AstraZeneca

Date: JUN 2 6 2003

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

RE: Written Comments – Federal Register Docket No. 02D-0526
Draft Guidance for Industry on Drug Product: Chemistry, Manufacturing, and Controls Information.

Dear Sir:

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Administration Dockets Management Branch with the following written comments on Federal Register Docket No. 02D-0526 (Draft Guidance for Industry on Drug Product: Chemistry, Manufacturing, and Controls Information).

- Lines 26-28: Please clarify if this draft guidance applies to biotechnology products.
- Lines 79-81: The use of alphanumeric designations in parentheses is confusing. AstraZeneca recommends that the draft guidance document adopt Common Technical Document (CTD) heading numbers, heading names, and sub-headings to reduce confusion and improve ease of use.
- Lines 91-93: The draft guidance recommends that Sponsors discuss cross-referencing of drug product quality information with appropriate review divisions. AstraZeneca believes this stipulation is unnecessary and that cross-referencing of quality information on file with the Agency should not ordinarily be a matter that requires discussion with review divisions.
- Lines 243-245: AstraZeneca requests that the Agency clarify that, by default, United States Pharmacopeia (USP) nomenclature are the standard for descriptions of dosage forms.
- Line 358: AstraZeneca requests that the Agency clarify that it is sufficient to delineate the specific sections and page numbers of the Drug Master File (DMF) that are pertinent to the application in the DMF holder's Letter of Authorization.
- Lines 450-454: AstraZeneca believes the recommendation for additional information, up to and including the level of information for novel excipients, for noncompendial, non-novel excipients is not warranted. The use of noncompendial, non-novel excipients should not routinely trigger the recommended stringent submissions requirements or the need for prior discussions with review division staff.

02D-0526 C10

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- Lines 514-524 and 531-539: AstraZeneca requests that the Agency clarify the differences between "overfill" and "overage."
- Lines 580-587: AstraZeneca believes that it is sufficient to provide summarized results from a bioequivalence study, linking the tablets used in pivotal clinical studies to the proposed commercial formulation. Alternatively, if a bioequivalence study has not been conducted, then a table should be provided that compares the equipment used to produce the clinical batches that support efficacy or bioequivalence and primary stability batches to the equipment proposed for manufacture of the production batches. The information should be presented in a way that facilitates comparison of the processes and the corresponding batch analyses information (P.5.4). The table should identify (1) the identity (e.g. batch number) and use of the batches produced using the specified equipment; (2) the manufacturing site; (3) the batch size; (4) any significant equipment differences (e.g. different design, operating principle, and size).
- Line 692: AstraZeneca believes that this level of detail is not needed for products which are not aseptically produced and requests that the Agency clarify what is meant by the terms multi-facility and multifunctional.
- Lines 693-695: The draft guidance recommends that for sites processing sterile drug substances, products, or packaging components, the sterile processing area (e.g. filling room) is included in the list of manufacturers (Section P.3.1). AstraZeneca suggests that this information is not needed here since it will be contained in the sterilization process validation document.
- Line 696: AstraZeneca believes that the information for the US agent should not be required in this section since this information is already provided in Module 1 of the Common Technical Document (CTD).
- Line 710: AstraZeneca believes that this information should not be required in this section since this information is already provided in Module 1 of the Common Technical Document (CTD).
- Lines 717-718: AstraZeneca requests that the Agency clarify if overfills are to be included in the proposed batch formula that includes a list of all components used in the manufacturing process.
- Lines 720-722: AstraZeneca believes that cross-reference to the quality standards contained in Section P.1 should be permitted.
- Line 748: AstraZeneca believes that cross-reference to the quality standards contained in Section P.1 should be permitted to eliminate redundancy.
- Line 800: AstraZeneca recommends that packaging steps should be described in the manufacturing process only when packaging is an integral part of the dosage form manufacture, such as in liquid fills, dry powder fills, and sterile packaging operations. Oral tablet packaging is typically a separate and distinct process that should not be included as part of the dosage form manufacture.

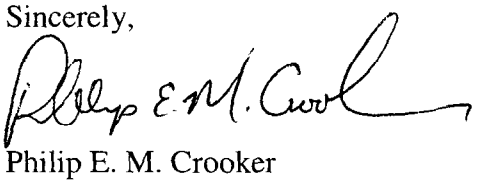
- Line 824: AstraZeneca believes this information is relevant only to inspection and cGMP compliance and should not be required for inclusion in a filing. AstraZeneca recommends that this information be made available for review during an Agency inspection to demonstrate that a Sponsor has appropriate controls in place for the potential of cross-contamination. In addition, AstraZeneca requests that the Agency provide additional guidance and clarification regarding the use of same and separate facilities when formulating products containing materials of possible animal origin, such as magnesium stearate, lactose and gelatin capsules.
- Lines 965-970: AstraZeneca requests that the Agency provide additional guidance and clarification, since the information in this section appears to be in conflict with information presented on line 885. AstraZeneca believes that it is generally accepted practice to not include validation data in an original application, and thus questions the need for these data for reprocessing operations. AstraZeneca believes that this information is relevant only to inspection and cGMP compliance and should not be required for inclusion in a filing. AstraZeneca recommends that this information be made available for review during an Agency inspection.
- Line 981 (Footnote 26): AstraZeneca believes that this statement implies that if an excipient is compendial but also "novel" then the same level of documentation required for a drug substance may be required for the use of such an excipient. AstraZeneca requests that the Agency clarify this interpretation. AstraZeneca believes that requiring such a stringent level of documentation for compendial materials represents a new regulatory standard that is not justified.
- Lines 981-986: AstraZeneca does not believe that the amount of test detail in an application depends on whether or not the applicant intends to perform full testing on each batch of excipient received versus vendor qualification and acceptance by Certificate of Analysis. AstraZeneca believes that full testing is not required by the Sponsor if a vendor has been certified, and that the testing documentation maintained by a certified vendor is a cGMP compliance issue and not a filing and review issue.
- Lines 1022-1024: The draft guidance recommends that the excipient specifications should indicate which tests will be performed by the manufacturer and which tests will be accepted by Certificate of Analysis. AstraZeneca believes this is a cGMP compliance issue and not a filing and review issue. AstraZeneca recommends that this proposed requirement be deleted from the draft guidance document.
- Line 1062-1067: AstraZeneca requests that the Agency clarify that validation of excipient methods is not required for compendial methods. AstraZeneca further requests that the Agency clarify what is meant by "verification" of analytical methods.
- Lines 1081-1082: The draft guidance recommends that the same degree of justification is necessary for noncompendial excipient specifications as for drug substance specifications. AstraZeneca believes that this level of detail is not necessary, particularly for non-novel excipients.

- Lines 1089-1091: AstraZeneca believes that only test data used to release a batch of excipient should be included in an application. Comparison of vendor data to drug product manufacturer data for an excipient is a cGMP compliance issue and not a review issue. AstraZeneca does not believe it is appropriate to include this information in an application and that these data should be made available during inspection.
- Line 1115: AstraZeneca requests that the Agency clarify if a new or different route of administration qualifies excipients as novel. The draft guidance recommends that the same degree of justification is necessary for novel excipient specifications as for drug substance specifications. AstraZeneca believes that this proposed requirement is unnecessary, particularly for compendial excipients that are considered "novel."
- Line 1162: The draft guidance recommends that both release and shelf-life specifications for drug product be filed. AstraZeneca believes this recommendation represents new regulatory policy. AstraZeneca requests that the Agency clarify this proposed recommendation and provide clear guidance on whether the Agency intends to require Sponsors to register in-house release limits.
- Line 1176: AstraZeneca believes that the implementation of the proposed PQIT is in direct conflict with the Agency's Process Analytical Technologies (PAT) initiative and has the potential to inhibit the effective development and application of PAT.
- Lines 1219-1221: The draft guidance recommends that a Changes Being Effected Supplemental New Drug Application (CBE) be submitted to the Agency to include a PQIT test in the drug product release specifications in the event of a batch failure. AstraZeneca believes that submission of a CBE should not be required, and recommends that a commitment to include the test in the release specification, if a failure occurs, be made in the original application.
- Lines 1277-1278: The draft guidance recommends that stability data be used to support validation of analytical methods. AstraZeneca requests that the Agency clarify if this is a new regulatory requirement and further clarify why this recommendation is needed, since it is expected that stability data will be generated using validated analytical methods.
- Line 1286: AstraZeneca recommends that this section should include results for all specification tests on appropriate batches and may also include additional tests which do not form part of the product specification as data to support justification for skip testing.
- Lines 1288-1289: AstraZeneca requests that the Agency clarify if all safety and clinical batches used throughout all development phases need to be included in the batch analysis documentation. AstraZeneca recommends the use of commercial formulation batches.
- Lines 1332-1334: AstraZeneca requests that the Agency clarify if "collated data" means, for example, that assay data for all batches be included in the same table. If so, AstraZeneca believes this represents a new regulatory requirement.

- Line 1386-1409: AstraZeneca recommends that if residual solvent and miscellaneous impurities are discussed and controlled in other parts of the application, there is no need to repeat that information here. AstraZeneca further believes that if residual solvents are not used in the drug product and compendial excipients are used in the formulation, there is no need for this section. Residual solvents and miscellaneous impurities are not required when these are controlled by component specifications.
- Lines 1533-1534: AstraZeneca requests that the Agency provide clarification and further guidance for the level of detail required for functional secondary packaging.
- Lines 1534-1536: The draft guidance recommends that a brief description be provided for nonfunctional secondary packaging components. AstraZeneca believes that this recommendation is unnecessary because these components do not provide an additional measure of protection to the drug product.
- Line 1560: AstraZeneca requests that the Agency clarify if the recommendation to provide a post-approval stability protocol includes a stability protocol for annual stability batches.
- Line 1607: AstraZeneca recommends that stability data for holding in-process materials less than 30 days is a cGMP compliance issue and is not a filing and review issue. Supportive data should be maintained on file with the Sponsor and available for review during an Agency inspection, and should not be required for inclusion in a filing.
- Lines 1644-1739: AstraZeneca requests that the Agency clarify that this information is in agreement with current guidance from the International Conference on Harmonization (ICH) and is only required in applications for biotechnology-derived products.
- Lines 1840-1843: AstraZeneca requests that the Agency clarify that this section can contain hypertext links to appropriate analytical methods and validation reports that permit the Agency reference laboratories to produce hardcopies.

Please contact me with any questions or requests for additional information.

Sincerely,



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