David W. Blois, Ph.D.
Senior Vice President
Global Regulatory Policy

Merck & Co., Inc.
West Point PA 19486
E-Mail: david_blois@merck.com
Tel 484 344 2304
215 652 5000
Fax 484 344 2335

June 27, 2003

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

Submit electronic comments: http://www.fda.gov/dockets/ecomments

RE: [Docket No. 02D-0526] *Draft Guidance for Industry on Drug Product: Chemistry, Manufacturing, and Controls Information*

Merck & Co. Inc is a leading, worldwide, health product company. Merck's corporate strategy – to discover new medicines through breakthrough research – encourages us to spend billions of dollars annually on worldwide Research and Development (R&D). Through a combination of the best science and state-of-the-art medicine, Merck's R&D pipeline has produced many of the important pharmaceutical products on the market today.

As an innovative research and development company, Merck is affected by regulations which impact new application filing requirements since we file full applications and supplements, routinely. Therefore, we are interested in and qualified to comment on this draft guidance. The draft guidance on "Drug Product Chemistry, Manufacturing and Controls Information" (CMC) is intended to assist sponsors with the content of CMC information for drug products submitted in original new drug applications (NDAs) and abbreviated new drug applications (ANDAs). Information requirements are specified according to the structure and format of the Common Technical Document (CTD), as harmonized under by the ICH process.

Merck commends the FDA on their scientific approach to recommendations made regarding drug product CMC information that should be submitted in original NDAs and ANDAs and supports the development of this draft guidance. To assist further development of this guidance, we are providing the following general comments, specific line comments and editorial comments for your consideration.

GENERAL COMMENTS

1. It is recommended that the terminology "Primary Stability Studies" incorporated in this guidance be revised to "Formal Stability Studies" to be consistent with ICH terminology.

   Several sections throughout this guidance discuss the acceptance of results on protocols from excipient manufacturers and testing from the drug product manufacturer. We consider this a cGMP issue and suggest that this subject-matter not be included in the guidance. Relevant cGMP sections dealing with component receipt, testing and

qualification are found in 21 CFR 211.22 and 211.84. Examples of this include, but are not limited to, the following line items that should be removed from the guidance:

- Lines 1022-1025 "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)."
- Lines 1035-1038 "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."
- Lines 1817-1819 "This should include a certificate of analysis (COA) from the component manufacturer and the test results for the same batch from the drug product manufacturer.

3. The guidance does not acknowledge the varying degree of TSE risk from ruminant tissues and/or processing techniques. For example: If a drug product contains a highly processed tallow derivatives, must the same level of detail be provided as a product utilizing bovine blood serum?
4. Does the FDA recognize and accept the guidelines set forth in European Pharmacopoeia Monograph 5.2.8 (or EMEA/410/10 "Note for Guidance on Minimizing the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human or Animal Medicinal Products"? If an excipient manufacturer has been granted an EP Certificate of Suitability, does FDA consider this sufficient documentation to demonstrate TSE risk minimization?

SPECIFIC COMMENTS

Lines 229-231 –The draft guidance states that Environmental Assessments information is considered part of the chemistry, manufacturing, and controls documentation. This may be ambiguous since it is requested to be included in Module 1 of the CTD. It could be less ambiguous if the sentence were to be revised stating that the Environmental Assessment information is to be included exclusively in Module 1. The sentence should therefore be revised **from**:

"Although included in Module 1 of the CTD, this information is considered part of the chemistry, manufacturing, and controls documentation in the United States."

to:

"Although this information is considered part of the chemistry, manufacturing, and controls documentation in the United States, it should be included exclusively in Module 1 per CTD."

Lines 335-339 – Waxed tablets contain a minimal quantity of wax for polished coating and historically, the amount per tablet has not been quantitated. The amount of wax for polishing coated tablets therefore need not be provided on a per unit basis and it is recommended the sentence be revised from:

"The following components should be listed in the composition statement, but the amount of each component on a per unit basis need not be provided: (1) processing agents, (2) purposefully added gases that are intended to remain as part of the finished drug product (e.g., nitrogen added to head space), and (3) imprinting inks."

to:

"The following components should be listed in the composition statement, but the amount of each component on a per unit basis need not be provided: (1) processing agents, (2) purposefully added gases that are intended to remain as part of the finished drug product (e.g., nitrogen added to head space), (3) imprinting inks and (4) waxes used for polishing coated tablets."

Line 358 (Table 1) and Line 769 (Table 2) – It is recommended that "Hydroxypropyl Methylcellulose" be changed to "Hypromellose" to be consistent with compendial nomenclature.

Lines 442-443, 454-456 and 991-993

Cross-referencing to Drug Master Files and locations for the information is confusing in these sections. It is therefore suggested that the wording of these sentences be revised **from:**

The CMC information or a cross-reference to a DMF that provides the CMC information should be included in A.3.

to:

The CMC information or a cross-reference to a DMF (or to the DMF LOA contained in Module 1) that provides the CMC information should be included in an appendix.

Line 495 – A summary of all formulations used in clinical trials can be quite voluminous. Therefore, it is recommended that this summary be included as an attachment or reference instead of contained in the body of the document for ease of review.

Lines 495-499 – Key safety and efficacy data come from batches included in the pivotal clinical studies and it is these batches that need to be clearly bridged to the commercial product. We therefore recommend revising the sentences **from**:

"The differences between clinical formulations and the proposed commercial formulation described in P.1 (i.e., composition statement) should be discussed. Any changes between the proposed commercial formulation and those formulations used in clinical batches and primary stability batches should be clearly described and the rationale for the changes provided."

to:

"The differences between clinical formulations used in pivotal studies and the proposed commercial formulation described in P.1 (i.e., composition statement) should be discussed. Any changes between the proposed commercial formulation and those formulations used in clinical batches used in pivotal studies and primary stability batches should be clearly described and the rationale for the changes provided"

Lines 503-505 – Since an in vitro/in vivo correlation is not always available and in order to align with the *M4: Common Technical Document for the Registration of Pharmaceuticals for Human Use* (Posted 10/15/2001) guidance on CTD, section **3.2.P.2.2.1 Formulation Development**, we recommend revising the sentence **from**:

"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.

to:

"Results from comparative in vitro studies or in vivo studies should be discussed when appropriate."

Line 601 – Footnote 15 includes reference to a single container system. Since this is specific and restrictive, it would be preferable to replace the current verbiage in Footnote 15 with a reference to the appropriate guidance: FDA: *Container Closure Systems for Packaging Human Drugs and Biologics* (Posted 7/6/1999).

Lines 704-706 – The proposed CMC Information guidance is specific for Drug Product information. Therefore, it is recommended that reference to laboratories that perform quality control testing of bulk drug substances be removed from that bullet. We recommend revising the sentence from:
"Laboratories that perform quality control tests on bulk drug substance(s), components, intermediates, container closure systems, and finished drug product, including stability testing"
to:
"Laboratories that perform quality control tests on components, intermediates, container closure systems, and finished drug product, including stability testing"

Lines 790 –796 – We feel it is appropriate to identify critical process controls that have direct and quantifiable impact on product quality. Steps may have several process controls, a subset of which may be critical. Definition of these critical process controls (not steps) is a more precise and direct description of process requirements. We therefore recommend revising "critical steps" to "critical process parameters" in the first bullet. For clarification purposes, it is recommended to revise "critical process controls" to "critical in-process material tests" in the third bullet. 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)

to:

- each manufacturing step, with identification of the critical process parameters, and any manufacturing step...
- the material being processed
- critical in-process material tests and the points at which they are conducted
- the type of equipment used (equipment model number is not needed)

Lines 821-822 – Executed Production Records are very large. Therefore, it is recommended that they not be included as the first part of the Regional Information section, as this might be cumbersome for review of paper versions of the application. We therefore recommend moving the Executed Production Records to the end of Regional Information section to facilitate ease of review.

Lines 824-826 – "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 94.11) are not used or manipulated in the same facility." This is stronger verbiage than is found on Lines 1100 through 1111 or Lines 1646 through 1739, which allow for explanation if materials from BSE countries are used. Given the recent

changes to the USDA list of BSE countries (Japan/Canada), it is suggesed that FDA assess TSE risk on measures in addition to geography. Ruminant-derived materials from BSE countries should be permitted provided other suitable measures are taken (i.e., processing, selection of tissues, use of controlled herds, etc.). The scope of "facility" should be clarified in this context.

SUGGESTED VERBIAGE:

"If ruminant-derived materials are used or manipulated in the same manufacturing equipment as the new drug product, a statement should be provided regarding control measures (such as sourcing, manufacturing processing conditions, and the nature of the tissues) used to minimize the risk of TSE."

Line 845 – There may be in-process material tests performed in order to adjust equipment (e.g. hardness). These tests may not always be used to monitor the quality of the product. So, the term "In-process material tests" may not be all-inclusive and might be more appropriate if revised to "Critical in-process material tests".

Lines 849-852 – In this paragraph, Merck considers "All process controls" too inclusive. Quite frequently there are processing controls that have no affect on the quality attributes of the product. These processing controls may be in place to monitor process yields or efficiencies. We therefore recommend revising the paragraph **from**:
"Steps in the process should have the appropriate process controls identified. Associated numeric values can be presented as an expected range. All process controls, critical or otherwise, should be included in the description of the manufacturing process (MPR or narrative). "
to:
"The appropriate process controls should be identified for each process step, including associated numeric ranges, limits, or acceptance criteria, and should be included in the description of the manufacturing process (MPR or narrative). Any process controls that are considered critical process control should be highlighted in the description."

Lines 867-875 – We made the recommendation to change "In-process material tests" to "Critical In-process material tests" as justified in line 845; therefore, since this does not need to be redefined and to add some clarity, we recommend revising the paragraph **from**:
"All in-process material tests and any of the operating parameters, environmental conditions, and process tests that ensure each critical manufacturing step is properly controlled should be specifically identified as critical in the flow diagram and description of the manufacturing process in this section of the application (P.3.3) and in P.3.4. All in-process material tests are considered critical process controls by definition because they directly assess the quality attributes of an in-process material and ultimately lead to a decision to accept or reject the in-process material or drug product. A summary of where information on drug product quality controls should be located in applications submitted in CTD-Q format is provided in Figure 1."
to:
"All critical process controls and critical in-process material tests (as defined above) should be specifically identified in the flow diagram and in the description of the manufacturing process in this section of the application (P.3.3) and in P.3.4. A summary

of where information on drug product quality controls should be located in applications submitted in CTD-Q format is provided in Figure 1."

Lines 891-892 – To be consistent with the first sentence of the paragraph (lines 887-889) where both in-process materials and drug products are included, we recommend revising the sentence below to include in-process materials **from**:

"For most drug products, reprocessing need not be described in the application."

to:

"For most drug products and in-process materials, reprocessing need not be described in the application"

Lines 1102 – 1104: - "Furthermore, for excipients derived from ruminant materials, the application should state whether the materials are from BSE countries as defined by the U.S. Department of Agriculture (9 CFR 94.11)." Given the recent changes to the USDA list of BSE countries (Japan/ Canada), it is suggested that FDA assess TSE risk on measures in addition to geography. Ruminant-derived materials from BSE countries should be permitted provided other suitable measures are taken (i.e., processing, selection of tissues, use of controlled herds, etc.).

SUGGESTED VERBIAGE

"Furthermore, for excipients derived from ruminant materials, the application should provide control measures (such as sourcing, manufacturing processing conditions, and the nature of the tissues) used to minimize the risk of TSE."

Line 1149 – We recommend including the definition for "sunset provision" in the glossary as "the criteria that must be met to eliminate a test".

Lines 1276-1278 – Validating compendial analytical procedures is not commonly done or necessary. Therefore, it is recommended that Validation of compendial methods are not applicable; however, the suitability of the method should be performed (e.g. sterility) be added and this section be revised **from**:

"This information should be provided for all analytical procedures listed in the specification (P.5.1). Stability data (S.7.3, P.8.3), including data from stress studies, should be used to support the validation of the analytical procedures."

to:

"This information should be provided for all analytical procedures listed in the specification (P.5.1). Validation of compendial methods are not applicable; however, the suitability of the method should be performed (e.g. sterility). Stability data (S.7.3, P.8.3), including data from stress studies, should be used to support the validation of the analytical procedures.

Lines 1277 – 1278 – It may not always be necessary to perform stability testing to validate analytical procedures. Therefore, We recommend adding "if appropriate" after Stability data thereby revising the sentence **from**:

"Stability data (S.7.3, P.8.3), including data from stress studies, should be used to support the validation of the analytical procedures."

to:

"Stability data (S.7.3, P.8.3) if appropriate, including data from stress studies, should be used to support the validation of the analytical procedures."

Line 1496 – It is recommended that footnote 34 be removed from the proposed Drug Product CMC Information guidance because it includes only those applications that fall within the scope of Q1A and negates interim specifications from being used for Q1C type products or ANDAs.

Line 1537 – A period should be added after P in P.2.4

Line 1555 – The underscore between "proposed" and "shelf life" should be removed.

Lines 1569-1571 –There is no mention of photostability studies, which we understand to be an oversight. We recommend that they be added as part of the Formal Stability Studies. The section might be revised **from**:
"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."
to:
"The results from long-term, accelerated and, when performed, intermediate studies undertaken on primary stability batches should be provided. The results from photostability testing should also be included. Stability study reports should also be included."

Line 1570 – We recommend defining "Stability study reports" in the glossary as "results from the formal stability studies that reference the tests used to generate the data".

Lines 1588-1590 – It is not necessary to list the exact date of a change since this should be documented internally as part of good cGMPs. Therefore, we recommend taking the example date out of this line and replacing it with the more generic term of in between which test stations the change was made. It is recommended to revise the sentence **from**:
"For example, a summary could state that the solvent system for the assay was changed on December 15, 1999, from A to B so that impurities Y and Z that co-elute using System A could be quantitated separately."
to:
"For example, a summary could state that the solvent system for the assay changed was changed between the 3 and 6 month test station of the FSS from A to B so that impurities Y and Z that co-elute using System A could be quantitated separately."

Lines 1639 – 1642 - "However, when contamination with viral adventitious agents or transmissible spongiform encephalopathy (TSE) agents is a concern or for protein products, additional information can be warranted and should be included in this section of the application." It is suggested to clarify the term, "concern."

SUGGESTED VERBIAGE

"When viral adventitious agents, TSE agents or protein products are used, and where there are not adequate control measures in place (such as sourcing, manufacturing processing conditions, and the nature of the tissues), additional information on measures to prevent cross-contamination should be included in this section of the application."

Lines 1713 - 1715: "Certifications and/or certificates relating to use of ruminant-derived materials and sourcing of materials from BSE countries as defined by the U.S. Department of Agriculture (9 CFR 94.11) should be provided, as appropriate." It is suggested that a declaration about the quality control systems in place to ensure any ruminant-derived tissues are taken from healthy herds and are collected in such a way as to minimize risk of TSE.

SUGGESTED VERBIAGE:

"Declarations relating to the use of ruminant-derived materials and sourcing of materials from BSE countries as defined by the USDA should be provided, as appropriate."

We welcome the opportunity to provide feedback on the *Draft Guidance for Industry on Drug Product: Chemistry, Manufacturing, and Controls Information.*

Sincerely,

Marie A Gray for

David W. Blois, Ph.D.
Senior Vice President
Global Regulatory Policy