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Food and Drug Administration  
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Boehringer Ingelheim  
Pharmaceuticals Inc.

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**Docket No. 00D-0186, International Conference on Harmonisation; Draft  
Guideline M4 Common Technical Document**

**Comments submitted electronically via e-mail 10/4/00, to  
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Dear Sir or Madam:

Boehringer Ingelheim Pharmaceuticals, Inc. wishes to provide the following general and specific comments on the subject draft ICH Guideline M4 Common Technical Document. Please note that these comments only address Module III, Quality, and focus on New Chemical Entities (NCEs).

We apologize that these comments are being submitted after the formal closing date for comments to the Docket; however, we hope they may still be taken into consideration

**General Comments**

1. We understand that the intent of the ICH M4 Guideline on the CTD-Quality is, at this stage, to provide a harmonized **format** for submission of information on the drug substance and drug product, in a registration application in the ICH regions. Therefore we believe that the section titles in the Table of Contents for the "common" part of Module III, Quality (sections "S" and "P") should reflect the topics which are required to be submitted in **all** of the three regions.  
We also agree that topics which are region-specific should be placed in section "**R Regional Information**".

In our specific comments below, we have identified a concern that the “Process Validation and/or Evaluation” topic is not common to all three ICH regions; and therefore, we question whether it should be listed in the section titles of the Table of Contents of the common portion of Module III.

2. We further appreciate that for certain topics, even though the **topic** of information is common to all three regions, the specific **content** of information submitted on the topic, may be different. An example of this is the Container/Closure System for the drug product, for which the submission requirements in Europe are quite different from those in the United States. We do agree that the Table of Contents of the common portion of Module III should provide for this common topic; however, we understand that the actual data that are submitted in the EU and in the U.S. under the section title will not necessarily be the same.
3. It has been publicly stated that the ICH M4 Guideline for a common format for a registration dossier is co-evolving with the ICH M2 Guideline for electronic submissions. Certain of our comments below reflect our company’s practice in document generation, and reflect the fact that electronic publishing of documents affords less flexibility than the creation and manipulation of paper documents.
4. As a final general comment, we wish to encourage ICH to continue to devote resources to the harmonization of submission requirements for Quality topics which are not currently covered by ICH Quality Guidelines. These topics include the description of the drug substance synthesis, drug product method of manufacture, container/closure for drug substance and drug product. The true benefit of a harmonized format for a marketing authorisation application will not be realized until full harmonization has been reached on the content of the application.

### **Specific Comments**

Our comments are placed under the section titles of the draft M4Q Guideline.

#### **S 1.3 General Properties**

The explanatory text suggests that this section contains a simple “*list of physicochemical and other relevant properties of the drug substance*” (italics added for emphasis). We do agree that a concise list of properties is helpful for the regulatory reviewer. However, it has been our company’s practice to submit additional information, in the form of technical report(s), on the studies performed to elucidate the physicochemical properties of the drug substance. These report(s) would describe, for example, how the  $pK_a$  was determined, how the solubility measurements were performed, the experimental design and results of the polymorph screening studies<sup>1</sup>, etc.

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<sup>1</sup>ICH Q6A Guideline, *Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*, Decision Tree #4: Investigating the Need to Set Acceptance Criteria for Polymorphism in Drug Substances and Drug Products

We believe that section **S 3.1** is the logical placement for the supportive information on the elucidation of physicochemical properties. Just as the structure presented in **S 1.2 Structure** is supported by the elucidation of structure studies placed in **S 3.1**, we believe that a brief list of physicochemical properties in **S 1.3 General Properties** should be supported by the reports of the elucidation of these properties placed in **S 3.1**.

This could easily be accomplished by striking “or Biological” from the section title of **S 3.1** so that it reads “**S 3.1 Elucidation of Structure and Characterisation**”.

As a second (less preferred) alternative, the text under section **S 1.3 General Properties** should be revised to allow the possibility that more detailed information than a simple “list” may be submitted.

## **S 2.2 Description of Manufacturing Process and Process Controls**

We presume that the text under **Filling, storage and transportation (shipping)** applies only to Biotech. We do not understand why “Storage and shipping conditions for the drug substance.” is placed in this section for biotech, whereas the recommended storage conditions for an NCE drug substance is placed in **S 7.1 Stability Summary and Conclusions**. We believe that the recommended storage conditions for both NCE and Biotech are appropriately located in **S 7.1 Stability Summary and Conclusions**.

## **S 2.4 Controls of Critical Steps and Intermediates**

The explanatory text for **S 2.4** does not make clear what information is to be placed in this section concerning the “controls of critical steps” versus that already placed in section **S 2.2**. The description of the process provided under **S 2.2** already “identifies critical steps” and “includes process controls”. In providing the description of the manufacturing process and process controls, to be placed under **S 2.2**, it is our company’s usual practice to identify the critical process controls in each step of the manufacturing process (as applicable), by listing the name of the test and the acceptance criteria.

Therefore it appears redundant to list the process controls (tests and acceptance criteria) for the critical steps in **S 2.2** and again in **S 2.4**. In principle, we object to redundancy in the submission, since it leads to the possibility of inconsistencies between what is provided in one section versus the same information provided in another location. If it is intended that the analytical procedures associated with the process controls are to be placed in **S 2.4**, then please so clarify in the text of the guideline.

Secondly, we do not agree with the text that states this section should contain “justification, including experimental data, performed at critical steps of the manufacturing process to assure that

the process is controlled.” Please delete this text from this section. This type of information is widely understood to be “Process Evaluation” data, and our comments on this concept are provided below under S 2.5.

## **S 2.5 Process Validation and/or Evaluation**

We consider this section (and the companion section P 3.5 for drug product) to be controversial.

### ➤ Process Validation

The term “process validation” lacks a harmonized definition, and is applied indiscriminately in U.S. and European guidelines to different concepts. Furthermore the term “process validation” may have different meanings in existing regulatory guidance for NCE and Biotech drug substances.

For purposes of our comments, we define “Process Validation” for an NCE to mean studies conducted under a formal validation protocol which involve the manufacture of full-scale production batches (typically three) according to defined target operating parameters and process controls. The results of the process validation studies demonstrate that the process, when operating under the defined target conditions and controls, can consistently deliver the product with the desired quality attributes.

In keeping with our general comment above, the section titles in the common part of the CTD-Q should represent topics for which **all** regions require submission of **some** information (although not necessarily the **same** information). Process validation data (as defined above) are not a submission requirement for drug substances in the EU or in the U.S., and therefore we question if this is an appropriate section title for the common part of the CTD-Q. In the absence of a harmonized definition, we would prefer the M4Q Guideline to avoid using the term “Process Validation” in any section title.

### ➤ Process Evaluation

With respect to the concept of “Process Evaluation”, this is also a term that deserves a harmonized definition. “Process Evaluation” data are typically considered to include those data mentioned above in the text of S 2.4, *i.e.*, “justification, including experimental data, performed at critical steps of the manufacturing process to assure that the process is controlled”.

Our company believes that “Process Evaluation” studies are those which define the critical steps of the process, identify the ranges which the process can “tolerate” and still produce acceptable product, and which justify the selection of the process controls at the critical steps. These data may be derived from laboratory-scale batches, pilot-scale batches, and even “failed” batches of product.

We appreciate that FDA's current 1987 Guideline requires submission of such "Process Evaluation" data<sup>2</sup>. However, these data are not a usual submission requirement in the EU, where such data are considered an aspect of cGMPs, and are available for inspection. Furthermore, we are concerned that the presence of a section titled "Process Evaluation" will result in an escalation of regulatory submission requirements in the EU, where typically no data are submitted on this topic. The presence of a section title may cause a regulatory reviewer to insist upon submission of information for that topic, even where there is no regional requirement to do so.

Therefore, like "Process Validation", the submission of "Process Evaluation" data is not a common topic for submission requirements in the ICH regions. In keeping with our general comment above, we do not believe that the common part of the CTD-Q should include a section title for a topic which is not "common" across the ICH regions.

We propose that section **S 2.5 Process Validation and/or Evaluation** be deleted from the Table of Contents of the CTD-Q, and that the concepts of "Process Validation" and "Process Evaluation" data be incorporated into the section **S 2.6 Manufacturing Process Development**.

The notion of "Process Development" logically encompasses those activities which are considered to be an "evaluation of the process" and, depending on the harmonized definition, could also encompass the concepts of "process validation", including "sterile process validation".

By relocating these concepts into section **S 2.6 Manufacturing Process Development**, it allows each region to submit the information that is consistent with the requirements of the region, but avoids giving an impression (to industry and regulators alike) that some kind of information on process validation/evaluation must be supplied in every country.

## **S 2.6 Manufacturing Process Development**

Consistent with our comments above under **S 2.5**, we propose that the text concerning NCEs in this section be modified to incorporate the concepts of process evaluation/validation, and to read as follows:

*NCE: A description and discussion should be provided of the significant changes made to the manufacturing process or manufacturing site of the drug substance used in producing nonclinical, clinical, scale-up, pilot, and if available, production scale batches.*

*For those drug substances which are manufactured to be sterile, data should be provided (if consistent with the requirements of the region) to demonstrate that the sterilizing process is capable of reproducibly producing a sterile drug substance.*

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<sup>2</sup>FDA CDER Guideline for Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances, Section E 1, "The basis for selecting control points and intermediates should be explained, and the adequacy of the specifications and tests to control the synthetic process demonstrated."

*For both sterile and non-sterile drug substances, experimental data should be provided (if consistent with the requirements of the region) to demonstrate that the critical steps in the manufacturing process have been appropriately identified and that the process controls adequately control the critical steps.*

### **S 3.1 Elucidation of Structure and/or Biological Characterisation**

Consistent with our comments under **S 1.3 General Properties**, we would like to see this section title modified to read **S 3.1 Elucidation of Structure and Characterisation**.

Also, we propose that the text of this section be changed to provide for placement in this section of studies which elucidate the physicochemical properties, as well as the elucidation of structure, of the drug substance. We propose the following change in the text:

*NCE: Confirmation of structure based on e.g., synthetic route and spectral analyses should be provided. Information on the potential for isomerism and the identification of stereochemistry should also be included.*

*The studies which elucidated the physicochemical properties of the drug substance (as listed under S 1.3) should be also be included in this section, as appropriate.*

### **S 6 Container Closure System**

We do not agree to place information on the suitability of the container closure system for packaging the drug substance, in section **P 2**. Suitability information on the container closure system used with the drug substance might include items such as 1) DMF Letters of Reference (U.S. only), 2) moisture permeation data, 3) data on extractables from the packaging components. This information should be located here in the drug substance section of the dossier. Please modify the text to delete “in **P 2**”, so that it reads “...additional information demonstrating suitability should be provided and placed in this section.”

### **P Drug Product**

#### **P 1 Description and Composition of the Drug Product**

Please delete from this section the “Type of container and closure used”. Our objection to placing this information in section **P 1** is related to electronic publishing and our company’s usual practice of document generation. It is our intention to create a single document that will be electronically published in this section of the dossier. Since the specific container/closure system proposed for marketing may be country-specific, multiple versions of this document will be required if the composition statement and the container/closure system are “linked” in a single document.

Alternative options for document generation would require the generation of separate small documents, with the individual “pieces” of the composition statement, and container/closure statement, which is unattractive from a document management perspective.

The text for “Type of container/closure used” appears to be a direct “carry-over” from the current Part IIA:2 format requirements, per the EU Notice to Applicants. We appreciate the desire in the EU to obtain an “at a glance” view of the drug product (description, composition, container/closure); however, the EU Application Form does provide for the “Container, closure and administration devices” to be listed (current Part 1A: Administrative Data). Therefore, we request that the listing of container/closure be removed from this section.

## **P 2 Pharmaceutical Development**

The explanatory text in this section is written as if a single report is placed in this section. However, it is our company’s practice to produce one or more technical reports to be placed under the topical heading “Pharmaceutical Development”. Depending on the specific dosage form being discussed, there may be several technical reports. Therefore, please delete from the text of this section any reference to a single report.

Please do not further subdivide this section into second level section titles, e.g., **P 2.1 Components of the Drug Product**. We are concerned that these secondary headings will become mandatory as part of the electronic CTD (ICH M2 Guideline), and they are not consistent with the manner in which our company produces the documentation which is placed in this section. We would like to reiterate that it is our practice to produce a number of reports, which taken together, will address all of the topics listed in the text under “Pharmaceutical Development”

The current text in this section appears to reflect a misunderstanding over the structure of a Pharmaceutical Development Report (which would be located in **P 2** along with other reports) versus the content of section **P 2** itself.

The subheadings under **P 2** must not be rigidly defined, so that companies have sufficient flexibility to adapt the secondary format of this section as needed for different dosage forms. Please appreciate that there are additional topics, not currently listed in the text, which would need to be addressed for certain dosage forms, e.g., metered dose inhalers.

Therefore please revise the text under section **P 2 Pharmaceutical Development** to eliminate the use of secondary section titles, by using bullet points or other listing designation.

## **P 3.4 Controls of Critical Steps and Intermediates**

We do not agree that this section should contain “justification including experimental data, performed at critical steps of the manufacturing process”. Please delete this text from this section.

This type of information is widely understood to be “Process Evaluation” data, and our comments on this concept are provided below under **P 3.5**.

### **P 3.5 Process Validation and/or Evaluation**

Our comments on this section are similar to those provided above under **S 2.5**, and for brevity we reference the above comments.

#### ➤ Process Validation

We refer to the definition of “Process Validation” above under **S 2.5**, for purposes of our comments here. As defined above, “Process Validation” data are not a submission requirement in the U.S. Furthermore, we question whether or not “Process Validation” data are a submission requirement in Europe. The recent draft European guideline<sup>3</sup> on this subject has been extensively criticized by EFPIA and other industry groups, who have argued that “Process Validation” data are a cGMP issue, and should not be a submission requirement for a marketing authorisation application in Europe.

In keeping with our general comment above, only those topics which are common to all three ICH regions should be listed as section titles in the common part of Module III. Since “Process Validation” (as defined) is not a common topic for submission in the U.S. and EU, we do not believe that the common part of the CTD-Q should include a section title for a topic that is not “common” across the ICH regions.

Upon finalization of the draft European guideline, the submission of “Process Validation” data (if in fact it is ultimately determined to be a submission requirement in the EU), may be accommodated in section **R Regional Information**.

#### ➤ Process Evaluation

“Process Evaluation” data are typically understood to include the data mentioned above in the text of **P 3.4**, *i.e.*, justification including experimental data, performed at critical steps of the manufacturing process”.

Unlike the situation for drug substance (per our comments above under **S 2.5**) we agree that “Process Evaluation” information is a common submission requirement in both the U.S. and Europe. However, we suggest that the concept of “Process Evaluation” is encompassed by the concept of “Pharmaceutical Development”, and such “Process Evaluation” data are logically placed in **P 2 Pharmaceutical Development**. The notion of pharmaceutical development studies includes the development and evaluation of the manufacturing process – for certain dosage forms, the two

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<sup>3</sup> Note for Guidance on Process Validation CPMP/QWP/848/96 *draft*

concepts are so inter-related that it would be impossible to “tease apart” the formulation development from the process development.

Therefore, we propose that section **P 3.5 Process Validation and/or Evaluation** be deleted from the Table of Contents of the CTD-Q, and that the concepts of “Process Evaluation” information be incorporated into the section **P 2 Pharmaceutical Development**. Note that the text in **P 2** already includes the topic “Manufacturing Process Development”.

### **P 3.6 Container Closure System**

We agree that section **P 2 Pharmaceutical Development** should discuss the suitability of the container closure system for packaging the drug product (in the context of the development of the packaging system). However, we do not agree to place in **P 2** the primary technical information on the suitability of the container closure system. Suitability information on the container closure system used with the drug product might include items such as 1) DMF Letters of Reference (U.S. only), 2) moisture permeation data, 3) data on extractables from the packaging components. This information should be located here in **P 3.6** with the other primary technical information on the container/closure system.

Please modify the text to delete “in **P 2**”, so that it reads “...additional information demonstrating suitability should be provided in this section.”

### **R 4 Process Validation Protocol of the Drug Product (EU)**

Consistent with our comments above under **P 3.5**, we suggest that this section be re-titled “**Process Validation of the Drug Product**”. With this change, the **R 4** section should provide a location for the EU regional specific submission of process validation data or the validation protocol, as appropriate.

### **Environmental Assessment**

It is not clear where the Environmental Assessment (EA) is to be placed. The EA is required for submission in both the EU and U.S., although we have no information on whether or not it is required in Japan. In the current EU MAA format the Environmental Assessment is placed in the Toxicology section, whereas in the current U.S. NDA format the EA is placed in the Chemistry Section. The ICH M4 guideline should recommend a location for placement of the Environmental Assessment.



In closing, we wish to thank FDA for the opportunity to comment on this important Step 2 ICH Guideline. Please contact the undersigned with any questions or comments on this correspondence.

Sincerely,

A handwritten signature in cursive script that reads "Patricia Watson".

Patricia Watson  
DRA Technical Director  
Drug Regulatory Affairs