

July 01, 2004



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

RE: Docket No. 2003D-0571–Draft Guidance for Industry on Drug Substance, Chemistry, Manufacturing and Controls Information

Merck & Co., Inc is a leading worldwide, human health products company. Through a combination of the best science and state-of-the-art medicine, Merck's Research and Development (R&D) pipeline has produced many important pharmaceutical products available today. These products have saved the lives of or improved the quality of life for millions of people globally.

Merck understands and supports the FDA's development of a guidance that outlines the recommended information for new drug applications (NDAs). This effort is as an integral part of good review management processes for both the agency and industry. Clear expectations of the content of an NDA will support seamless dossier preparation and review, to reach toward our shared goal, to facilitate the approval (and accommodate the post-approval life cycle) of safe and effective medicines for all patients. Merck & Co., Inc. has vast experience with drug and biological development, as well as the submission and approval of regulatory dossiers worldwide. As such, we welcome the opportunity to provide comment to this important draft document intended to provide manufacturers with guidance for information to be submitted in the chemistry, manufacturing and controls section of a dossier.

The following comments are intended to address important considerations for the further development of the draft guidance. We have separated our comments into significant concerns followed by an Attachment detailing specific comments. Overall, we believe that the draft guidance is somewhat misaligned with other Agency initiatives in the area of risk management and quality by design. Quality systems have been formalized and implemented throughout the pharmaceutical industry. As such, conveying *knowledge* of the development and manufacturing of a product has become more valued in the preparation of a dossier than providing onerous levels of detail that obscure the critical information concerning the chemistry, manufacturing and controls of the product. Our comments are intended to provide textual criticism in support of an alignment between this draft document and important initiatives such as the development of topics within the International Conference on Harmonization (ICH), Pharmaceutical Development (topic Q8) and GMP Risk Management (topic Q9), and overall Agency quality by design and

risk management initiatives. There are valuable concepts outlined in the draft guidance, including provisions for sunset testing, the use of interim acceptance criteria and Periodic Quality Indicator Tests (PQITs). Additionally, noting that the executed batch records are not required (Line 1630) in the submission is beneficial guidance.

SIGNIFICANT CONCERNS (Summarized by Section):

MANUFACTURE (S.2)

A. Manufacturers (S.2.1)

•Lines 383, 384: *“Building numbers or other specific identifying information should be provided for multifacility campuses.”* Current post-approval change (PAC) guidance documents (November 1999 and BACPAC I) allow changes between buildings on the same site (campus) with no regulatory impact. The requirement to specify the building number is inconsistent with PAC requirements, and we therefore recommend the removal of this sentence.

•Lines 392, 393: *“Facilities should be ready for inspection when the application is submitted to FDA.”* We recommended the revision of this statement to allow site readiness to be tied to acceptance of the file by FDA, rather than submission to FDA, and to allow the possibility to communicate a later inspection ready date, if appropriate.

B. Description of Manufacturing Process and Process Controls (S.2.2)

1. Flow Diagram

•Lines 406 – 910: The requirements specified for the manufacturing process description and flow diagram represent a significant increase in the level of detail expected in the original NDA. These requirements appear in direct conflict with FDA’s approach toward more risk based regulation. Merck believes the process description and controls should focus only on the critical parameters and critical quality attributes. In addition, the flow diagram should only provide an overview of the synthetic pathway. Increased level of detail in the filing will increase the Agency efforts for review, will significantly increase the number of post approval supplement, and most importantly does not provide a higher degree of assurance of product quality, safety, efficacy or purity. Additionally, certain information specified in this section has no regulatory impact for post approval changes.

Specific Examples

- Detailed requirements for the flow diagram (lines 414 - 431)
- Specifying equipment type in process description (lines 454, 455)
- Providing all process controls, as opposed to all CRITICAL process controls (lines 457, 458)

- Identification of and requirements for steps which use recycled/recovered materials, second crop recoveries (lines 462 - 465 and lines 622 - 626)
- Identification of and requirements for steps that use recovered solvents or auxiliary materials (lines 466 - 467 and lines 628 - 637)
- Increased information on fractional collection (chromatographic purification) procedures (lines 468 – 470)
- Specifying process steps which involve combining intermediate or API batches (lines 471 - 472)
- Inclusion of the requirement to specify “*All process controls, critical or otherwise*” (lines 521 - 522)
- The need for inclusion of supporting information (e.g. comparative data) for reprocessing/rework, etc. in the filing (lines 557 – 560)
- Repetition of multiple steps being universally defined as reworking (lines 578 - 579); as well as the rationale for this being considered a rework (lines 605 - 609)
- Inclusion of procedures/specifications for regeneration of column resins and catalysts (lines 647 – 653)
- The requirements for starting materials (lines 683 – 719 and Attachment 1)
- Inclusion of non-critical process tests and tests on intermediates, etc. (lines 772 – 777)

V. CHARACTERIZATION (S.3)

B. Impurities (S.3.2)

•Lines 1057 – 1062: The requirement to provide structural characterization data, physical and chemical properties, the route of synthesis and summaries of unsuccessful attempts to identify impurities would contribute an insignificant increase in the quality of the API, while significantly increasing the development efforts. Merck suggests these requirements for impurities be removed from the guidance.

VI. CONTROL OF DRUG SUBSTANCE (S.4)

D. Batch Analyses (S.4.4)

1. Batch Analyses Reports

•Lines 1263 – 1265: “*The batch analysis reports should include results from all tests performed on the batch, including tests that are not part of the proposed specification.*” We consider this requirement unnecessary and believe it may discourage industry from conducting non-routine testing in order to gain a better understanding of the API during development. Consistent with our belief that the NDA should focus on critical information required for manufacture and control of the API, we suggest the removal of this requirement.

Justification of Specification (S.4.5)

- **Test**

•Lines 1308 – 1311: “*However, exclusion of a test..., or one that was reported in the batch analyses (S.4.4) should be justified.*” As discussed above, we believe it is unnecessary to include results for development tests not included in the final specification in the batch analysis section; thus justification of their exclusion is also considered unnecessary. We do agree that exclusion of tests, which are generally required for API control, should be justified.

ATTACHMENT 1: STARTING MATERIALS FOR SYNTHETIC DRUG SUBSTANCES

Overall, this section appears to be misaligned with current Agency initiatives. Current definitions and existing guidance documents, coupled with the submission of supporting DMFs, or other appropriate mechanisms as determined through discussions with the Agency, should be considered a more appropriate way to handle definition of starting materials. We suggest that commercial availability of the material be the primary consideration for acceptability of a compound for use as a starting material, regardless of whether that availability is for non-pharmaceutical or pharmaceutical use.

- **Starting Materials without a Significant Nonpharmaceutical Market**

•Lines 1714 – 1716: “(3) *an existing manufacturer of the chemical had to scale up its process to produce sufficient quantities...*” For most commercial supply agreements, the applicant may not be aware of activities undertaken by the supplier for a compound with an existing commercial market. A vendor increasing its capacity to meet increased market demands for material should not impact the suitability of that compound as a starting material.

I. SELECTION PRINCIPLES FOR STARTING MATERIALS WITHOUT A SIGNIFICANT NONPHARMACEUTICAL MARKET

A. Propinquity

Lines 1742 – 1743: “*A chemical proposed as a starting material should be separated from the final intermediate by several reaction steps that result in isolated and purified intermediates.*” There are examples when the final intermediate or even the final API is formed by a simple coupling of fragments. It is possible that one or more compounds which introduce fragments of the molecule may be suitable for definition as a starting material. It is also unclear what is meant by “*several reaction steps*” and why steps which result in non-isolated intermediates should be universally excluded.

We recommend that the burden to justify the selection of starting materials be based not on the step in the process in which the material is used, but instead should reflect sound scientific rationale and the availability of suitable controls for both the material and the process.

C. Carryover of Impurities

•Lines 1775 – 1797: Sound justification based on scientific rationale should dictate the suitability of materials for classification as a starting material, rather than the universal and somewhat arbitrary requirements contained in this section. An understanding of the fate of an impurity introduced by a starting material should be sufficient to allow this material to qualify.

D. Complexity of Structure

•Lines 1815 – 1818: “*If advanced techniques suitable for complex structures....*” We believe the listed analytical techniques, especially chiral HPLC, should not be considered *advanced*. The use of these techniques should not preclude definition of starting materials if they are applied to distinguish the starting material from potential isomers or analogs.

II. DOCUMENTATION

B. Flow Diagram of the Complete Synthesis

•Lines 1831 – 1841: It should not always be necessary to provide flow diagrams showing reaction steps before the defined starting materials, whether they have significant pharmaceutical use or not. Suitable starting materials without a significant non-therapeutic use can be available from multiple sources, which utilize different manufacturing routes. It is more appropriate that suitable controls are in place for acceptance of the starting material in the API process.

D. Justification

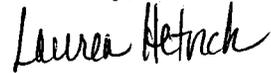
•Lines 1869 – 1971: The justification for starting materials should not be limited by the contents of this section of the guidance. It should be determined on a case by case basis utilizing sound science, specific to the individual process.

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Information - page 6

We appreciate the opportunity to share our comments with respect to FDA's Draft
Guidance for Industry Drug Substance Chemistry, Manufacturing and Controls
Information. Please do not hesitate to contact me, should you have any questions.

Sincerely,



for Donald Black, MD, MBA
Vice President
Global Regulatory Policy

Enclosure: Specific Comments-03D-0571

Specific Comments-Docket No. 2003D-0571: Draft Guidance for Industry on Drug Substance; Chemistry, Manufacturing and Controls Information- page 1

Line Number	Draft Guidance Section	Comment	Rationale
multi	all	All references to drug substance (including in the Glossary) should be replaced with active pharmaceutical ingredient.	Consistency with currently accepted industry terminology
48	I.	Modify line to read " <i>Drug substances manufactured by chemical synthesis, except as noted below</i> "	Peptides and oligonucleotides can be considered a subset of APIs manufactured by chemical synthesis
52	I.	Bullet 4 should be modified or deleted.	The introductory language indicates the guide applies to these types of drug substances. Bullet 4 does not describe a type of drug substance.
66	I.	It is unclear why fermentation products are universally excluded from the guidance	Fermentation processes are no longer uncommon, are generally well understood and controlled, and could potentially be the subject of this guidance.
140	II.B	Should read "...for approval under the application. It may be appropriate to designate certain sections or subsections as "not applicable" in the submission.	It is our experience that not all subsections will apply to all applications for API approval
238	II.D.2	It should not be necessary to specify contract laboratories used for testing of APIs	The site responsible for release or acceptance of the material should be specified; flexibility should be allowed to use different contract laboratories without regulatory impact, provided that the responsible site has evidence that these contract facilities are qualified. The qualification documentation would be subject to review at any site inspection.
307	III.A	Footnote 11 is potentially unclear.	Footnote 11 can be interpreted as excluding nomenclature for non-USP compendia
383	IV.A	The need to specify building numbers should be removed.	Changes within facilities currently do not need to be reported post approval. Providing this information would require a mechanism to handle changes
389-392	IV.A.	Requirement for contact name and telephone number for facilities are more appropriately given in the accompanying Form 356H, not in the original application.	This information is subject to change, and no mechanism is in place to update this information post approval.
392	IV.A	This statement should read " <i>Facilities should be ready for inspection when the application is accepted for submission by FDA, or FDA should be notified when a facility will be ready for inspection.</i> "	FDA PAI's do not typically occur before formal acceptance of the filing; current forms allow specifying of inspection-ready dates

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395 - 910	IV.B - IV.F	General comment on Manufacturing Section - these requirements go beyond providing the Agency with a working understanding of the process and process controls. Too much detail will require a significant increase in review time and the need for post approval submissions	This section is a significant deviation from FDA proposed risk based review and will not provide increased assurance of public safety
399	IV.B	Suggested revision " <i>A flow diagram and a complete description of the processes and critical process controls...</i> "	Process in NDA should reflect only critical parameters and quality attributes
407-435	IV.B.1	The requests to provide certain information on the flow diagram regarding critical unit operations (e.g. extraction, crystallization, etc.) appear redundant to the requirements for the narrative description as described on lines 438-473. Specifically, the requirements of line 414 appear to be duplicated on Line 456, those of line 425 are duplicated on lines 452-3, those of line 427 are duplicated on lines 457-8, and those of line 431 are duplicated on Line 473. The content of the Flow Diagram should be sufficient to give the Agency reviewer an overall view of the processing to be conducted and the chemistry. Other information is better reserved for the narrative description where the applicant can provide the necessary detail regarding critical operations, critical control parameters and the manner in which they are monitored and controlled in the processing.	While Merck agrees that information regarding the process such as critical operations, parameters and controls should be reported to the Agency, it should not be required to repeat this type of information in multiple areas of the application.
440, 441	IV.B.2	Suggest the following deletion: " <i>A narrative description of the...steps undertaken and the scale of production should be provided.</i> "	Changes to the manufacturing batch size need not be reported per current guidance; thus this information should not be required in the application
454	IV.B.2	Type of equipment should only be mentioned when critical to the operation	Changes to equivalent equipment need not be reported per current guidance; thus this information should not be required in the application
457	IV.B.2	Revise as follows: " <i>All critical process controls and their associated numeric ranges, limits, or acceptance criteria, with critical process controls highlighted</i> "	Merck believes it should only be necessary to include critical process controls in the application; tests used only for process information, troubleshooting, business reasons, environmental (EPA) reasons, etc. and not needed for quality control, should not be reported.

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460 - 472	IV.B.2	Inclusion of the information requested in these bulleted items is not necessary for the reviewer to gain an understanding of the process. These issues are often implemented for business reasons, with assurance that API quality is not impacted. Supporting information and data for these practices should be maintained on site and available for review at an inspection.	The addition of this level of detail does little to further assure public safety; will increase initial review time and ultimately result in the need for increased numbers of post approval filings.
473	IV.B.2	Suggest the following revision: " <i>Yield ranges (weight and/or percent) for each manufacturing step resulting in an isolated intermediate or the final API. Typical yields are provided for information only, and are not considered registered parameters; explained deviations from these typical yields generally need not be considered operating outside the registered process.</i> "	The yields for individual steps are often not critical quality-indicating parameters, and may be impacted by a number of external parameters. If yields are requested for information, it should be clear that deviations from the yield generally need not be considered a regulatory deviation.
508 - 517	IV.B.2	Each of the four bullets should be updated to reflect the need for only those operating parameters, environmental controls, process tests and in-process tests which are critical to assure intermediate or API quality	This request is consistent with the theme that the manufacturing process description should reflect only critical information.
538 - 545	IV.B.2	Reword as follows: " All of the <i>The operating parameters, ...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 (S.2.2) and in S.2.4. All critical tests on...</i> "	Only critical information need be included in the application
552 - 563	IV.B.3	The need to provide supporting information (comparative data) for reprocessing seems unwarranted, as reprocessing can theoretically be done at many stages of the process under many conditions. Presentation of data supporting reworks may be appropriate; however the data may be limited. Merck does not believe it is appropriate to include the supporting data in S.2.2, as this will needlessly complicate the process description. If required, this data should be included in the process development section, S.2.6, without the need for specific cross reference in S.2.2.	Merck believes that S.2.2 should contain only the critical information on the manufacture of the API, with other supporting information provided elsewhere in the application, or preferably retained on site for review at an inspection when warranted.
553	IV.B.3	The Agency should define the terms recycling and salvaging in the guidance, or reference their definition in an existing guidance.	These terms can be used to describe different types of operations

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555-557		Suggested change to: <i>Moreover, reprocessing and reworking operations should be capable of bringing one or more quality attribute of the material within the acceptable range without causing significant, adverse change in the remaining quality attributes of the material.</i>	The current sentence is too restrictive. It would suggest that, for example, a slight increase in moisture, within the acceptance ranges for the process, could prevent the implementation of a reprocessing to reduce impurity levels within their acceptable range
578	IV.B.3.a	Strike the sentence: " Repetition of multiple reaction steps is considered to be reworking, rather than reprocessing (see section IV.B.3.b) "	Merck does not agree that repetition of multiple steps contained in the process should always be considered reworking. The repetition of multiple reaction steps should normally constitute reprocessing when the applicant has sufficient data to provide in the application to claim that such processing will allow for the alteration of quality attributes of a material to an acceptable range. Merck agrees that re-introduction of an intermediate through multiple reaction steps without thorough evaluation of the impacts to substance quality attributes should be avoided. However, if development data support the submission claim that such processing is acceptable, it should be deemed reprocessing. This is consistent with the FDA statement (line 611) that reworking procedures are typically developed post-approval.
581	IV.B.3.a	The statement " <i>For most intermediates and drug substances, reprocessing need not be described in the application.</i> " appears to conflict with line 552. Brief clarification of when it would be appropriate to include reprocessing should be included in this section.	The guidance should be internally consistent and clear
605	IV.B.3.b	See comment for line 578; There are instances where it is required to break a salt and then take the compound back through the existing process steps, which should technically be considered a reprocess. It is recommended that this type example be added or the sentence re-worded to allow for certain justifiable situations. The salt break process could be described in the application to facilitate this reprocessing.	Generally Merck would not consider a demonstrated salt break as a step which has significant potential to adversely impact the impurity profile of the material, especially in light of the fact that the resulting material will be subjected to repeat of the processing, purification and isolation steps of the process.
611-616	IV.B.3.b	The statement that post approval supplements are typically required for reworking operations is inconsistent with the BACPAC I guidance, and should be appropriately modified.	Under BACPAC I, the addition of a rework for an early process intermediate does not require a PAS if supporting data are generated prior to the final intermediate.

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622-643	IV.B.3.c	Merck considers the requirements on recovered solvent use unnecessary and recommends this section be deleted.	Recovered solvents must meet the same quality requirements in RM tests and expected values section - there is no risk using recovered solvents in the vast majority of cases. Merck considers this to be needlessly restrictive detail, which will result in an increase in post approval changes
642, 651	IV.B.3.c/d	It should not be necessary to specify the maximum number of times a recycle can be used, assuming the recycled filtrate has meaningful specifications established and continues to meet these specifications	The need for a post approval change to perform additional recycles is unwarranted provided the filtrate continues to meet the registered specifications
642-643	IV.B.3.c	Suggest deletion of the sentence " Data on impurity levels should be provided to justify recycling of filtrates. "	The need for including this type of supporting data in the application is unclear; data supporting the acceptance specifications for recycled solvents should be available for review at an inspection
657-664	IV.B.3.e	Suggest deletion or modification of Item (2).	As long as the drug substance is reprocessed by the original filed steps and meets the acceptance criteria, the age of the material or whether it has been released is irrelevant. The procedure is still technically reprocessing
688	IV.C.1	The statement " <i>In general, the starting material and API starting material should be the same for a synthetic drug substance.</i> " is confusing and should be clarified.	Based on the content of Attachment 1, it appears that there may be many cases where this statement is inaccurate
713	IV.C.1	It is unclear what type of flow diagram is requested for starting materials; this should not be necessary in the majority of cases	Often synthesis of SM is not relevant if the compound is available from multiple sources and meets our acceptance criteria
769-777	IV.D	This section is unclear; the first sentence states that <i>all critical operating parameters...</i> should be provided. Line 773 then provides guidance on those judged to be non-critical. It is recommended that non-critical parameters, etc. be excluded from the application	Non-critical information is not necessary for inclusion in the submission, and should have more flexibility to be changed post approval without regulatory implication
780, 781	IV.D	Experimental data supporting the critical control ranges should not be included in the application.	It should not be necessary to provide extensive experimental data supporting control ranges in the submission; these should be held and available for inspection.

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797-812	IV.D	The option to use in-process testing in place of release would relieve testing for impurities that could be controlled earlier in the process. However, an expectation that the in-process limits would be equal to or tighter than finished API is not appropriate as down stream processing can be shown to sufficiently reject an impurity.	It is not always meaningful to have tighter specifications for intermediates; these types of specifications may be applicable to impurities which are not further reduced down stream; however there are cases where it is appropriate to have a looser limit coupled with good knowledge of downstream rejection.
818	IV.D	The requirement of assay testing for intermediates should be removed.	Assay is not always a meaningful requirement to determine the suitability of an intermediate for further processing; this is process dependent.
839-854	IV.D	This section should be moved to the definitions section.	This section provides greater value when relocated from the main guidance to the definitions section.
845	IV.D	We suggest that material has different stereochemical identify than drug substance should not be included as an example of "Postsynthesis Materials".	It is necessary to break/create a bond to change stereochemistry; technically the isomer could be considered as the final intermediate
856	IV.D	A replacement for the term "Unfinished" should be considered	The term unfinished is not commonly used in the industry; perhaps "crude" is more appropriate
858-861	IV.D	These sentences should be moved to the definitions section	These sentences provide greater value when relocated to the definitions section.
877	IV.E	Suggested revision of footnote 15 - " The appropriate parts of all manufacturing processes should be validated. However, in most cases, the validation information is reviewed during facility audits. "	It is currently not required to validate all parts of manufacturing processes (e.g., formal validation of early process steps is often not performed).
894, 895	IV.F	Suggested rewording: "...relationship between changes outside normal variabilities in the manufacturing process or changes in the manufacturing site... "	The term "changes" as it relates to the process is too broad
984, 985	V.A.2	Suggest deletion of the sentence " However, screening a variety of solvents with different polarities and hydrogen-bonding properties can be valuable for early detection of other polymorphs. "	By including this statement in the guidance, it may be considered an expectation for development rather than a helpful hint.
1009	V.B	The Agency is requested to clarify whether the impurity discussion should address only actual experience (i.e. those impurities observed in development) or those which can be projected from the route of chemistry, whether or not they have been observed	The term " <i>most likely to arise</i> " can be interpreted in different ways. Our recommendation would be to focus on impurities observed in development
1019, 1020	V.B	Suggest deletion of bullet 2.	See rationale for comment to line 1009, above

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1021, 1022	V.B	Suggest deletion of bullet 3.	Early process impurities are not typically discussed/described under S.3.2. It seems more appropriate that these be discussed in S2.6 Process Development and that S.3.2 focus on the final process for commercialization.
1038	V.B	Suggest deletion of the sentence " The studies to characterize these impurities should be described. "	The types of studies used to characterize impurities have previously not been included in the application. This increased level of information is not critical to the review of the NDA.
1057 - 1062	V.B	Suggest deletion of bullets 4, 5 and 6	Merck believes these requirements are unwarranted, in that they are not relevant to assuring the quality of the API.
1063 - 1065	V.B	Suggest the deletion or revision of bullet 7	Merck believes this information is required but is more appropriate in other sections of the submission, and at most should be referenced in this section. With the implementation of electronic, linked submissions, redundancy of information should be avoided
1111 - 1115	VI.A	Suggest deletion of the sentences " The specifications from the application and/or drug product manufacturer should identify the tests that it will routinely perform and the test results that will be accepted from the drug substance manufacture's certificate of analysis (COA). ⁴⁸ Presentation of information in a tabular format is suggested. "	Merck believes this recommendation is not appropriate in this API guideline; it would be more applicable in a guidance for the drug product.
1127	VI.A	Although noted as an "illustrative example", we suggest that additional disclaimers be added to Tables 1 and 2	The tables contain poor examples of meaningful tests and acceptance criteria for an API
1154- 1156	VI.A	Suggested change: " If sufficient data (e.g. data from multiple batches, representative of the all-proposed manufacturing sites and processes) are available... "	Sites are expected to produce the same quality material; if demonstrated at site A it is a minimal risk that site B would produce different quality material via the same process.
1180	VI.A	It would be helpful to provide meaningful examples of PQIT tests.	This would help illustrate Agency thinking on this new concept.
1196	VI.B	It is suggested that this reference be deleted until the guidance is published	It is a risk to cite unpublished guidances
1229, 1230	VI.C	Suggested rewording: " This information should be provided for all the appropriate analytical procedures listed in the specification (S.4.1). "	Compendial or certain limit or identity tests should not require presentation of validation data.

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1230, 1231	VI.C	Suggest deletion of the sentence regarding stability data or rewording it as follows: " Stability data (S.7.3), including d Data from stress studies, should be used to support the validation of the analytical procedures, where appropriate. "	The requirement to use stability data beyond chromatographic stress studies to support validation is unclear.
1258, 1259	VI.D	Suggest the addition of a qualifier like "We discourage the use terms such as conforms or meets specification for tests which have defined numerical limits. "	It should be acceptable to report conforms or passes for identity and similar tests, provided the specification is included in the batch analysis table
1263, 1264	VI.D.1	The sentence should be modified as follows: " The batch analysis reports should include results from all the tests performed on the batch, including tests that are not part of the proposed specifications. "	One interpretation of this requirement (i.e. to include in-house or supplemental test results) would actively discourage applicants from running additional tests during development to gain additional information on the process or API. If the intent is to list the results for tests run under the IND, but subsequently removed or changed, the statement should be reworded to reflect this intent more clearly.
1282	VI.D.2	Suggested modification: " However, collated data should be provided for assay and impurities... "	Assay data would not appear to require collation
1310	VI.E	We suggest the clarification (e.g. examples) of "a relevant FDA guidance"	Examples would be useful to lead applicants to appropriate guidances
1310	VI.E	See comments for lines 1263, 1264 above; if the purpose of that requirement is to include the results for developmental tests in the application, we would suggest deletion of the statement "... , or one that was reported in the batch analysis. " here also.	See rationale for lines 1263, 1264, above
1401, 1402	VII.	Suggested rewording "A list of any available reference standards required for testing of for impurities and intermediates should be included in S.5."	Information should only be required in the application for reference standards which are needed to perform testing specified in the application.
1409 - 1411	VIII.	Suggested revision "A description of the container closure system for the drug substance should be provided, including the identity of materials of construction of each primary packaging component and its specification where appropriate (e.g., when a unique or non-standard material is used in the container closure system). "	Merck considers the request to provide specifications for commonly used packaging components (e.g. HDPE or LDPE bags) as unwarranted. Merck believes it should be sufficient to simply state the material of composition for most container closure systems, unless a unique system is required.

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1412	VIII.	Suggest deletion of the sentence " For nonfunctional packaging secondary packaging components (e.g., those that do not provide additional protection), only a brief description should be provided.	No information should be necessary for non-functional secondary packaging components; this requirement would result in the need for a post approval submission to change the nonfunctional secondary package even though this change would have essentially no potential to adversely impact the quality of the API
1465	IX.C.1	Suggested revision "A summary of any critical changes in the analytical procedures should be provided. ". It is further requested that FDA clarify by examples the type of changes to be reported.	Merck believes not all analytical changes need be discussed; some are very minor
1482-1483	IX.C.2	Suggest the following clarification " <i>Stability data to support holding times for intermediates or during processing should also be provided in this section when warranted (e.g. certain proteins). Holding times are generally not expected for synthetic API processes.</i> "	It is assumed that FDA does not consider holding times necessary for synthetic processes.
1490, 1491	IX.C.3	Suggested revision "Any results from drug substance stress testing should be provided in this section of the application, or referenced from other sections."	Stress studies performed as part of method validation would be better reported directly in S.4.3 and referenced in S.7.3 if relevant to the stability studies for the API or the specifications.
1494	IX.C.3	"drug product" should be changed to " drug substance "	Typographical error expected
1671	Attach 1	Suggest changing the word "element" to " fragment "	The term element can be misleading in this context
1671	Attach 1	A better example of a minor structural element should be considered	Hydride ion may not be important since it is a small structural element (fragment) but maybe a critical to the quality or safety of drug product
1683 - 1685	Attach 1	Suggested revision; replace the sentence " A drug substance that is used to synthesize another drug substance is not an appropriate candidate for designation as a starting material. " with the sentence " A drug substance can be the starting point for the synthesis of another drug substance in the application; however, the appropriate information on the starting drug substance should be provided (e.g., by reference to a DMF or an approved NDA). The starting drug substance technically is not considered a starting material. "	The current statement lacks guidance on how to handle situations where the process starts with another approved API.

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1686, 1687	Attach 1	Suggested revision " <i>For NDAs, FDA recommends that the choice of starting material be included in the IND and/or discussed during the investigational period (e.g., at end-of-phase 2 (EOP-2) meeting).</i>	Discussion at the EOP-2 meeting may be too late since many companies may have already made critical clinical/stability batches using the designated starting materials. Designation of the starting materials in the IND provides FDA with an opportunity to comment on the selection earlier in the developmental period.
1690	Attach 1	The existence of a significant non-pharmaceutical market should be irrelevant with respect to the amount of information required to support the use of the compound as a starting material – Merck prefers the generally accepted criterion that the material should be an article of commerce.	If an item of commerce can be identified as an appropriate starting material, its usage outside the pharmaceutical industry should have no bearing on its suitability for use. Instead, its suitability should be judged based on available controls on that material
1714 - 1716	Attach 1	We recommend deletion of item (3).	An API manufacturer may not be aware of the activities of suppliers for a compound for which a market already exists. If an existing supplier for a material increases production to accommodate increased demands in the market resulting from the preparation of API for clinical studies, this should not impact the status of the material for consideration. Should the market quality be insufficient for production of API, the applicant will submit information on additional purification or processing required to make the material suitable for use.
1740 - 1766	Attach 1, I.A	The propinquity argument should be reconsidered or significantly revised. We recommend that the burden to justify the selection of starting materials be based not on the step in the process in which the material is used, but instead should reflect sound scientific rationale and the availability of suitable controls for both the material and the process.	The Agency clearly indicated its intention for requirements for API SM in lines 1730-1733. The applicant should be able to justify how the body of controls employed (e.g. raw material specifications, in-process analysis, intermediate's specifications, the study of the fate of impurities in the synthetic process, and the ability of purification steps to reject impurities) during the preparation of the API from the API SM provides sufficient control and assurance of the on-going quality of the API. We suggest maintaining a focus on the ability of the applicant to demonstrate control through process robustness and raw material and in-process controls. The additional requirement of propinquity is inconsistent with this philosophy. The requirement for having 'several' isolated intermediates between a starting material and the API appears to be an arbitrary requirement lacking sufficient scientific basis to be required a priori.

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1759-1766	Attach 1, I.A	We recommend deletion of this paragraph	Merck believes this discussion, is too general and potentially misleading. Continuing this argument a pure intermediate from a clean reaction would not qualify since no purification step took place.
1770	Attach 1, I.B	Merck recommends significant revision of this section such that the use of solutions, oils or even non-purified materials may be considered suitable, provided adequate information exists supporting their use.	We understand that in most cases, a starting material will be an isolated and purified substance. However, the Agency should not preclude industry selecting a solution as the starting material as long as it is well characterized and the impact of the impurities on the API is established. Regarding crude vs. purified materials, we believe the degree of characterization and an understanding of the impact of the starting material impurities on the API are often more important than the absolute purity of the starting material.
1777, 1778	Attach 1, 1.C	Suggested revision " <i>The impact of impurities present in a chemical proposed as a starting material should be understood and discussed in the application. Generally, the starting material should not be the source of significant levels...</i> "	This current text may be misleading in some instances. For instance, if the starting material is an unpurified pro-chiral compound with the following step inducing the chirality and a pure isolation, it would be better to designate the impure pro-chiral compound as the starting material rather than the pure chiral intermediate, since the chiral induction is a critical step in the synthesis and has a potentially dramatic impact on the API. The key consideration should be that the starting material is well characterized for those impurities and the effect of the impurities on the API is established.
1784 - 1790	Attach 1, 1.C	These proposed impurity limits appear arbitrary and should be deleted.	There is no significant risk in selecting a starting material that leads to impurities in the final product that are more significant than the limits in the statement as long as there is established correlation between the specifications of the starting material and the qualified levels of impurities in the API.
1792 - 1797	Attach 1, 1.C	The rationale for selecting the starting material at a point prior to introduction of TSE agent should be explained.	The rationale for this broad requirement is not clear; TSE qualification should potentially be treated as other quality attributes of the SM, with the rationale for selection of the material with respect to TSE provided in the application
1807 - 1811	Attach 1, 1.D	This requirement should be replaced with a more meaningful expectation of the Agency regarding the acceptable structural characteristics of starting materials	It is difficult to quantify what constitutes a " <i>limited number of functional groups and structural features...</i> "; thus the current guidance is subject to a high degree of interpretation

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1815 - 1817	Attach 1, 1.D	We recommend that elemental analysis, mass spectrometry and chiral HPLC be removed from the list of advanced techniques.	Mass spectrometry and elemental analysis cannot be used to distinguish potential isomers and analogs. Chiral chromatography should not be considered an advanced technique for the purposes of API starting material analysis. It has become a routine technique in the pharmaceutical industry and in API processing. Consequentially, there should not be a limitation on its use. Further, this requirement may provide incentive to an applicant to list a less specific test for chiral features (such as specific rotation) in the specifications for an API starting material to avoid this requirement. Such practice will discourage the use of the most appropriate and specific technique and impede the application of the best available technologies for control of API processes.
1827	Attach 1, II.A	The request of providing "CAS Registry Number" for starting material should be removed.	The inclusion of CAS numbers for starting materials is not critical for review of the application.
1828-1829	Attach 1, II.A	We request that "melting or boiling range" to be removed.	Specifying the melting or boiling range for a starting material is not necessary as this information is not generally relevant to the assessment of suitability of the material for its intended use.
1831 - 1841	Attach 1, II.B	This section of the guidance should be deleted	Consistent with our belief that a starting material should not be judged based on its non-pharmaceutical market but rather its being an item of commerce, we do not see a need for expanded flow diagrams. The flow diagram in S.2.2, which would start with the designated starting materials, should be sufficient. Even if this Agency approach is adopted, a defined starting material without a significant non-pharmaceutical market could be obtained from multiple sources, which may not use the same synthesis to achieve suitable quality material. The need to show these multiple early pathways to the starting material seems excessive and non-value added.
1857-1858	Attach 1, II.C	Merck suggests the following revision <i>"Acceptance criteria for class 1 or 2 residual solvents and certain inorganic impurities (e.g. palladium) should also be considered, taking into account the potential for carryover."</i>	We generally only need to control class 1 or 2 solvents and those inorganic impurities which typically require control in the finished API at this early stage of the process. This statement can be interpreted as a requirement for additional solvent/inorganic controls beyond these.

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1869 - 1971	Attach 1, II.D	General comment - Merck suggests this section be revised based on an approach more consistent with current definitions and guidances on starting materials.	As summarized by the comments above, we believe the Agency should reconsider this proposal regarding starting materials. Comments to individual items in II.D are provided below in the event FDA does not significantly modify the contents of Attachment 1.
1889- 1891	Attach 1, II.D.1	For item (2), see comments above for line 1714. Additionally, the term "scale up" should potentially be qualified.	API manufacturer may not know about the activities of suppliers to the market.
1919 - 1937	Attach 1, II.D.2.c	See comments as on lines 1777, 1778 and 1784 - 1790.	These requirements appear arbitrary
1926	Attach 1, II.D.2.c	An allowance could be added that the impurity has been appropriately qualified	This could provide additional flexibility without compromise of safety
1949	Attach 1, II.D.2.c	Suggest adding " An example of a possible approach follows: Two samples... "	The qualifier helps identify this as an approach to consider; however, the applicant may use other approaches or a sound scientific justification to achieve the same endpoint.
1961- 1971	Attach 1, II.D.2.d	See comments to lines 1807 - 1811 above	Clarification of expectations would be helpful
1967	Attach 1, II.D.2.d	UV should be removed from the list.	UV usually is not capable to distinguish isomers
2184- 2191	Glossary	It is suggested to remove the term <i>Postsynthesis Material</i> .	Requirements are the same as intermediates, that term should be expanded to include this group of compounds.
2192- 2193	Glossary	Also remove the term <i>Postsynthesis Material Tests</i> .	See above
2215	Glossary	Further clarification is needed on the statement " <i>used immediately</i> "; alternately, this term should be removed.	This term is subject to interpretation. To support removal of the term, if stability data exists to justify the application of a retest period, it should be acceptable to provide for a longer acceptable use period beyond retest as supported by the data. For example, an API reaching its retest date that is tested and found to be unchanged from the initial release data should be considered acceptable for an equivalent period as the original retest.