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APPLICATION NUMBER:

21-995

CHEMISTRY REVIEW(S)

ONDQA Division Director's CMC Memorandum on NDA 21-995

Date: October 15, 2006
From: Chi-wan Chen, Acting Director, Division of Pre-Marketing Assessment I, Office of New Drug Quality Assessment
To: DA 21-995 File

Applicant: Merck and Co., Inc.
Drug Name: Januvia (Sitagliptin) tablets, 25, 50, 100 mg
Indication: Type 2 diabetes mellitus

The CMC portion of this NDA was submitted on December 16, 2005, under the ONDQA Pilot Program to explore science- and risk-based approaches to assuring product quality. An expanded pharmaceutical development section was submitted. Several quality-by-design (QbD) elements were presented with respect to product design and process understanding.

Drug Substance

The following critical process parameters (CPPs) for the drug substance manufacturing process were identified:

The major issues identified and resolved during the review are:

1. The applicant proposed no measurement of even though the has been shown to have an impact on drug product processing (e.g.,

   - A batch made at site was and incurred a . The applicant agreed to include in their process description.
   - While the applicant has demonstrated a higher than usual level of understanding of the , the data provided does not provide sufficient assurance over the range of operation proposed in the application. A test was added to the specification sheet to ensure the desired is obtained.

2. No specific designation of critical quality attributes (CQAs) or design space was discussed in the process development section, and the process description for the commercial scale production was vague. The applicant revised the process description and provided a table capturing established design space and initial control space with a few identified CQAs. The revised version contains much more information than a typical process description and provides additional value to reviewers for post-approval changes and for field inspectors.

Drug Product

The application included detailed studies on Process risks associated with scale-up were proactively identified, which include

The process development studies were focused on defining a robust operating space that effectively minimized the inherent process risks. The applicant claimed that none of the process parameters were found to be critical. They defined a critical step or operation as "one that requires process conditions or parameters to be carefully controlled within a predetermined operating range" to assure quality. The applicant established a design space for

The applicant proposed a non-traditional approach to the drug product control strategy. Assay by are tested on , in-process only, though the criteria are included in the specification. The remaining attributes in the drug product specification includes

will be used for stability testing.

The major issues identified and resolved during the review are:

1. Although was conducted to assess the potential risks related to drug substance or excipient variability, the applicant proposed to monitor the

. They did not investigate and understand the effects of material attributes on process or product performance and relied instead on th to ensure and on pharmacopeial standards for the excipients. And the applicant did not intend to monitor or control during commercial production.

At our request and after the PAI of the drug product facility in ne applicant agreed to control the variability in excipients, including , against a set of quality specifications as defined in their quality standard, and include key attributes for all excipients in their drug product design space and control space table.

2. No specific designation of critical quality attributes (CQAs) or design space is discussed in the process development section. The applicant revised the process description and provided a table capturing established design space and initial control space with a few input variables, rather than product attributes, as CQAs. The applicant has identified which design spaces for the unit operations are dependent upon scale or equipment. The revised version contains much more information than a typical process description and provides additional value to reviewers for post-approval changes and for field inspectors.

3. was proposed, but no in-process control for was considered. The applicant addressed FDA's concern by incorporating additional controls to help prevent or minimize These additional controls are:

4. The proposed acceptance criterion for ssay is abel claim (LC) for the mean of a pre-determined number of ablets without an acceptance limit for the SD or a tolerance limit for the number of outliers allowed. The sample size is typically ablets for a tablet batch of the 100-mg strength sampled during the The applicant has agreed to include an acceptance limit for the standard deviation (SD) of the individual assay concentrations to ensure that greater than of the individual ablets assay values, when converted to %LC, are within LC.

5. The proposed acceptance criterion for [redacted] s [redacted] LC. Typically [redacted] ablets for a [redacted] tablet batch of the 100-mg strength were sampled during the [redacted]

- The applicant has agreed to change the acceptance limits to ensure that the [redacted]
- The applicant also agreed to add a [redacted] test [redacted]

The revised procedure and criteria are more scientifically sound and provide an increased level of quality assurance.

6. The proposed [redacted] was found unacceptable by Office of Clinical Pharmacology [redacted] The applicant agreed to replace [redacted] with dissolution for product release and to add dissolution to future stability testing.

7. The proposed established name did not correspond to the labeled strength. The applicant was advised of the FDA policy that the name and the strength should match. They agreed to drop "phosphate" from the established name at the next printing in January, 2007.

As a footnote, the applicant proposed a CMC regulatory agreement outlining the regulatory mechanisms for managing changes related to process, equipment, scale, site, and design and control spaces for the drug substance and drug product post-approval. The agreement will not be approved at this time since FDA has not established a regulatory pathway to allow us to approve such an agreement.

Recommendation

The applicant has provided sufficient scientific information to demonstrate product knowledge and process understanding of the drug substance and product, and made necessary changes to their control strategy to increase the level of assurance in product quality. Other traditional aspects of the NDA, including demonstration of stability and establishment of retest period (36 months) and shelf life (30 months), are satisfactory. The application is recommended for approval from the chemistry, manufacturing, and control standpoint.

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/s/

Chi Wan Chen
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