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

Comments to: Process Analytical Technology – A Framework for Innovative Pharmaceutical Manufacturing and Quality Assurance; Federal Register, Volume 68, Number 172, pages 52781-52782
Friday, September 5, 2003
Docket No. 2003D-0380

To whom it may concern:

Novartis Pharmaceuticals Corporation is a world leader in the research and development of products to protect and improve health and well-being. Novartis researches, develops, manufactures and markets leading innovative prescription drugs used to treat a number of diseases and conditions, including central nervous system disorders, organ transplantation, cardiovascular diseases, dermatological diseases, respiratory disorders, cancer and arthritis. The company's mission is to improve people's lives by pioneering novel healthcare solutions.

As a global pharmaceutical corporation, Novartis is supportive of efforts to improve and to harmonize the technical requirements for registration of pharmaceutical products. We appreciate the opportunity to comment on this guidance in accordance with FDA's Good Guidance practices.

Novartis is generally supportive of FDA's proposed Guidance on Process Analytical Technologies (PAT) and of efforts to stimulate the use of modern pharmaceutical manufacturing technologies for those products that could benefit from such technologies.

However, Novartis is concerned about the following key points:

> To further the effective implementation of PAT concepts and maximize the benefits of real time process control by way of reduced regulatory requirements, additional clarification is requested on how the requirements could change, in particular for end product testing or for statistical analyses.

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This draft Guidance makes reference to PAT specialists and PAT teams. It would be useful to clarify the role of this proposed group in the context of the current known roles of FDA reviewer and inspectional staff.

These points are elaborated and additional comments are provided in the attached tabular format, for ease of FDA use.

These comments are being provided in written form and electronically as directed in the Federal Register Notice.

Novartis appreciates the opportunity to submit these comments and looks forward to continuing to work collaboratively with the Agency on this important initiative to enhance drug product quality.

Thank you for the opportunity to comment. If you have any questions, please contact me at 862 778-3379 or at e-mail: joan.materna@pharma.novartis.com.

Sincerely,

(signed in original)

Joan A. Materna
Global Regulatory CMC

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Novartis Pharmaceuticals Corporation
East Hanover, New Jersey

Novartis' Comments on the FDA Draft Guidance for Industry:

PAT—A Framework for Innovative Pharmaceutical Manufacturing and Quality Assurance
Docket No. 2003D-0380

General Comments

1. Novartis agrees with the FDA that PAT is optional, and can be developed and applied most effectively for certain drug products, not as a general rule for all pharmaceutical drug products.

   Additional clarification is requested on reduced regulatory requirements, such as:

   - reduction of end testing for release;
   - simplification of post approval changes;
   - reduced validation efforts;
   - better risk classification, and;
   - fewer or more specific inspections.

2. The application of the registered specifications for release will not be identical for PAT controls. Large sample sizes or even 100% controls will require different specifications taking statistical aspects into account. For PAT, other OOS rules are seen as necessary and requiring clarification.

3. This draft Guidance makes reference to PAT specialists and PAT team. It would be useful to clarify the role of this proposed group in the context of the known roles of FDA review and inspection staff.

Lines	Comments	Rationale
Lines 350-351	'...the mechanisms of degradation, drug release and absorption.' It is unclear if PAT tools such as multivariate analysis and NIR can lead to an understanding of the **mechanisms** of degradation, although they could be used to indicate a change from a previous state, or to correlate properties of raw materials and process variables to dosage form performance. In this manner, PAT tools could be considered "indicators".	Hard data will still be needed to establish mechanisms of degradation The empirical evidence revealed by PAT can be an aid in identifying mechanisms; however, they will not replace the need for a fundamental understanding of the physical, chemical, and physiochemical properties of the dosage form.
Lines 435-443	It is unclear why the draft Guidance discusses processing time ranges (process windows) as distinct from other kinds of	If the vision of PAT is "real time release", the distinction should be made between critical and non-critical

	process parameters. Most process parameters operate in a range of non-critical values. We expect that this evaluation of range of acceptable process times does not mean that extensive validation studies of potential ranges are necessary. While it is agreed that considerations for addressing significant deviations from acceptable process times should be developed (if these times are critical), the same should be done for all critical parameters. Thorough risk analysis and multivariate analysis should reveal critical parameters and their ranges. Process understanding results from a physical and physiochemical understanding of the dosage form and its components, analysis of critical parameters, and multivariate analysis. These should reveal which parameters and ranges are critical to product quality, and which may be controlled in-process for other reasons (cycle time, machine efficiency, etc.)	parameters, rather than between in-process controls and process end points. A distinction should not be made between critical parameters used for real-time release and those used only for in-process control.
Lines 457-466	Manufacturing Execution Systems (MES) provide procedural control at the manufacturing floor level, where personnel are not trained to evaluate statistical data. The Agency should be promoting the use of such systems to greatly enhance control at the manufacturing floor level. MESs can also collect real-time data that could be used for real-time release; however, the MES batch record is not the appropriate place to include charts depicting acceptance ranges, confidence intervals, and distribution plots. Instead, information technology systems should be in place that allows real-time access and statistical evaluation of critical data. This data, which could be in the form of acceptance ranges, confidence intervals, and distribution plots, could be linked to batch records as a means of making a quality decision for release. The IT systems should enable statistical evaluation of data for real-time release, and ensure that all data used for real-time release is evaluated against the existing body of data.	
Lines 445-	Certainly, consideration should be made for	The goal should be to provide a

455	differences in sample size for on-line testing compared to laboratory testing. However, caution should be exercised in defining acceptance criteria based on more rigorous statistical analysis that could lead to excessively stringent acceptance criteria. Conversely, on-line testing of an increased number of dosage units could also lead to detecting occasional individual results that would fail USP standards. This could lead to the unintended consequence of withholding release, consistent with the requirements of 21CFR 211.192, even though statistical analysis indicates that all critical parameters of components and process are within normal ranges. We recommend that the Agency address the decision to release/withhold a batch through evaluation by a statistical comparison of the batch in question to accumulated historical data that includes critical parameters of the components and the process, and the performance attributes of the finished dosage form.	greater degree of assurance that compendial standards, such as the USP, are met.