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GlaxoSmithKline

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Management Dockets, N/A
Dockets Management Branch
Food and Drug Administration
HFA-305
5630 Fishers Lane, Rm 1061
Rockville, MD 20852

Re: Docket Number 02D-0526
Draft Guidance for Industry on Drug Product: Chemistry, Manufacturing, and Controls Information

Dear Sir or Madam:

Enclosed please find specific comments from GlaxoSmithKline for the Draft Guidance for Industry on Drug Product: Chemistry, Manufacturing, and Controls Information. These comments are presented for consideration by the FDA. The specific comments are presented in order by the section of the guidance with line numbers included for clarity.

GlaxoSmithKline appreciates the opportunity to provide feedback and suggestions for this guidance. I am submitting this document by hardcopy. Therefore you will receive a paper copy of this letter with the comments and two additional copies through the USPS.

If you have any questions about these provided comments, please do not hesitate to contact me at (919) 483-5857. Thank you for your consideration.

Sincerely,

Mary Faye S. Whisler

Mary Faye S. Whisler, Ph.D.
Assistant Director
New Submissions, North America

02D-0526

C12

Specific Comments

III. DESCRIPTION AND COMPOSITION OF THE DRUG PRODUCT (P1.)

A. Description of Dosage Form

We recommend a standardized list of dosage forms be provided by FDA. The list should be aligned with European Pharmacopoeial Standard terms. (Lines 244-245)

C. Composition Statement

By first intent, the Drug Master File (DMF) and qualitative information should be referenced. If it is not available, quantitative information will be provided. (Lines 289-296)

IV. PHARMACEUTICAL DEVELOPMENT (P.2)

A.2. Excipients (P.2.1.2)

An updated list of known excipients from FDA is needed, because a company would only have information on its own products. The inactive ingredient list (published by the FDA) should be updated on a regular basis. (Lines 460-466)

An updated list of known agents that impart pharmacological activity is needed from FDA. (Lines 468-483)

B.1. Formulation Development (P.2.2.1)

Clarity is needed about the special features of drug product discussed. (Lines 507-512)

B.1. Overages (P.2.2.2)

The last sentence is too constraining. It should be changed to "Use of an overage to compensate for degradation must be justified by data on the basic stability of the drug substance and data on drug product manufacture and stability. Information must also be provided demonstrating that the excess active ingredient added to compensate for instability does not compromise safety nor efficacy of the medication and that the level of degradation products associated with the need for an overage do not pose safety nor tolerability issues." (Lines 537-539)

B.3. Physicochemical and Biological Properties (P.2.2.3)

More clarity is needed relative to establishing a relationship between biobatches and in vitro release (dissolution) testing. (Lines 543-550)

We agree, as these seem scientifically reasonable, that 1) the drug substance concentration in the drug product should be compared to the solubility of the least soluble

solid state form and 2) when the drug load is close to saturation, the solid state forms of the drug substance that can crystallize from the drug product vehicle should be discussed. (Lines 552-556)

C. Manufacturing Process Development (P.2.3)
Only equipment specified as part of critical step(s) should be defined by its basic operating principle. The additional level of detail should be handled during a pre-approval inspection (PAI) or a Good Manufacturing Practices (GMP) inspection. (Lines 580-587)

F. Compatability (P.2.6)
Clarity is needed for which dosage forms to which this should be applied. This needs to be tied to label use; not off-label use of the drug product. (Lines 655-666)

V. MANUFACTURE (P.3)

A. Manufacturer(s) (P.3.1)
This information should be put in the Establishment Information (in Module 1). As is, this reduces the reusability of this module for Common Technical Document (CTD) submissions. (Lines 685-708)

B. Batch Formula (P.3.2)
Clarity is needed as to how this relates to the ±10% range that is assumed is acceptable variability following GMP. The concern is that this may apply to film coating quantities that are specified as ranges (since an exact quantity is not practical). The agency should clarify how this guidance on ranges applies to processing agents/solvents that may change during granulation, for example. (Lines 745-746)

C. Description of Manufacturing Process and Process Controls (P.3.3)
Replace the phrase "the material might be held for a period of time prior to the next step" with "including holding times as appropriate for the product and manufacturing process". (Lines 787-796).

Comments related to the statement in the guidance "A statement should be provided that ruminant-derived materials from bovine spongiform encephalopathy (BSE) countries as defined by the US Department of Agriculture (9CFR 94.11) are not used or manipulated in the same facility." follow: (Lines 824 –830)

1) This appears to be an issue that would more typically be addressed through GMP inspection rather than within the NDA as it relates to site quality practices and procedures, which are not product specific.

2) If FDA insists that such information be presented in the NDA, further clarity is needed regarding the typical expectations for new chemical entity (NCE) products as compared to biologics and biotech products.

3) If FDA insist on provision of this information for NCE products, they must qualify their requirements with suitable exemptions for low risk materials such as milk derivatives, tallow derivatives, gelatin, etc. As reflected in the CDER guidance on sourcing and processing of gelatin, provided certain measures are taken, it is acceptable to use animals that have resided in BSE countries in the production of gelatin. Similar guidance is required for other such low risk materials i.e. tallow derivatives, milk derivatives, etc.

D. Controls of Critical Steps and Intermediates (P.3.4)
The company should have flexibility to determine which batches are included for giving data that support the process. These would not necessarily have to be batches for which full batch analysis data according to specification are given, or for items that would be more appropriate in P.5.4, e.g., (a) portion(s) of a batch may be used to establish mixing times. (Lines 927-929)

VI. CONTROL OF EXCIPIENTS (P.4)
For non-novel, non-critical excipients (i.e. excipients which do not have a major impact on the quality or safety of the finished product), this escalation is unwarranted. FDA will have ample opportunity to review the rationale and justification for reduced testing and/or substitution of analytical methods during a PAI or a routine GMP inspection. (Lines 977-1004)

Clarification of information on pharmaceutical proprietary mixtures (filmcoats and flavors) is needed.

A. Specifications (P.4.1)
For non-novel, non-critical excipients (i.e. excipients which do not have a major impact on the quality or safety of the finished product), this escalation is unwarranted. FDA will have ample opportunity to review the rationale and justification for reduced testing and/or substitution of analytical methods during a PAI or a routine GMP inspection.

It is unclear why information on the quality control (specification, analytical methods, validation and justification of specifications) of novel excipients should not be presented in sections P.4.1-P.4.4 along with other excipients. Other manufacturing and controls information logically resides in P4.6 and A.3, but it would seem sensible to keep all excipient specs and methods etc in one place.

It is assumed that composition and DMF references etc. for proprietary mixtures should be given in P.4.1 with methods in P.4.2 etc. Clarity would be helpful.

B. Analytical Procedures (P.4.2)
For non-novel, non-critical excipients (i.e. excipients which do not have a major impact on the quality or safety of the finished product), this escalation is unwarranted. FDA will have ample opportunity to review the rationale and justification for reduced testing and/or substitution of analytical methods during a PAI or a routine GMP inspection.

It is unclear why information on the quality control (specification, analytical methods, validation and justification of specifications) of novel excipients should not be presented in sections P.4.1-P.4.4 along with other excipients. Other manufacturing and controls information logically resides in P.4.6 and A.3, but it would seem sensible to keep all excipient specifications and methods etc in one place.

It is assumed that composition and DMF references etc. for proprietary mixtures should be given in P4.1 with methods in P4.2 etc. Clarity would be helpful.

C. Validation of Analytical Procedures (P.4.3)
For non-novel, non-critical excipients (i.e. excipients which do not have a major impact on the quality or safety of the finished product), this escalation is unwarranted. FDA will have ample opportunity to review the rationale and justification for reduced testing and/or substitution of analytical methods during a PAI or a routine GMP inspection.

It is unclear why information on the quality control (specification, analytical methods, validation and justification of specifications) of novel excipients should not be presented in sections P.4.1-P.4.4 along with other excipients. Other manufacturing and controls information logically resides in P.4.6 and A.3, but it would seem sensible to keep all excipient specifications and methods etc in one place.

It is assumed that composition and DMF references etc. for proprietary mixtures should be given in P.4.1 with methods in P.4.2 etc. Clarity would be helpful.

D. Justification of Specifications (P.4.4)
As stated above, the requirement to provide information to justify the use of reduced testing regimes for standard excipients is excessive. (Lines 1089-1094)

E. Excipients of Human or Animal Origin (P.4.5)
Further clarity is required from FDA as to the extent of information that must be presented for NCE products as compared to biologics and biotech products. (Lines 1102-1104)

Should FDA require information regarding the risk of transmission of TSE agents via the use of ruminant derived materials in the manufacture of NCE products, further guidance is required from FDA regarding appropriate sourcing and processing criteria. Currently, guidance is only available for gelatin for pharmaceutical use and is not available for other low risk materials such as milk and tallow derivatives etc.

F. Novel Excipients (P.4.6)
Instead of US only, consideration should be given to those excipients with approval in well-regulated markets. (Lines 1118-1119)

The rationale for including the specification for novel excipients in this section and all other details, including analytical methods, validation of analytical methods and justification of specification in Appendix A.3 is unclear. Rather than fragment basic information (specification, methods etc) regarding quality control of excipients over three sections, it is suggested that such details be presented in sections P.4.1 – P.4.4 for all classes of excipients.

VII. CONTROL OF DRUG PRODUCT (P.5)

A. Specification(s) (P.5.1)
We recommend that method numbers are listed in a separate table so as to support CTD. (Lines 1144-1146)

The acceptance criteria for the description should not be as prescriptive to give exact measurements (of the tablet). (Line 1174)

- **Periodic Quality Indicator Tests**
  Clarification is needed, as PQIT is not well defined. In creating a number of different analytical information sheets/tables, the information supplied makes the submission more complex. This information seems to "muddy" the issue of what is needed for a 'non-routine' test (recommend an option to footnote the specification) and why. The justification of these non-routine tests should be provided in the justification of specification section. Inclusion of this information will make the module not usable in other regions. (Lines 1178-1235)

A. Batch Analyses (P.5.4)
The batch information for tests performed that are not a part of the specification (content uniformity, microbiological testing, etc.) should be presented in a more relevant section (manufacturing process development or validation), but not here because not directly relevant to the proposed specification. (Lines 1313-1315)

The text should be changed to the following. "A detailed summary of any changes (when the change occurred, differences between old and new methods, impact of significant differences between methods on the data) may be provided, as appropriate" (Lines 1317-1322).

Clarification of the text is needed. The text states that judgement is allowed for inclusion of data then contradicts itself by stating specific data to be included. (Lines 1330-1334)

Collated data in this section is excessive as the information for relevant information can be found in the batch analysis tables. (Lines 1332-1334)

B. Characterization of Impurities (P.5.5)
The information that is needed is not clear; therefore clarify what is needed. This section needs to address typical and/or identified formulation related (i.e. product specific) impurities that may not be covered by cross-reference to the drug substance section. However, discussion on qualified levels is best placed in the product justification of specifications section. (Lines 1343- 1351)

Cross-reference should ONLY be to non-clinical sections (at a high level). This section should be in the justification of specification section, where reference to qualification of impurities and relevant studies are discussed. (Lines 1349-1351and 1379-1382)

Change opening sentence of paragraph to "Summary information on the characterization..." (Lines 1362-1363)

F. Justification of Specification(s) (P.5.6)
Use of jargon terminology (sunset test) should be avoided. Replace with definitive text or provide a definition of the term. (Lines 1456-1465)

IX. CONTAINER CLOSURE SYSTEM (P.7)

This information needs to be located ONLY in Section.P.2.4, not here. (Lines 1536-1537)

XI. APPENDICES (A)

A. Facilities and Equipment (A.1)
The guidance on facilities and equipment requires extensive clarification, especially with regard to the requirements related to the potential for cross-contamination with viral and non-viral adventitious agents. The original M4Q guidance stated clearly that facilities and equipment information was required for biologic and biotech products only and the FDA guidance appears to have ignored this distinction. While materials of human or animal origin are used in the manufacture of NCE products, the risks associated with their

use are generally accepted to be low, by virtue of the types of materials typically used, the processing applied to them, and the eventual route of administration. While it is not suggested that companies should ignore the possibility of direct or indirect (via cross-contamination) transmission of viral and non-viral agents via NCE products, it is suggested that the level of risk is such that this may be managed through GMP rather than registration activity. (Lines 1638-1678)

B. Adventitious Agents Safety Evaluation (A.2)

As with A.1, the guidance in this section requires extensive clarification, as there is no clear distinction made between the requirements for NCE and biotech/biologics. (Lines 1682-1742)

C. Excipients

- **Novel Excipients**

  For non-novel, non-critical excipients (i.e. excipients which do not have a major impact on the quality or safety of the finished product), this escalation is unwarranted. FDA will have ample opportunity to review the rationale and justification for reduced testing and/or substitution of analytical methods during a PAI or a routine GMP inspection. (Lines 1753-1755)

XII. REGIONAL INFORMATION (R)

A. Executed Production Records (R.1.P)

The amount of information requested is excessive. This information can be addressed during PAI or GMP inspections. (Lines 1817-1819)

ATTACHMENT 1

Rheology

Add the end of the section add this statement. "If rheological measurements are inappropriate for control of consistency or viscosity, the reasons for lack of such control should be listed." (Line1900)