); Lines 580-582: The statement can be extended to include: ". . . . if differences in the equipments used in the various phases could have impact on quality, safety and efficacy".

While thinks he understands the commenter's motivation, this reviewer must object because it does not provide the Agency with information about the comparison of equipment across all phases without regard to whether, *in the manufacturer's opinion*, the differences "**could have impact on quality, safety and efficacy**" to ensure that all that end up being provided.

To address this in a manner that ensures all should be captured and reported, this reviewer suggests the following sentence be added to give:

"**A table should be provided that compares the equipment used to produce clinical batches that support efficacy or bioequivalence and primary stability batches to the equipment proposed for production batches.** To facilitate review, those changes that may affect the quality, safety and efficacy of the drug product and those that cannot may be presented in separate tables."

Done in this manner, the guidance provides flexibility and assures that the information supplied should assist the application reviewer to see what the change are and what their impact may be.

"2. Section IV-D (P.2.4); Lines 596-597: The statement needs to be explicit with regard to other (non-protein) drug products."

This reviewer concurs with the commenter's suggestion

"3. Section V-C (P.3.3); Lines 808-809: The meaning of 'equipment identify by type' should have a more extensive explanation."

This reviewer supports the commenter's suggestion.

"4. Section VI-A (P.4)/(P.4.1); Lines 996-1011: There is no need to provide information in P4.6 that is given in A.3. Cross reference to A.3 should be sufficient.

Since the information requested is both extensive, this reviewer tends to agree with the commenter's suggestion unless the Agency's experience with similar has found that duplicating the information facilitates the application review process – in which case, the information should be duplicated.

"5. Section VII-A (P.5.1); Line 1176: Provide the definition of Periodic Quality Indicator Test in the Glossary."

This reviewer again supports the commenter's suggestion.

"6. Section VII-A (P.5. I); Lines 1187-1 189: The sentence 'A PQIT can be warranted when a test, performed and reported as part of the batch analyses, has value as an indicator of product quality, but information indicates that the test need not to be performed on each batch of drug product' is somewhat ambiguous and should be re-written."

This reviewer concurs with the commenter's remark and offers the following to address the ambiguity in the draft's text:

"A PQIT may be warranted when a test, reported as a part of the batch analyses, has value as an indicator of product quality but the test is: a) one that has been done in addition to the set of tests required for routine production control and b), based on in-depth analysis of the data and previous experience, not required to be performed on each batch. For example, a test for the distribution of magnesium (as an indicator for the distribution of magnesium stearate added to the formulation as a tableting lubricant) in tablet cores when the routine in-process uniformity assessment control tests are weight, non-destructive NIR assessment of active level and disintegration."

"7. Section VII-A (P.5.1); Lines 1212-1215: Should not an Out of Specification (00s) investigation for a PQIT be resolved before any new production of batches?"

This reviewer agrees with the commenter's remark and offers the following curative modification to the draft's language:

"• failure to meet the acceptance criteria for the PQIT will be handled (e.g., investigation, batch rejection decision) in the same manner as a failure of a test included in the drug product specification and, after the possible causes for the PQIT failure have been identified, appropriate corrective action has been initiated and the *quality control unit* permits production to resume, the PQIT will be performed on each subsequent batch until ~~the failure is~~ all data indicate that the corrective actions taken have truly identified and resolved the root cause or causes of the failure.

"8. Section VII-A (P.5.1); Line1216: Delete the word 'all' from the sentence."

While this reviewer agrees with the commenters that, as written, the scope is overly broad but suggests that a better remedy would be to remove the text "batches produced, in particular, the" and change the end to "the last batch tested" to give:

"• any investigation will assess the effect on all ~~batches produced, in particular, the~~ batches between the last batch tested with a passing test result and the last batch ~~that failed~~ tested

"9. Section VII-A (P.5.1); Lines 1223-1224: This sentence should be revised by adding the following text (underlined here): "A list of PQITs.....should be included in P.5.1 of the application, listed separately from drug product regulatory release specifications." This will help differentiate the product's release specifications from the product's PQIT specifications."

While this reviewer understands the commenter's intent and agrees that the PQIT listing should be separated "from the drug product regulatory release specifications," this reviewer thinks that a more grammatically correct, and perhaps more helpful, text is needed and suggests the following:

"After the drug product release specifications have been listed, a list of PQITs, with associated acceptance criteria and reference to analytical procedures, should be included in P.5.1 of the application."

"10. Section VII-D (P.5.4); Lines 1288-1291: With regard to batch analysis information, if not used for the stated purpose, does this mean preclinical/ toxicological batch need not be included in batch tables?"

This reviewer understands and agrees with the commenter's concern and would suggest the following curative language for Lines 1288 – 1289:

"Batch analysis data should be provided for all batches used in studies conducted to assess clinical efficacy and safety, bioavailability, bioequivalence, and primary stability."

"11. Section VII-D (P.5.4); Lines 1288-1309: An illustrative example of a batch analysis table would be beneficial. The illustrative examples of a composition statement (Table 1), a batch formula (Table 2), and a specification sheet (Table 3) provided in the respective sections of the guidance are informative. A similar illustrative example of a batch analysis table in section P.5.4 could be useful."

This reviewer again supports the commenter's suggestion.

12. Section VII D (P.5.4), Lines 1328-1339: Collated batch analyses data should be provided in P.5.6 as part of the justification for determining proposed acceptance criteria for the drug product.

This reviewer supports the commenter's suggestion and believes that this commenter's suggestion is better than the corrective text changes that this reviewer proposed in previous reviews where this section of the text was discussed.

13. Section VII-F (P.5.6), Line 1457: The definition for the Sunset test protocol should be provided in the Glossary.

This reviewer again supports the commenter's suggestion.

14. Section VII-F (P.5.6); Line 1480: The definition for the Interim acceptance criteria should be provided in the Glossary.

This reviewer again supports the commenter's suggestion.

A REVIEW OF FORMAL COMMENTS TO PUBLIC DOCKET 02D-0526

Bristol-Myers Squibb's Submission Posted June 25, 2003 To Docket 02D-0526: "C-07"

Note: The original INTRODUCTORY comments are quoted in a condensed font (Perpetua), the quotes directly from the draft guidance are quoted in a stylized font (Lydian) and this reviewers comments are in a publishers font (News Gothic MT) to make it easier for the reader to differentiate the "speaker" in the various text passages that follow. In the tables, this reviewer's comments are made a) after the commenter's comments.]

The commenter's introductory remarks begin by stating:

"Bristol-Myers Squibb is a diversified worldwide health and personal care company with principal businesses in pharmaceuticals, consumer medicines, nutritionals and medical devices. We are a leader in the research and development of innovative therapies for cardiovascular, metabolic and infectious diseases, neurological disorders, and oncology. In 2002 alone, Bristol-Myers Squibb dedicated $2.2 billion for pharmaceutical research and development activities. The company has more than 5,000 scientists and doctors committed to discover and develop best in class therapeutic and preventive agents that extend and enhance human life. Our current pipeline comprises of approximately 50 compounds under active development.

For these reasons, we are very interested in and well qualified to comment on this FDA proposal to provide further clarification and information on the chemistry, manufacturing, and controls (CMC) content for original new drug applications (NDAs) and abbreviated new drug applications (ANDAs). Our responses our structured in the context of the Common Technical Document (CTD) format.

We commend the U.S. FDA for allowing us the opportunity to provided our comments and we have made specific comments on the attached table, that is based on the CTD structure as presented in this draft guidance.

BMS appreciates the opportunity to provide comment and respectfully requests that FDA give consideration to our recommendations. We would be pleased to provide additional pertinent information as may be requested."

Table of Contents	Line #s	Excerpts from Guidance with Comments
III. Description & Composition of the Drug Product		
A. Description of Dosage Form	243-245	Official dosage form terminology used in the US differs from that used in the EU. The applicant should be permitted to use clear but non-standard terms so common filing content can be shared between US CTD and European CTD applications. Note: In the future, an initiative to harmonize dosage forms between the US and EU would eliminate this inconsistencies. Until such time as the disharmonies in terminology alluded to by the commenters are rectified or accepted by the Agency, this reviewer would suggest that current issues be resolved as the draft guidance suggests in Footnote 9 (page 7) – in consultation with "the appropriate chemistry review team."
C. Composition Statement	276-296	There are differences between the US and EU DMFs systems which make it cumbersome to prepare a global CTD. US DMFs cover active ingredients, excipients, intermediates, packaging, and processes, etc. whereas, European DMFs are only for active ingredients. Thus, many sections of the CTD must be customized because they refer to DMFs that are not accepted in Europe or Japan. In the future, efforts to harmonize DMF filings should be pursued.
	328	Add (after the words "... size of the container"): "Similarly, the amount of weight per unit weight should be on a per gram (g) basis regardless of the size of the container."
Footnote 10		The footnote should be clarified to list the three US official compendia, i.e., USP, NF, and Homeopathic Pharmacopeia.
	358	Replace "Hydroxypropyl Methylcellulose" with "Hypromellose", the official title in USP XXVI
A. Components of the Drug Product 2. Excipients.	420	In general it is awkward that excipient discussions occur in various places throughout the CTD. It would be better to consolidate this information contained in the multiple excipients sections into one section.
	429	Add (following the sentence.. shelf life should also be discussed.): "Reference should be made to any relevant stability data presented in P.8 to demonstrate the level of functional excipients over the intended use-time remains within an acceptable range." Suggest that the proposed sentence be changed to: "Reference should be made to any relevant stability data presented in P.8 to demonstrate the level of functional excipients remains within their predetermined acceptable ranges over the intended use-time."
• Non-compendial - Non-novel excipients	447	For clarity, define 'non-novel', e.g., used in EU, listed in Inactive Ingredient Guide, etc.
B. Drug Product	503	In the sentence, "A summary of the development of an in vitro/in vivo correlation and a cross-reference to the studies (with study numbers) should be provided." Add: "If available," a summary of .....should be provided.
D. Container Closure System	606	Add (following the sentence.... provided as warranted.): Suitability tests for the container may include Deliverable Volume (USP <755>). if relevant. Because the proposed is intended to be used as guidance, this reviewer suggests that the commenter's proposed text be changed to: "Where relevant, suitability tests for the container should include Deliverable Volume (USP <755>)."

Table of Contents	Line #s	Excerpts from Guidance with Comments
E. Microbiological Attributes	636	Add (after "inherently antimicrobial") "... with justification for not adding a preservative for such self-preserving systems."
	646	Add (at the end of paragraph) "Appropriate use-time data should be included (or appropriate reference to the Stability section (P.8) to demonstrate the preservative(s) remains within effective levels over the intended use time of the product." Agreed but the text proposed should be corrected to: "Appropriate use-time data should be included (or appropriate reference to the Stability section (P.8)) to demonstrate the preservative(s) remains within effective levels over the intended use time of the product," to make it grammatically correct.
F. Compatibility	653-679	A better distinction is needed between development compatibility studies and compatibility studies to support the labeling. This section should also discuss incorporating literature reference data.
	667-676	It is not precisely clear what the terms diluent and admixing mean in this section. It would be useful to add to the glossary the following terms for clarity: admixture, diluent, and flushing agent.
	676	Add (to the end of the sentence): "... and referenced in this section (P.2.6)."
	769	Replace "Hydroxypropyl Methylcellulose" with "Hypromellose", the official title in USP XXVI

Table of Contents	Line #s	Excerpts from Guidance with Comments
VI. Control of Excipients		
General	981-986	"Compendial-Non-novel Excipients: When a compendial excipient is tested according to the monograph standard with no additional testing and the applicant intends to perform full testing on each batch received, 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." Delete "and the applicant intends to perform full testing on each batch received," from the sentence. This reviewer does NOT support this deletion and, as he will explain, finds that the supposed justifications for the deletion either do not directly bear upon incoming component acceptance or, by their incompleteness, are misrepresentations of the applicable CGMP. This implies that a sponsor cannot utilize vendor qualification in order to accept via COA without providing additional information in the filing. The commenters are almost correct; the text cited ONLY implies that a sponsor should not do so. This is in conflict with the General Notices in the USP, which state that application of every analytical procedure is not required for assuring that the batch meets the compendial requirements. Contrary to what the commenters state, the **USP** text paraphrased here ONLY applies to the RELEASE of a batch by the firm that manufactures the ingredient – not to the firm who tests incoming lots of it. Additionally, 21 CFR 211 also allows the sponsor the ability to accept via COA, provided qualification has occurred. The commenter's remark is, at best simplistic. **21 CFR 211.84(d)(2)** states (emphases added): "**Each component shall be tested for conformity with all appropriate written specifications for purity, strength, and quality. In lieu of such testing by the manufacturer, a report of analysis may be accepted from the supplier of a component, *provided that at least one specific identity test is conducted on such component by the manufacturer,* and provided that the *manufacturer establishes the reliability of the supplier's analyses* through appropriate validation of the supplier's test results at appropriate intervals.**" Though ignored by the commenters and misrepresented by many as "one identity test" or, almost correctly, "one appropriate identity test," the requirement is "**at least one specific identity test is conducted on such component by the manufacturer**" on representative samples (**21 CFR 211.160(b)(1)**) from each shipment of each lot (**21 CFR 211.84(b)**). Thus, the requirement does not permit the sponsor to "accept via COA, provided qualification has occurred" as the commenters state; much more needs to be done. It is unreasonable to require the pharmaceutical manufacturer to commit to fully test every excipient lot at this point in the filing. Since this document is guidance, it cannot establish any requirement and, as written, it does not. **The current text simply and rightly states the conditions under which the sponsor can list the compendial references to the ingredient testing it is proposing without any additional information.** For all of the preceding reasons, the proposed deletion is, at best, inappropriate.

Table of Contents	Line #s	Excerpts from Guidance with Comments
A. Specifications	1022-1024 & Foot-Note 27	Delete: "In addition to listing all the tests for an excipient, the specification should identify the tests that the drug product manufacturer will routinely perform and the test results that will be accepted from the excipient manufacturer's certificate of analysis (COA). [27]" For the reasons that this reviewer has presented in the previous reviews where the commenters suggested changing this section as well as those presented in response to the suggests of this commenter, this reviewer opposes this deletion and thinks that sponsors who chose not to provide the information requested may not be operating their component acceptance systems in compliance with the applicable CGMP regulations. Replace the sentence above with the following sentence, and move footnote "27" to the end of the second sentence: "The specifications for excipients should list the full testing requirements," i.e., "At a minimum, the drug product manufacturer must perform an appropriate identification test (21 CFR 2 11.84(d)(1)) [27]." This reviewer knows that the sentence, "**At a minimum, the drug product manufacturer must perform an appropriate identification test (21 CFR 211.84(d)(1))**," does NOT accurately reflect what the CGMP regulations require and would propose, given the lack of understanding of this that he has seen, that that sentence be replaced with the following sentence to: 1) accurately reflect this CGMP requirement and 2) make the text consistent with the additional testing requested in the following sentence: "**At a minimum, the drug product manufacturer must perform at least one specific identify test (21 CFR 2 11.84(d)(2))** when the manufacturer elects to use information from the supplier's COA in lieu of testing." [**Note:** If the applicant elects to follow the other permitted course of action, full testing, there is no need to cite **21 CFR 211.84(d)(1)**.] Add (insert the following clause to the beginning of footnote "27a"): "For the tests accented by the manufacturer on Vendor COA, the drug product manufacturer must establish the reliability..." The proposed change cannot be supported. This is the case because it conflicts with the requirements of the CGMP which requires that the manufacturer must establish the reliability of the supplier's analyses – not just some that the manufacturer chooses to validate. If a manufacturer wants to adopt this approach then that manufacturer must comply with what the clear language of the applicable CGMP regulations require, Delete (the following two sentences in footnote "27."): "The reliability of the analyses need not be established at the time the application is submitted. However, the specification should indicate the tests that will be performed once the reliability of the supplier's results has been established in accordance with current good manufacturing practices." This reviewer does not agree; but would recommend changes to the last sentence to better align the text in the draft with the specific requirements of the CGMP: "**However, the specification should indicate the test or tests used to establish the specific identity of the excipient and the other tests that will be performed once the reliability of the supplier's analyses has been established in accordance with current good manufacturing practices.**"

Table of Contents	Line #s	Excerpts from Guidance with Comments
A. Specifications	1022-1024 & Foot-Note 27 cont. 1	*It isn't always known at the time of submission which tests the manufacturer will eventually accept vendor COA results for, versus those tests which will be routinely performed by the manufacturer. At the time of NDA submission the drug product manufacturer may have limited experience with some of the excipients; this is especially true when new excipients or new suppliers are used. The implementation of a reduced testing program by the drug product manufacturer would likely occur well after submission of the NDA. This requirement and the last sentence of footnote 27 should be deleted.* While the preceding makes interesting reading, it ignores two realities: The first reality is that a manufacturer regulated by CGMP must develop, establish (**21 CFR 211.160(b)** [bolding added]) "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**" BEFORE the first batch is manufactured for release for distribution. To have such, the manufacture must know what his specifications and testing procedures are. The second reality is so commonly known that this reviewer is surprised the commenters seemed to not know it. That reality is that there is NO prohibition in the CGMP for incorporating contingent specifications (commonlyt hese are expressed in terms of "hierarchical plans") into their filings. Thus, not knowing the future, in terms of what the manufacturerwil I want to do and/or what will be the future quality of the materials that suppliers may provide, the prudent CGMP-regulated manufacturer simply develops scientifically sound and appropriate contingent plans that address the contingencies that may arise. For example, even if a valid "COA acceptance" plan is in place and being used, the firm needs to have a predetermined plan to handle such contingencies as changes in a) supplier, b) compendial requirements, and c) internal quality standards as well as, God forbid, failure of the supplier to provide 1) material or 2) results that conform to their established norms for acceptance. Based on the realities presented, hopefully the Agency, and even the commenters who have espoused this position, will realize that the preceding position is unsupportable and adopt and submit *scientifically sound* and *appropriate*, contingent *specifications, standards, sampling plans, and test procedures.* In any case, the commenter's final remarks should be ignored and the proposed revisions not incorporated into the guidance for all of the reasons stated.

Table of Contents	Line #s	Excerpts from Guidance with Comments
A. Specifications	IO26-1027 & 1027-1030 cont. 2	In the statement "However, when there are specific safety concerns relating to an excipient, testing in addition to an identity test would be warranted." Change "would" to "may" *The statement starting with "testing in addition." implies that the additional testing must be performed by the drug product manufacturer. Rather, from the example given in the draft guidance, it seems the intent of this statement should be that the excipient specifications include a requirement for additional testing where there are specific safety concerns.* First of all, this document is guidance and represents the Agency's current thinking in this case based on experience. Second, this reviewer understands that ingredients having known safety concerns arising from contaminants that are supposed to be removed but have not are real. It is up to the firm's quality units to approve the firm's **"procedures and specifications impacting on the identity, strength, quality, and purity of the drug product (21 CFR 211.22(c))**. The only intent that this reviewer reads into what is suggested is to remind the sponsor that assuring the safety and efficacy of each batch of drug product is the sponsor's responsibility; and, as such, expecting the application to address ingredient "concerns" as a part of that responsibility, theA gency is suggesting one way that the sponsor can discharge that responsibility in the application. Based on the preceding, this reviewer would object to the change proposed. Delete or replace the example, i.e. "For example, diethylene glycol contamination of polyols such as glycerin and propylene glycol has caused numerous fatalities." *This example of diethylene glycol does not seem entirely appropriate, as it represents an extreme case of 'things gone wrong.' While it is acknowledged that the deaths were tragic, they were also the result of a lack of fundamental GMPs and unethical business practices. There are better ways to ensure the safety of excipients through appropriate application of GMPs by both the excipient manufacturer and the drug product manufacturer, and the by establishment of a reliable supply chain. Also, USP 26 asserts in General Notices, Foreign Substances and Impurities that "Tests for the presence of foreign substances and impurities are provided to limit such substances to amounts that are unobjectionable under conditions in* which the article is customarily employed *". The case cited by FDA was an unusual case (i.e. under conditions which the article is not customarily employed) that could not have been anticipated by a drug product manufacturer or the compendia. The compendial monograph at the time would not have uncovered the impurity. Compendial tests are not established to compensate for poor GMPs or unethical business practices. We recommend that this example be excluded.* Rhetoric aside, the reality is that the example exactly supports the point that the Agency is raising, an applicant may need to develop and implement additional tests when there is a known risk of a safety hazard. In the example provided, the risk in the example arises because the processes used to manufacture glycerin and polyols produce mixtures that the manufacturers separate by distillation. Thus, there are risks for product mix-up and product contamination that should not be ignored. In such cases, the sponsor needs to address the issue in a manner that ensures each container of each lot is safe. The example is on point and should be retained.

Table of Contents	Line #s	Excerpts from Guidance with Comments
A. Specifications	1034-1035	Delete "... full monograph testing will be performed on each batch of excipient." Full monograph testing need not be performed on every batch. Acceptance of data from the vendor can be done if such data has been confirmed to be comparable to the data generated internally. See comment for Lines 981 - 986. This reviewer is disappointed that the commenters would attempt to suggest that a portion of a sentence be removed by stating facts that have nothing to do with the statement in its original context. The text in question (Lines 1032 – 1035) states (emphasis added), **"Only a citation to the appropriate official compendium need be provided when the excipient specification is identical to the compendial monograph and full monograph testing will be performed on each batch of excipient,"** addresses when it is appropriate to ONLY cite the appropriate official compendium. The text does NOT limit, as the commenter's remarks attempt to convey, the sponsor to full monograph testing. Based on the reasons cited here as well as in response this commenter's remarks to Lines 981 – 986 and this reviewer's prior comments in other reviews, this reviewer object to the deletion of this phrase from the suggested guidance.
	1038-1041	**"If the specification for an excipient is based on a compendium other than an official compendium, the excipient should still conform to the monograph in an official compendium if there is such a monograph."** *The terms "official compendium" and "conform to the monograph" are confusing and need clarification.* What compendia are not official with respect to this guidance? The statute (FDC Act at **21 U.S.C. 321(j)**) defines the term "official compendium" as follows: **"The term ``official compendium'' means the official United States Pharmacopoeia, official Homeopathic Pharmacopoeia of the United States, official National Formulary, or any supplement to any of them."** By statute, any other compendium is undefined and is, therefore, not official. Just as the USP has no legal standing in Japan, the "JP-JPE have no legal standing in the United States. Thus, though the monographs therein may be scientifically sound, they cannot be used without complete validation.

Table of Contents	Line #s	Excerpts from Guidance with Comments
A. Specifications	1038-1041 cont. 1	Reference is made, in Footnote 10 (p. 8), in Footnote 21 (p. 20), and again in Footnote 26 (p. 27) of the Draft Guidance to the official compendium as defined in the Federal Food, Drug, and Cosmetic Act. Perhaps the Footnotes could simply state the titles for the three official compendia: USP, NF and Homeopathic Pharmacopeia. It would be helpful if Lines 1038-1041of the Draft Guidance stated more clearly the specific status of the Ph. Eur., BP, and JP-JPE. This is important for a few excipients that have monographs in one of these other compendia, but not in the USP, NF or Homeopathic Pharmacopeia. Simply stating the titles would be incorrect. Given the selective understanding demonstrated by this and other commenters, the Agency should quote the definition in all cases. With respect to Lines 1038 – 1041, this reviewer that the preferable course of action would be to add the following text to Footnote 28 located coincidently at the bottom of page 28: "In the United States the current status of other recognized compendia, including, but not limited to, the British Pharmacopeia (BP), the Pharmacopeia of Europe (PhEur), the Japanese Pharmacopeia (JP) and the Japanese Pharmacopeia for Excipients (JP-E), is that they have no official status with respect to products regulated by the US Food and Drug Administration under the Federal Food, Drug and Cosmetic Act as amended. Thus, the FDA can legally only recognize them as sources from which tests and specifications may be developed and validated. Sponsors submitting applications to the FDA should do likewise." Conforming to the "monograph" has a different meaning that conforming to the "compendia", e.g., meeting compendia means complying with GMPs and Compendial Notices. Also, it is recognized that the "official compendia" for the FDA are the USP, NF and the Homeopathic Pharmacopeia (this is found in several documents on the FDA Webpage). Factually, conforming to the specifications in a monograph in an official compendium has a different meaning than conforming to the compendium. If one asserts that one is conforming to a monograph in an official compendium then that is the same as asserting that one is conforming to the official compendium. In the case of the USP and the NF, simply using the compendial name is an assertion of conformance to the compendium in general and its compendial monograph in specific. Those who believe otherwise are asked to read the applicable General Notices portions of the USP and the NF.
B . Analytical Procedures	1055	A more complete listing of "FDA-recognized" standard references would be useful. Because these "FDA-recognized" standard references are subject to annual, or more frequent, change, a better option would be to put a footnote pointing to the web address where the current listcan be found PROVIDED the Agency is in a position to assure that the address will not change – otherwise, the footnote should simply cite the official name of the list and suggest that those needing assistance in this regard contact the appropriate FDA office.

Table of Contents	Line #s	Excerpts from Guidance with Comments
C. Validation of Analytical Procedure	1066-1072	*Clarify the statement to exclude the requirement of submitting validation for compendial excipients.* For example, **replace the underlined clause** from the following statement "Submission of validation information in the application is normally not needed for excipients. Validation information should be submitted if there are special circumstances. For example, submission of validation information for an excipient can be appropriate if a characteristic of the excipient or the excipient itself is critical to product quality (e.g., adjunct, carrier) but the critical nature of the excipient cannot be or is not assessed as part of the drug product testing" **with** "Validation information should be submitted for additional test(s) required by special circumstance for test(s) that are not covered in or performed as described in an official compendium. For example, additional testing beyond the monograph requirements may be needed if a characteristic of the excipient or the excipient itself is critical to product quality (e.g., adjunct, carrier) but the critical nature of the excipient cannot be or is not assessed as part of the drug product testing." This reviewer understands that the commenters want to limit validation to tests not in an official compendium. Moreover, this reviewer's experience and training has provided ample evidence that a) the validation (as defined in this guidance to include verification of the method under actual conditions of use for compendial methods [Lines 1062 – 1066]) is needed and b) the Agency's request is valid and places the emphasis where it should on asking the applicant to submit proof that the validity of the firm's process controls for "critical control points" has been established. The alternative suggested is much less desirable because it would, if adopted, result in the omission of important information for some critical control points – definitely an anti-quality position. Therefore, this reviewer strenuously objects to the change proposed and strongly recommends, for the reason cited, that the draft text be retained without modification.
D. Justification of Specifications	1076	In general the guidance would be more useful if an example justification for an excipient specification is provided. This reviewer concurs and suggests, since the commenters have access to many to choose from, the commenters should submit a blinded version of the one thought to be most enlightening to the Agency to assist the Agency in adding what they are requesting.

Table of Contents	Line #s	Excerpts from Guidance with Comments
D. Justification of Specifications	1089-1091	Pharmaceutical companies often qualify vendor results for specific tests and accept material on COA, thus full monograph testing need not be performed by the drug product manufacturer on every excipient batch. Acceptance of data from the vendor can be done if such data has been confirmed to be comparable to the data generated internally. The guidance offered only requests that the testing be performed on certain lots of the components and the results from the vendor's COA and those of the applicant be submitted so that the Agency can independently verify (confirm) that all the tests on the COA have been confirmed by the applicant to be the "same" as the results obtained by the applicant's laboratory analysis so that, if (as the commenter's remarks suggest) the sponsor submits a request to use the "accept COA" approach, the Agency reviewer can ascertain compliance without wasting valuable but limited inspection time having a compliance officer visit the site and, by searching through the site's records, find the requested information. Moreover, because it is guidance, the commenters can choose to ignore it and thereby "request" the Agency to include it as an inspectional issue to be resolved. If the commenters are interested in expediting the application review process, then this is one area where providing the information requested could certainly expedite the process. Therefore, this reviewer would again recommend that the draft language be incorporated "as is" into the final guidance.
	1092-1094	In the sentence "Test results should be expressed numerically or qualitatively (e.g., clear, colorless solution), as appropriate," change "as appropriate" to "where practical". Delete "Use of terms such as conforms or meets specification is discouraged." *It may be difficult to express all results numerically or qualitatively. For example, some identity tests have several acceptance criteria within one identity test. Identity A in the USP monograph for Aluminum Monostearate specifies that fatty acids are liberated, they float as an oily layer on the sulfate of the liquid, and the water layer responds to the test for Aluminum. In these cases, the use of the terms conforms or meets specifications should be acceptable.* If the proposed change were made then the sentence would mean: "Test results should be expressed numerically where practical or qualitatively (e.g., clear, colorless solution), where practical." Obviously, the first instance would permit the applicant <u>not</u> to report the analytical results obtained on the grounds that to do so is <u>not</u> practical. Therefore, the "as appropriate" language should be retained and the commenter's proposal in this regard should be rejected. With respect to the deletion of the second sentence, this reviewer would prefer stronger language than the guide offers. However, the language in the draft appropriately balances the objection that the commenters have raised because it does, as the commenters request, accept the use of terms such as "conforms" or "meets specification." Based on the preceding, this reviewer recommends that the second sentence be retained as it is and incorporated into the final draft. In such cases, the Agency should consider adding a request for the applicant to include the specification on the report in cases where such terms are used.

Table of Contents	Line #s	Excerpts from Guidance with Comments
E. Excipients of Human or Animal Origin		All potential SRMs (Specified Risk Materials) should be presented in this section, including supplier declarations for SRMs that are from vegetable origin. (Note: Various SRMs, e.g., magnesium stearate can be sourced from either animal or vegetable sources). Add a cross reference to any TSE (Transmissible Spongiform Encephalopathies) CEPs (Certificate of European Pharmacopoeia) that may be included in the Regional Section (3.2.R.3)
VII. Control of Drug Product		
A. Specifications	Foot-Note 30	Replace "VI.B" with "VIA" in the note "[30] See section VI.B for guidance on USP General Chapters that are interchangeable..." The information on interchangeable chapters is provided at the end of section VI.A in the Guideline, not in section V1.B. Also see comments on section VI.A lines 1045-1046 where deletion is recommended. This reviewer agrees that the cite should be to "VI.A" instead of to the draft test's "VI.B." However, this reviewer could find no comment that referenced the line range cited – perhaps it was removed prior to submission and the removal of this comment overlooked.
B. Analytical	1252	"...and the referenced analytical procedure is not modified...". This would indicate that any Procedures change to an FDA recognized method would require filing. The term "modified" is not clear and could have different interpretations. It would be helpful to provide specific examples of modifications that would require filing of the modified compendial procedure. As a Ph.D. analytical chemist with more than twenty years of experience dealing with the issue of what constitutes a modification of a procedure as opposed to operational adjustments within permitted ranges, the answer is dependent upon whether or not the procedure has adjustment ranges that are well-defined and validated. For example most AOAC International reference methods are well-controlled controlled and fully validated. The USP monograph procedures for HPLC are at the other end of the spectrum – they are <u>not</u> well defined and, *as written*, they cannot be carried out in a determinate manner without significant interpretation and translation. In between are the analytical procedures that are completely "defined" in one of the up-to-date harmonized General Chapters – fairly well defined procedurally with specified limits on the adjustment range allowed for key parameters. Rather than ask the FDA for guidance, thisrev iewer would suggest that they form a task force with the USP and the other ICH members to upgrade the text of compendial test methods to specify the equipment to be used and the durational flexibility allowed for its use for each operation that uses equipment. As things stand now, since different firms interpret and translate methods differently, the applicant should be submitting the written analytical procedures that they use, if for no other reason than to ensure the FDA lab will use the same procedure.

Table of Contents	Line #s	Excerpts from Guidance with Comments
C. Validation of Analytical Procedures	1273-1274	Revise the statement "Analytical validation information, including experimental data, for the analytical procedures used for testing the drug product should be provided, unless they are established in an official compendium." According to USP 26 <1225> "... users of analytical methods described in the USP and the NF are not required to validate accuracy and reliability of these methods, but merely verify their suitability under actual conditions of use." Paraphrasing the CFR 211.194, "If the method employed is in the current revision of the USP, NF, AOACs, Book of Methods, or in other recognized standard references, or is detailed in an approved new drug application and the referenced method is not modified, a statement indicating the method and reference will suffice." First, this reviewer would request the commenters to carefully reread this reviewer's comments to the commenters' remarks. Second, **USP 26 <1225>** is a guidance chapter and not a binding requirement. Third, the general **CFR** reference cited is "**Sec. 211.194 Laboratory Records.**" As such, it only addresses what constitutes the minimum degree of compliance with the requirement that the manufacturer maintain a record of the method that contains **a)** the name of the method and **b) the location of data that establish that the methods used int the testing of the sample meet proper standards of accuracy and reliability as applied to the product tested."** The only exemption that this **21 CFR 211.194(2)** grants is, for unmodified compendial methods, the **CGMP** regulations permit the citation of the **USP**, **NF** or **HP-US** in lieu of "**b).**" Even then, the regulation requires "The suitability of all testing methods used shall be verified under actual conditions of use." Moreover, **21 CFR 211.110(a)** states: "To assure batch uniformity and integrity of drug products, written procedures shall be established and followed that describe the in-process controls, and tests, or examinations to be conducted on appropriate samples of in-process materials of each batch. Such control procedures shall be established 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." What manufacturing process is more in need of monitoring and validating than the analytical test process? Isn't validating the analytical testing procedure as critical, or more, critical than many of the processing steps the procedure will be used to test the required samples? You would think that applicants would not be objecting to providing the requested information when the CGMP regulations clearly require the applicant to have that information – yet they have and are. Based on the preceding, this reviewer finds that the CMC section of the application should provide the requested information because 1) providing it could again expedite the review by reducing the inspection workload and 2) the firms are required by CGMP to have validated the analytical procedures they use before they use those procedures to test samples for any purpose covered by the CGMP regulations.

Table of Contents	Line #s	Excerpts from Guidance with Comments
C. Validation of Analytical Procedures	1277-1278	"Stability data (S.7.3, P&3), including data from stress studies, should be used to support validation of the analytical procedures." We propose, that the stability indicating nature of the method should be demonstrated in an independent investigation using forced degradation studies, as described in ICH Q2B. The results of this investigation, including chromatograms, would be included in the validation report. Since a validated method is required to initiate the stability studies presented in sections S.7.3 and P.8.3, these studies cannot be used to validate the analytical methods. Apparently the commenters do not understand the nature of validation. Validation is a journey and not a destination. The initial development and qualification of a method as suitable for its intended use is just the start of that journey. Each use of the method not only yields test results but it also validates, or when the test procedure is found to fail, invalidates the current "is valid" state of the analytical procedure (usually this is crouched in terms like system suitability or "control standards inside of their defined range"). Because the stability data is a significant body of data over an extended period of time supposedly from the testing of representative samplesf rom the same lots or batches, it is of sufficient breadth and depth for the application reviewers to properly asses whether or not the test procedures used are truly valid for their use as well as provide the reviewers with a good understanding of the variability in the drug product being tested. Based on the preceding, one would think that the commenters would be eager to submit it because its submission could again expedite the review. Based on all of the preceding facts, the commenter's remarks are invalid. This misguided and factually incorrect comment should be ignored. The draft text discussed should be incorporated into the final guidance without any modification thereto.
D. Batch Analyses	1288	In general this paragraph is very broad. The section also appears to be redundant, requesting the same information but in different formats. We would normally not include COAs in addition to batch analysis tables. Also including information such as container closure system, API source batch, and excipient batches does not add any value and should not be included. As an investigator having in-depth experience in investigating production process for the root causes of the differences between batches and the factors that affect or correlate with drug-product batch values, the requested informationi s crucial to determining whether or not a process and the controls on it are a) operating in compliance with CGMP and b) capable of producing batches of drug product that are sufficiently defined and controlled to the point that the data obtained predict that all of the units in the batch would, if tested, pass. The request for the COAs for the batch is obvious, it informs the Agency how the applicant's quality unit is interpreting the data results and allows the Agency to easily confirm that the firm is, or is not, operating in compliance with the applicable CGMP. Based on the preceding, the request is more than justified and most certainly should be in the final CMC guidance.

Table of Contents	Line #s	Excerpts from Guidance with Comments
D. Batch Analyses	1313	"The batch analysis reports should include results from all tests performed on the batch". This does not add value to the reports and would be burdensome. We would not want to report every single bit of data, especially those that may have been generated for investigative purposes but do not necessarily contribute toward evaluation of the product quality, safety and performance. Since the Agency is entitled to inspect all of the data in question. The commenter's remarks about every bit of data are at odds with the request – the test measurements are not requested, the standard values are not requested, the blank values are not requested, the baseline data are not requested, the calibration check data on the balances used to weigh the samples are not requested, etc. – **all that the guidance requests are the result values** (*typically, these are less than 15 % of all of the data collected*). Contrary to the commenter's remark, "We would not want to report every single bit of data, especially those that may have been generated for investigative purposes but do not necessarily contribute toward evaluation of the product quality, safety and performance," the results requested do bear directly on a) the validity of the testing performed and b) the Agency's **evaluation of the product quality, safety and performance.** Thus, again, this reviewer recommends that the draft text again be incorporated into the final guidance.
	1317	"A summary of any changes in the analytical procedures should be provided..." We would propose to include a table summarizing method changes in section 3.2.P.5.2. Appropriate cross-references to this section would be included when applicable. The commenter's proposal only provides a fraction of the information requested by the Agency, "A summary of any changes in the analytical procedures should be provided if the analytical procedures (1) changed over the course of generating the batch analyses data and/or (2) are different from the analytical procedure included in P.5.2. The summary should identify when an analytical procedure changed, the differences between the analytical procedures, and the impact of the differences with respect to the data being reported." The commenter's proposal makes no mention of providing: 1) the dates of the changes, 2) the differences between the analytical procedures, and, most importantly, 3) the impact of the differences on the data being reported. Recognizing that the value of the information requested, the Agency's need for the requested information, and the fact providing it should expedite the review process, this reviewer again understands that the draft text should be left as is.
	1330	"Presentation of results from all batches for a particular test in tabular and/or graphical format is often helpful in justifying the acceptance criteria." Requiring data from all batches, may not be appropriate since, including data from early batches where development work was still ongoing could cause confusion. The batches required should be limited to the final commercial product as opposed to requesting presentation of "all" batches. This reviewer cannot understand how the commenters can misconstrue an obviously observational comment that happens to be valid into a request when the statement makes no request whatsoever. However, *provided the rest of the text in the paragraph is kept as it,* this reviewer does not oppose the removal of this introductory sentence.

Table of Contents	Line #s	Excerpts from Guidance with Comments
E. Characterization of Impurities Residual Solvents	1384	Why is this section in this guidance? One would refer to Q3C for appropriate guidance and we suggest that is what this guidance should refer to. All that the text provided here does is simply remind the applicanto f what is expected of the applicant; it requests nothing.. In addition, the guidance document the commenters mention was provided in a highlighted box (**Line 1335**) at the beginning of **Section E.** Based on your comment, this reviewer would suggest that the phrase "(See Q3C)" after the heading to give: "**• Residual Solvents (See Q3C)**"
D. Batch Analyses	1308-1309	Refer to comments, references and rationale given for lines 1092-1094 Refer to this reviewer's comments to the commenter's remarks for Lines 1092 – 1094.
VIII. Container Closure System		
	1533-1534	It should be clarified that secondary packaging for child-resistance should be considered non-functional and only a brief description provided
IX. Stability C. Stability Data		
	1569-1571	Reword the first sentence to state, "The results.. . . . . should be provided along; with a discussion of the data." Delete the second sentence, "Stability study reports should also be included." This reviewer believes that the draft text, "**The results from long-term, accelerated and, when performed, intermediate studies undertaken on primary stability batches should be provided. Stability study reports should also be included,**" would: a) provide the Agency reviewer with a better understanding of the stability of the drug product and b), because the stability study reports are pre-existing documents, would relieve the applicant from having to generate "a discussion of the data" – the alternative proposed by the commenter.
	1569	Clarify if and when (original submission, updates) it is acceptable to submit data in a summary format (means of individual values), where appropriate, or if individual values with a mean are required in the reports.
	1597-1599	Clarification needed for difference between compatibility studies to be reported in P.2.6 and 8.3.
	1601-1613	Clarify what supporting stability data should be included in P.8 and what data can be provided in P.2.

Table of Contents	Line #s	Excerpts from Guidance with Comments
	1607-1610	Generation of stability to support holding in-process materials is a GMP related issue and should be removed as an expectation for the formal stability study being conducted on the finished dosage form in the proposed market package(s). Contrary to the position stated by the commenter, in addition to the drug product ("finished dosage form"), the Agency is charged with evaluating whether or not the production processes, controls and drug products do, or do not, comply with CGMP. Apparently the commenters have overlooked the specific requirements that address the issue the commenters raise. The applicable section is **Sec. 211.111 Time limitations on production.** That section states (emphasis added): **"When appropriate, time limits for the completion of each phase of production shall be established to assure the quality of the drug product. Deviation from established time limits may be acceptable if such deviation does not compromise the quality of the drug product. Such deviation shall be justified and documented."** Thus, while the applicant is required to establish time limits for the completion of each phase whether that limit is one (1) day, one (1) week, one (1) month or longer. The Agency recognizing the burden that supplying all of the required studies would impose has judiciously limited their request to those where the hold period is 30 days or longer." The reviewer finds that this is a reasonable request and one that should be honored. Moreover, were it to be removed, each application would be subject to the judgment of the application reviewers as to what the time-delay start point should be for requesting such studies – thought that the industry was all for uniform reviews. Thus, the reviewer again finds that keeping the draft text is both reasonable and appropriate.
	1618-1619	Suggest rewording "The information should be used... " to "The stress information, as well as information from the formal and supporting stability studies, may be used..." First of all, the correct line range for the text provided is Lines 1619 – 1622. Second, this reviewer disagrees with the commenter's proposal based on the substantiated relevant information provided in the prior comments on the results obtained from stability testing. In addition, the commenter's insertion of the word "may" in place of the "should" is inappropriate in a guidance document when the guidance is intended to elicit the requested information as is the case here. The use of the word "may" is only appropriate in guidance when more than one alternative is being offered to meet an Agency request – that is not the case here. For example, the applicant may fill out and submit Form FDA nnnn or submit the following information: ...

Table of Contents	Line #s	Excerpts from Guidance with Comments
XI. Regional Information		
A. Executed Batch Records 2. Information on Components	1819-1821	Refer to comments, references and rationale given for lines 1092-1094 Refer to this reviewer's comments to the commenter's remarks for Lines 1092 – 1094.
XIII. Literature References		
Attachment 1	1893	Add to beginning of the sentence: "For unit of use packages, a test for...." This reviewer knows that it is important for the semisolids that the manufacturer determine the uniformity regardless of the packaging. This is the case because this reviewer has been involved in several product investigations involving hydrocortisone creams and triple antibiotic ointments. The problem in all but one case was significant non-uniformity across the batch in the filled tubes. Obviously, this information should be submitted. The draft text should be retained, if nothing else, because the commenters have failed to present any rationale, much less a substantive scientifically sound rationale, for the change the commenters have proposed.
	Foot-notes 28 & 32	The two footnotes "28 For example, the National Formulary (NF) should be cited rather than NF 20", and "32 For example, the USP should be cited rather than USP 25" are correct. However, they are not consistent with 21 CFR 314.70(d)(1) and another FDA Guidance, i.e., "Changes to an Approved NDA or ANDA". Perhaps the CFR should be revised and other FDA Guidance. Since 21 CFR 314.70(d)(1) states, "(d) Changes described in the annual report. An applicant shall not submit a supplement to make any change in the conditions in an approved application, unless otherwise required under paragraph (b) or (c) of this section, but shall describe the change in the next annual report required under Sec. 314.81. Some examples of changes that can be described in the annual report are the following: (1) Any change made to comply with an official compendium," this reviewer fails to find need for the text herein to be modified. If, for example, the pH range on component XYZW changed from "4.0 to 7.0" to "4.6 to 5.9," when the second supplement to USP 26 was published, all this regulation requires in the annual report is a statement such as: "Effective 15 May 2003, Company ABCDE has changed the pH specification for XYZW from "4.0 to 7.0" to "4.6 to 5.9" to comply with a change in the USP." Therefore, this reviewer did not find the conflictth at the commenters allude to in their comment. As to the referenced guidance document, *if it does contain inappropriate referencing*, then, the Agency should issue a technical correction addendum to that guidance.

A REVIEW OF FORMAL COMMENTS TO PUBLIC DOCKET 02D-0526

P&G Pharmaceutical's Submission Posted June 25, 2003 To Docket 02D-0526: "C-06"

Note: The original INTRODUCTORY comments are quoted in a condensed font (Perpetua), the quotes directly from the draft guidance are quoted in a stylized font (Lydian) and this reviewers comments are in a publishers font (News Gothic MT) to make it easier for the reader to differentiate the "speaker" in the various text passages that follow. In the tables, this reviewer's comments are made a) after the commenter's comments.]

The commenter's introductory remarks begin by stating:

"Thank you for the opportunity to comment on the draft FDA Guidance Drug Product Chemistry, Manufacturing, and Controls Information. This is an extensive document that clearly represents a considerable investment of FDA resources and contains some important considerations for presenting the drug product CMC sections of an application. Comments to this draft Guidance, made by Procter & Gamble Pharmaceuticals Inc., Mason, Ohio, are presented in the following pages for Agency's consideration."

The commenters have, as several others have, elected to present the comments in tabular form.

This reviewer is therefore inserting his review comments into a tabular format to preserve the overall view that the commenters have selected.

Guidance Line #	Proposed Revision	Rationale
General comment	Replace reference to the term CMC with Quality wherever possible. While this reviewer supports consistency, this reviewer would suggest changing the phrase "where possible" with "where appropriate."	Consistency with ICH. Consistency with GGP.
67-70	Eliminate reference to drug substance requirements. This reviewer cannot and does not agree.	This is a drug product guidance. Drug substance requirements should be addressed in the drug substance guidance. Contrary to the statement, this guidance is NOT a "drug product guidance" it is a guidance to the CMC (or "Quality") controls that drug manufactures must meet for their application to provide the evidence that their proposed "Quality" systems and drug product conform to the requirements of CGMP (both statutory and regulatory). Thus, the commenter's rationale is based on a flawed premise and should therefore be ignored.
249, 334, 342	It is suggested that the ICH numbering convention be adopted throughout the referenced lines (e.g., in line 249, change 1V.B. 1 to P.2.2.1). Agreed.	Ease of use and improved clarity. Consistency in referencing.
3 11 and 358	Delete DMF holder's standard. The proposed change should not be made.	Quality standards should be pertinent to acceptance criteria of the drug product manufacturer. While the DMF holder's standard could be used as a starting point for setting internal specifications, it may not be appropriate to use the DMF holder's specification as a drug product manufacturer's regulatory specification. The commenters have OBVIOUSLY misunderstood what the term "DMF standard" means in this case and, further, confused the term "standard" with the term "specification." The term "DMF Standard" means the DMF holder's *reference standard substance* –N OT the DMF holder's *specification.*
320-322	Delete the sentence that starts "Components should be identified as processing agents". This reviewer cannot agree.	This is very prescriptive. It may be appropriate to state "granulating agents - removed during processing, or solvent for ink / marker". Consistency of naming and clarity of classification among applications.
328-329	Reference to the metric system is good and should be maintained.	
362-680	Delete the pharmaceutical development section in this FDA guidance and refer to ICH's in case ICH issues one. This reviewer disagrees.	This section in the FDA guideline is very detailed. My understanding is that there may be an initiative in ICH to develop a harmonized guideline. FDA should not preempt that effort. The FDA is charged with assisting the industry to operate in compliance the requirements of the FDA Act and CGMP. What the ICH may, orm ay not, do in the future isn ot certain. Though detailed, the guidance offered is both rational and needed.

Guidance Line #	Proposed Revision	Rationale
461	Provide clarification on what is meant by tracers or markers. Based on the commenter's rationale, agree and suggest that the Glossary option be used.	These concepts may not be familiar to everyone. They could be explained briefly here or in the glossary. By defining the terms in the Glossary, the message in the narrative is not diluted by information that some would deem extraneous.
495	Revise to say "A summary of formulations used ina ll relevant clinical trials should be provided". This reviewer cannot agree.	Early clinical formulations might have no relevance to the final commercial formulation or have been applied to an indication other than that for which approval is sought. The most pertinent information is the formulations critical to supporting the suitability of the intended commercial product for the intended indication. The information requested is PERTINENT to establishing how the formulation was developed and NEEDED to provide the Agency with some evidence that the development process supports that applicant's final formulation. By asking for "all," the Agency eliminates the risk that a decision by an applicant may fail to provide a formulation that, during the review process, the Agency finds should have been provided.
501	Revise to say "... that linkr elevant clinical formulations to ..." This reviewer disagrees.	For meaningful comparative in-vitro and in-vivo analysis, it is valuable to discuss phase III and proposed commercial formulations. See this reviewer's comment to at Line 495.
549	Replace "study numbers" by "appropriate cross reference" identifiers. This reviewer disagrees but in the interest of flexibility and to recognize that not all use numbers, would suggest changing "study numbers" to "study identifiers"	As written, implies that there will be stability "reports" with title pages, etc. in the Quality section, such as is done for the Clinical section. This is not necessarily the case. We do not present stability data as reports, and while study numbers are included in the stability information provided, they are not presented as a primary identifier (i.e., in the table title). Suggest that this be left more open to allow for variation in approach. One of the valid goals of guidance is the normalization of practice to facilitate consistency and facilitate the review process. This text adheres to that goal. The use of the word "numbers" is does not reflect the reality that most such identifiers are alphanumeric.
667-669	Revise the first sentence to say "For drug products that are intended to be mixed with diluents prior to administration (e.g., constitutable suspensions, powders for injection) compatibility studies should be performed with commonly used diluents even if they are not mentioned in the labeling". Agreed.	Clarity.

Guidance Line #	Proposed Revision	Rationale
696	Delete "name address and phone number of the U.S. agent for each foreign drug establishments." This reviewer disagrees	Personnel information is provided elsewhere in a registration (drug establishment information attachment to Form 356H). This form is updated and submitted with every registration filed. It should not be necessary to repeat this information within the body of the Quality module. Making personnel information part of the regulatory commitment is not appropriate, as it would result in personnel changes having regulatory implications. The commenters ignore the facts: **a)** upon submission the applicant is supposed to be ready for inspection, **b)** the applicant is already required to keep the referenced information up to date, **c),** since the inspectorate gets a copy of the CMC "Quality" module, providing this would expedite the review process, and **d)** the Agency has no leverage that ensures the excipient manufacturers update these forms other than annually; the applicants, as direct customers, do. Based on the preceding facts, the Agency has properly included a request for the applicant to provide the up-to-date contact information the Agency needs for, PAI scheduling.
710-712	Delete "To facilitate preapproval inspection related activities, it is recommended that the name, telephone number, fax number and e-mail address of a contact person be provided for each site listed in the application." This reviewer cannot agree.	Same rationale as for line 696. Same counter rationale as provided in table row "696."
756	Delete "DMF holder's standard" This change should NOT be made **(see Row** "311 and 358").	Quality standards should be pertinent to acceptance criteria of the product manufacturer. While we may use the DMF holder's standard as a starting point for our internal specification, we would not consider it appropriate for the DMF holder to either dictate what should be our regulatory commitment or be responsible for changes to that regulatory commitment. To imply that for a material specification we would just refer to a material DMF is inappropriate.
769	Delete and change to "In-house standard": DMF Holder Y Standard DMF Holder Y Standard DMF Holder Z Standard These changes should NOT be made.	See the counter rationale provided in Row "311and 358." As stated, the commenters are proposing to force the applicant to develop reference-grade standards for **all** those standard materials that the supplier provides – a needless and wasteful duplication of effort.
769	Change "Proposed" to "Typical". This reviewer disagrees. If any change is warranted then this reviewer suggests the Agency replace "Proposed" with either "Example" (a self-denoting word) or the generic phrase "<identifying label>"	All commitments in an application are "proposed" until the application is approved, so use of the word proposed is unnecessary in this single case. Given that this is an example, this reviewer thinks that the commenters are, at best, splitting hairs. If hairs are to be split, then "Example" or "<identifying label> is more appropriate as the use of "Typical" which implies the existence of the "Atypical." Since the table is an example, the use of "Example" is the more linguistically appropriate.

Guidance Line #	Proposed Revision	Rationale
784-786	Delete "(e.g. weighing of components through finished product release.)" and change to "(e.g. product sampling)". This reviewer agrees that this should be changed, but it should be changed to address the entire process as defined by CGMP. Thus, the phrase should be "(e.g. weighing of components through finished product release.)" should be changed to "(e.g. receipt of components through product release)"	Details like weighing and finished product release do not add value in many cases and will add to the complexity of the diagram charging of components through finished without providing useful information. The flow diagram should focus on the manufacturing unit operations. Discounting the initial sentence as a mixture of unsubstantiated claims and irrelevant facts, this reviewer agrees with the commenters – "the flow diagram should focus on the manufacturing unit operations." However, regardless of the complexity, or the lack thereof, the routine manufacturing unit operations addressed by **CGMP** start with: a) receipt of components; b) sampling of components; c) testing of components; d) release of components to production; e) allocation of components for a given batch; f) start of production of a batch; g) charging of components for the first phase of manufacture; h) in-process control of the first phase of manufacture; i) – k) sampling, testing and/or examination, and release of the output of the first phase in the manufacture of a batch to the next phase; and ends with unit operations: ia) – ic) the inspection (sampling and testing and/or examination), and release of the finished packaged batch of drug product; and id) the transfer of the released batch from manufacturing to warehousing or distribution. Therefore, the requested diagram (which may be composed of a series of "sub" diagrams) should address all regulated manufacturing unit operations. Since that is the case, the preceding should be included in said diagram or set of "sub" diagrams.
785	Revise to say "The entire manufacturing process should be depicted, including packaging,...". Agreed but this reviewer would suggest that the language in **21 CFR 210.3(b)(12)** should be adapted and used. Based on this, suggest changing the wording to conform to **Sec. 210.3(b)(12)** and the realities discussed in this reviewer's remarks in commenter's table row "784 – 786."	As presented it is not clear that the packaging process needs a flowchart as well. In line 800, packaging is mentioned. For consistency it should be mentioned here as well. The text should include all the regulated unit operations that should be addressed, not a few that the commenter's firm or the Agency or, for that matter, this reviewer believes should be mentioned.

Guidance Line #	Proposed Revision	Rationale
824-830	Move this paragraph to P.3.1 Manufacturers, or preferable the appendices. This reviewer does not agree.	This is not part of the manufacturing process description. To have the requested statement here introduces US specific information into a document that otherwise would be suitable for use in most geographic regions. Additional regional requirements should be addressed in Module 1 or the Appendices to Module 3. Apparently, the commenters forgot that the title of the heading under which this information is being requested is "Description of Manufacturing Process and Process Controls." The requested information is a "description of the process controls" that are required. This is the case because the certification of the safety of the components a firm uses is an integral part of the controls mandated by the **FDC Act**. Moreover, becauseit is a safety control it is very appropriate that the Agency request it here.
891-894	This is a significant improvement in documenting that no documentation is required to be able to carry out reprocessing work. No change needed.	The principle that, for most products, reprocessing need not be described in the application is important and should be retained.

Guidance Line #	Proposed Revision	Rationale
927-929	Add a statement such as "Although they are considered critical process controls, some tests on intermediate product may not need extensive justification if they are consistent with current industry practice or compendial standards, for example, hardness or assay of a core tablet prior to coating." This reviewer not only opposes this addition but is also surprised to find that the commenters have *apparently*: **a)** Not carefully read **Sec. 211.110 Sampling and testing of in-process materials and drug products, or**, *having carefully read it*, **b)** Failed to understand: **i)** The clear requirements of **21 CFR 211** for process controls **or** **ii)** What is needed for a firm's process control to be both ***scientifically sound*** and ***appropriate***?	FDA has chosen to define tests done on intermediate products as critical process controls, however, the acceptance criteria for some of these is well established and needs little further justification. The commenter's statement is false. Factually, the CGMP regulations define the types of control procedures (tests) to be considered for use on each batch and specifies, **"Such control procedures shall be established 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."** Thus, whenever a firm finds that any of these are required to control each batch they become critical controls. If they are not such, then they should eithern ot be being used by the firm or their use should be justified in as PQIT. In addition, the CGMP regulations require each manufacturer to establish (justify that) that the controls they use are ***scientifically sound*** and ***appropriate*** **(21 CFR 211.160(b))**. As the Agency knows, factually it has been established that the requisite controls are not those in the **USP** or **NF** because these are ONLY *scientifically sound* and *appropriate* for drug-product in commerce – not *per se* for in-process materials. In addition it has been established that the sample numbers and/or used in many cases by the industry, including most published examples, do not, as Agency management is aware, meet the requirements of **21 CFR 211.160(b)(2)** and/or are, for other reasons, not ***scientifically sound***. Based on the preceding it is, or should be, obvious that: **a)** *This added text should be rejected* and **b)** *Each submission should provide a* ***regulation-compliant, scientifically sound,*** *and* ***appropriate*** *justification forany in-process control that is required to be used on each batch to ensure compliance with* **21 CFR 211.110**.