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Dockets Management Branch
Food and Drug Administration, HFA-305
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 02N-0509; Proposed Rule/Draft Guidance, ***International Conference on Harmonization; Draft Guidance on the M4 Common Technical Document – Quality: Questions and Answers/Location Issues; Availability, Reference to Federal Register*** *[67 Federal Register 79639 (December 30, 2002)]*

Dear Sir or Madam:

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 2001 alone, Bristol-Myers Squibb dedicated $2.1 billion for pharmaceutical research and development activities. The company has nearly 6,000 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 more than 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 on the relationship of linked sections and the location of specific information contained in M4Q: The Common Technical Document (CTD) – Quality.

We commend the U.S. FDA for allowing us the opportunity to provided our comments and have several general comments, which we have cited below. In addition, we have made specific comments on the attached table concerning the Question and Answers/Location Issues Table, that was presented with this draft guidance.

1. The CTD does not clearly delineated where information related to the Drug Master Files (DMF), i.e., DMF references and Letters of Access, should reside.

   Recommendation: FDA should consider placing DMF information related to the drug substance, excipients, drug product manufacture, and/or packaging suppliers in the CTD sections listed below:

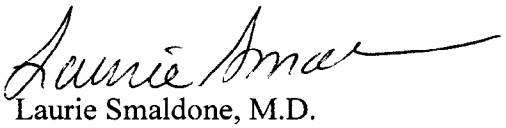
Drug Substance = Section 3.2.S.2.1 (Manufacturers)
Excipients = Section 3.2.P.2.1.2 (Excipients)
Drug Product Manufacture = Section 3.2.P.3.1 (Manufacturers)
Packaging = Section 3.2.P.2.4 (Container Closure Systems)

2. A question was posed on page 9 of 32 in the draft guidance under Section 3.2 Particle size: *"How is information on the particle size for the drug substance submitted?"*

   Recommendation: FDA should consider including intrinsic dissolution data for the drug substance in Section 3.2.S.3.1 (Elucidation of Structure and Other Characteristics) of the CTD. The reference to the data in this section can be linked to the discussion presented in 3.2.P.2.1.1 (Drug Substance) and 3.2.P.2.2.1 (Formulation Development), e.g., influence of particle size on dissolution performance.

Bristol-Myers Squibb 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.

Sincerely,



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CTD - Q Section	Issues / Questions	Answers – *BMS Response*
S.3.1 Elucidation of Structure	Where should studies conducted to determine the physiochemical characteristics be included?	Information on the studies conducted to determine the physicochemical characteristics should be included in 3.2.S.3.1. Only a list of the general properties of the drug substance is included in 3.2.S.1.3. ***BMS Response:*** *Please clarify that the section title is Elucidation of Structure and Other Characteristics and not as shown, i.e., Elucidation of Structure. Without such clarification, we are opposed to splitting the physicochemical information and other characteristics between 3.2. S.1.3 and 3.2.S.3.1.*
S.4.4 Batch Analyses	2. Should all tests performed be reported if not included in the specification?	2. Yes, all data from relevant batches should be reported in 3.2.S.4.4. ***BMS Response:*** *2. No, data should be limited to those tests in the regulatory specification plus any relevant data needed to justify the specification, e.g., XRPD could be shown to justify why a specification isn't necessary.*
S.7.3 Stability Data	2. Should information on any changes in analytical procedures over the course of generating stability data be included in 3.2.S.7.3?	2. Information on historical analytical procedures used to generate the stability data included in 3.2.S.7.3 should be included in 3.2.S.7.3.

CTD - Q Section	Issues / Questions	Answers – *BMS Response*
		BMS Response: *2. Recommend editing the sentence for better clarity, i.e., "Information on historical analytical procedures used to generate the stability data, should be included in 3.2.S.7.3."*
P.1 Description and Composition of DP	1. Where should information related to the composition of inks used on the drug product be placed?	1. All drug product recommendations should be listed in 3.2.P.1. The composition (e.g., components of the capsule shell, components of inks) should be included in 3.2.P.1 also. In some regions the qualitative composition of proprietary components can be replaced with reference in appropriate DMFs. ***BMS Response:*** *1. Recommend that response is clarified to indicate that excipient DMF References and Letters of Access be included in 3.2.P.2.1.2.*
	2. Where should information on reconstituted diluents be included?	2. If the diluent is co-packaged with the drug product, the information on the diluent should be placed in a separate P section. If not co-packaged, the compatibility of the diluent with the drug product should be discussed in 3.2.P.2.6. ***BMS Response:*** *2. Even if the diluent is co-packaged with the drug product and has a separate P section, the compatibility of the diluent with the drug*

CTD - Q Section	Issues / Questions	Answers – *BMS Response*
		product should still be discussed in the drug product 3.2.P.2.6 compatibility section.
P.2.1.2 Excipients	7. Where should a discussion of the ability of a functional excipient to perform through shelf-life be included?	7. Discussion of ability of functional excipients to perform through shelf-life (e.g., antioxidants, penetration enhancers) should be included in 3.2.P.2.1.2. ***BMS Response:*** *7. In addition, some of this information might be better discussed (or cross-referenced) to appropriate Stability (3.2.P.8) sections.*
P.2.2.3 Physicochemical and Biological Properties	1. Where should any discussion on dissolution development be included?	1. A summary of dissolution development should be included in 3.2.P.2.2.3 with cross reference to studies in Module 5 as appropriate. The justification for the dissolution test should be included in 3.2.P.5.6. ***BMS Response:*** *1. A cross-reference to any discussions of analytical method development provided in section 3.2.P.5.2 would also be appropriate.*
P.2.6 Compatibility	1. Where should data from constitution or dilution studies performed as part of the formal stability studies to confirm product quality through shelf-life be provided?	1. Information on the compatibility of reconstitution diluents to support claims in the label is included in 3.3.P.2.6. Data from constitution or dilution studies performed as part of the formal stability to confirm product quality through shelf-life are reported in 3.2.P.8.3.

CTD - Q Section	Issues / Questions	Answers – *BMS Response*
		BMS Response: *We are in agreement with the answer provided above however, the section is incorrectly stated as 3.3.P.2.6. The correct section is 3.2.P.2.6.*
	2. Should compatibility of co-administered drugs be provided in 3.2.P.2.6?	2. Compatibility with co-administered drugs should be included in 3.2.P.2.6. ***BMS Response:*** *2. Information on compatibility with co-administered drugs should be included in 3.2.P.2.6 and data should be presented in 3.2.P.8.3, if applicable.*
	3. Should information on incompatible diluents be provided in 3.2.P.2.6?	3. Yes. ***BMS Response:*** *3. Information on incompatible diluents should be included in 3.2.P.2.6 and data should be presented in 3.2.P.8.3, if applicable.*
P.3.2 Batch Formula	1. Are overages included in 3.2.P.3.2?	1. Yes, overages are included in the batch formula in section 3.2.P.3.2. ***BMS Response:*** *1. Overages should be included in the batch formula section 3.2.P.3.2 and justified in 3.2.P.2.2.2.*

CTD - Q Section	Issues / Questions	Answers – *BMS Response*
P.3.3 Description of the Manufacturing Process and Controls	2. Should critical steps and intermediates be identified in P.3.3?	2. All process controls should be identified in 3.2.P.3.3. For critical controls, additional information should be provided in 3.2.P.3.4. ***BMS Response:*** *2. Remove the word "All" or better define the word "process controls" (e.g., manufacturing process parameters vs. process control tests). That is, "Process controls should be identified in 3.2.P.3.3. For critical controls, additional information should be provided in 3.2.P.3.4."*
P.4 Control of Excipients	1. Where would additional scientific data for noncompendial, non-novel excipients be placed?	1. For noncompendial, non-novel excipients additional scientific data can be included in 3.2.A.3. ***BMS Response:*** 1.Additional data for noncompendial, non-novel excipients should be placed in 3.2.P.2.1.2. and not in 3.2.A.3, which is the section titled Novel Excipients. Note: 3.2.A.3 is for novel excipients and not for non-novel excipients as referenced in the Guidance for Industry M4: Organization of the CTD, August 2001.
P.4.5 Excipients of Human or Animal Origin	1. Where should information on excipients of human or animal origin be located?	1. Information on excipients of human or animal origin in 3.2.P.4.5. Information on adventitious agent safety evaluation should be included in 3.2.A.2. For location of certifications relating to TSE/BSE see region

CTD - Q Section	Issues / Questions	Answers – *BMS Response*
		specific guidance. ***BMS Response*** *1. Information on excipients of human or animal origin, a.k.a as Specified Risk Materials (SRMs) should be included in 3.2.P.4.5. Also, included in 3.2.P.4.5 should be supplier declarations certifying that the material is not of animal or human origin, e.g., vegetable origin. TSE Certificates should be included in the regional section 3.2.R.3, i.e., European Pharmacopoeia TSE Certificates of Suitability.*
P.5.4 Batch Analysis	2. Should all tests performed be reported even if not included in the specification?	2. Yes, all data from relevant batches should be reported in P.5.4. ***BMS Response:*** *2. No, only data relevant to the proposed regulatory specifications should be included or data demonstrating that a particular specification is not appropriate.*
P.5.5 Characteristics of Impurities	1. Should all observed impurities be listed in 3.2.P.5.5 even if they are not included in the drug product specification?	1. Yes, all observed impurities should be listed. Justification for not including an observed impurity in the specification should be included in 3.2.P.5.6. ***BMS Response:*** 1. Yes, all observed impurities, except those reported in 3.2.S.3.2 (Impurities in Drug Substance), should be included in 3.2.P.5.5.
P.6 Reference Standards or Materials	1. Reference standards may be available for	1. If information is required for a reference

CTD - Q Section	Issues / Questions	Answers – *BMS Response*
	the active moiety and impurities. Should information on all reference standards be included in 3.2.P.6?	standard, the information should be included in 3.2.P.6. ***BMS Response:*** *1. Information on reference standards specifically required for the drug product should be presented in 3.2.P.6. Information on reference standards used for both the drug substance and the drug product should be included in 3.2.S.5.*
	2. Where should characterization data for a reference standard be placed in the CTD-Q?	2. Characterization data for the reference standard should be included in 3.2.P.6. Cross reference to information in other sections can be included as appropriate. ***BMS Response:*** *2. Information on characterization data specifically required for the drug product should be presented in 3.2.P.6. Information on characterization data used for both the drug substance and the drug product should be included in 3.2.S.5.*
P.8.1 Stability Summary and Conclusion	1. Should shelf-life specifications be repeated under this section?	1. Shelf-life specifications should be included here and as appropriate in 3.2.P.8.3. ***BMS Response:*** *1. The shelf-life specifications included in 3.2.P.5.1 should be repeated in 3.2.P.8.1 and as appropriate in 3.2.P.8.3.*

CTD - Q Section	Issues / Questions	Answers – *BMS Response*
P.8.3 Stability Data	2. Should information on any changes in analytical procedures over the course of generating stability data be included in 3.2.P.8.3?	2. Information on historical analytical procedures used to generate the stability data included in 3.2.P.8.3 should also be included in 3.2.P.8.3. ***BMS Response:*** *2. Recommend editing the sentence for better clarity, i.e., "Information on historical analytical procedures used to generate the stability data, should be included in 3.2.P.8.3."*