Johnson & Johnson
PHARMACEUTICAL RESEARCH
& DEVELOPMENT, L.L.C.

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
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1125 Trenton-Harbourton Road
P.O. Box 200, Titusville, NJ 08560

Attn: Dr. Rajendra Uppoor (CDER)/ Dr. Dennis Bensley (CVM)/ Dr. Robert Coleman (ORA)

Docket No: 2003D - 0380
Re: Draft Guidance for Industry: PAT - A Framework for Innovative Pharmaceutical Manufacturing and Quality Assurance

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Dear Drs. Uppoor, Bensley and Coleman:

The above referenced FDA draft guidance entitled PAT – A Framework for Innovative Pharmaceutical Manufacturing and Quality Assurance, issued August 2003 has been reviewed by scientists at Johnson & Johnson Pharmaceutical Research and Development, LLC and Johnson & Johnson affiliates. The following comments are provided for your consideration.

Provided in the General Discussion Section are the general impressions of our scientists including comments on issues of greatest concern to our business. Other comments (as well as those discussed in the General Discussion Section) are presented in the Comments Section by section, line and page number. To assist you during the review, the draft guidance text appears in italics.

General Discussion:

Our scientists appreciate and commend the collaborative effort between the scientists at CBER, CVM and ORA to create this draft guidance. The following comments are intended to promote further discussion and the ultimate creation of highly informative and practical final guidance for the pharmaceutical industry:

- Guidance vs. Policy Statement
  The first part of the guidance introduces the concept of the scientific risk-based framework of Process Analytical Technology (PAT) and emphasizes FDA's commitment to facilitate the implementation of PAT concepts within the FDA and industry. The second section is general and discusses the "Guidance Development and Scope" of the guidance, while the third section provides the "Background" of the PAT initiative. The final section introduces the "PAT Framework", discussing the philosophy of PAT, current industry principles and "PAT" principles and tools" that may be implemented by industry. Little specific guidance on implementation is actually provided. Our scientists felt that the draft guidance functions more similarly as a policy statement and could therefore be published via different means (Position Paper, Preamble etc.)

- Guidance Organization and Content

  As stated above, the draft guidance provides little specific guidance on how and under what circumstances industry should implement PAT concepts during drug development and post approval. Industry would be bettered served if specific guidance for drug development and post approval activities were broken out into separate documents. A guidance document, containing specific guidance for drug development issues under PAT could be developed. Likewise, a guidance document could be prepared for post approval drugs or specific guidance regarding PAT added to existing SUPAC guidances.

- Introduction of New Regulatory Policies

  There is general concern that additional FDA policies will be imposed without extensive and thorough discussion with industry. The establishment of a "New Regulatory Strategy" (page 20, line #713) describing the formation of a "PAT Team" to coordinate CMC review, compliance and inspection staff activities is an example of a major policy and procedure change that should be discussed with industry because of possible impacts with industry operations and approval times. Another concern is FDA's proposal that an inspection could be performed "*if necessary*" by a PAT Team or PAT certified investigation prior to implementation of a CBE, CBE-30 or PAS supplement (PAT Guidance, page 20, line #713). This new policy could delay the implementation of immediate changes under CBE supplements and rapid changes under CBE-30 supplements currently permitted if the FDA determines an inspection is necessary.

- Industry Adoption of PAT Concepts - Incentives

  Industry's incentive to adopt PAT concepts could be enhanced if FDA provides specific guidance on such issues as CBE and CBE-30 supplements (coordination of FDA inspection teams, PAIs and FDA Reviewers) in order to assure that approval times are not negatively impacted. Industry incentives might also include increased opportunities for rolling submissions, binding FDA/Industry agreements made early on and/or the sunset of regulatory methods with replacement of PAT methods.

Other Comments (by Section):

All Sections

General Comments:

Throughout the guidance and particularly in sections IV and V, specific examples would be extremely useful to illustrate how PAT processes and principles might be applied to actual manufacturing and quality assurance situations.

Section II

General Comments:

Please include in Section II the definition of *analytical* as provided in Section IV., lines 161-163 of the draft guidance *"It is important to note that the term analytical in PAT is viewed broadly to include chemical, physical, microbiological, mathematical, and risk analysis conducted in an integrated manner".*

Section III

Line 87-90, page 6:

In order to be consistent with lines 162 and 163 that include "microbiological" as part of the term *analytical* in PAT, please insert "and microbiological" between the words "*chemistry*" and "*tools*". The sentence should be revised to read "*However, today, significant opportunities exist for improving the efficiency of pharmaceutical manufacturing and quality assurance through the innovative application of novel product and process development, process controls and modern process analytical chemistry and ***microbiological*** tools".**

Line 96 – 97, page 6

This sentence should be deleted from the guidance because it implies traditional manufacturing approaches may have produced inferior (less than high-quality) products to the public.

Section IV

Line 203 – 206, page 8

Please provide additional clarification/information regarding how *"small-scale equipment ...and dedicated manufacturing facilities"* and *Improving energy and materials use and increasing capacity."* **(examples given on lines 204-206 of the draft guidance) relate to the main bullet for facilitating continuous processing.**

Line 242 – 244, page 9

The inclusion of additional guidance and examples supporting the statement *"Several new technologies are available that can acquire information on multiple attributes with minimal or no sample preparation."* **would be extremely useful.**

Line 559 – 591, pages 16-17

Please comment on the following questions related to the information provided in subsection 5, Real Time Release:

1. If real time release data is shown to be equivalent or better than established regulatory quality attributes, will real time release data eventually replace traditional quality tests?

2. Would sampling or testing frequency be expected to increase when using real time data?

3. How do you develop pass/fail acceptance criteria? Do you reject for one failing test result?

4. Under PAT, the risk of product failure would appear to be more formula dependant. Doesn't this represent a greater burden and a disincentive for companies developing and marketing highly innovative, complex formulations?

We greatly appreciate the opportunity to comment on this draft guidance and look forward to working closely with the FDA on future documents. If you have questions or need assistance, please contact me directly at 609/730-3425.

Sincerely,

Sue Halley
Manager
Global Chem-Pharm Regulatory Sciences
Johnson & Johnson Pharmaceutical Research and Development, LLC.