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

Re: Docket No. 02D-0526; Draft Guidance for Industry on Drug Product: Chemistry, Manufacturing, and Controls Information: Availability, [68 Federal Register 4219-4220 (January 28, 2003)]

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 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and we have made specific comments on the attached table, that is based on the CTD structure as presented in this draft guidance.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.

Sincerely,

Laurie F. Smaldone, M.D.
Sr. Vice President
Global Regulatory Sciences
Bristol-Myers Squibb Company

Bristol-Myers Squibb's Comments on FDA's Draft Guidance for Industry on Drug Product: Chemistry, Manufacturing, and Controls Information

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.
	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."
	• 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 invitro/invivo correlation and a cross-reference to the studies (with study numbers) should be provided." Add: "<u>If available</u>," a summary of .....should be provided.

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	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.
	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."
	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
VI. Control of Excipients		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 implies that a sponsor cannot utilize vendor qualification in order to accept via COA without providing additional information in the filing. 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. Additionally, 21 CFR 211 also allows the sponsor the ability to accept via COA, provided qualification has occurred. It is unreasonable to require the pharmaceutical manufacturer to commit to fully test every excipient lot at this point in the filing.

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VI. Control of Excipients	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]" 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 211.84(d)(1))[27]." Add (insert the following clause to the beginning of footnote "[27]"): "For the tests accepted by the manufacturer on Vendor COA, the drug product manufacturer must establish the reliability…" 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." *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.*

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		1026–1027 & 1027–1030	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.* 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.*
		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 .

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		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? 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 1038-1041 of 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. 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).
	B. Analytical Procedures	1055	A more complete listing of "FDA-recognized" standard references would be useful.

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	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."
	D. Justification of Specifications	1076	In general the guidance would be more useful if an example justification for an excipient specification is provided.
		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.
		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 surface 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.*

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	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 "VI.A" 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 VI.B. Also see comments on section VI.A lines 1045-1046 where deletion is recommended.
	B. Analytical Procedures	1252	"...and the referenced analytical procedure is not modified...". This would indicate that any 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.
	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."
		1277-1278	"Stability data (S.7.3, P.8.3), 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.

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	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.
		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.
		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.
		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.
	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.
	D. Batch Analyses	1308–1309	Refer to comments, references and rationale given 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 <u>along with a discussion of the data</u>." Delete the second sentence, "Stability study reports should also be included."
		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.

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		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.
		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).
		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..."
XI. Regional Information	A. Executed Batch Records 2. Information on Components	1819-1821	*Refer to comments, references and rationale given for lines 1092-1094*
XIII. Literature References	Attachment 1	1893	Add to beginning of the sentence: "For unit of use packages, a test for...."
		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.