

PDA Commentary on:

Current Good Manufacturing Practice: Amendment of Certain Requirements for Finished Pharmaceuticals; Proposed Rule, May 3, 1996 (61 FR 20103), [Docket No. 95N-0362]

Explanatory Note:

On May 3, 1996 FDA published proposed revisions to the GMP regulations, 21 CFR 210 and 211. A PDA working group drawn from across the membership spectrum convened in early June to draft comments. The comments were submitted to FDA on July 31, 1996, even though the comment period was extended until September 30.

PDA Staff Contact: James C. Lyda, x121
July 1996

July 31, 1996

Dockets Management Branch (HFA-305)
Food and Drug Administration
12420 Parklawn Drive, Room 123
Rockville, MD 20857

Re: Docket No. 95N-0362

Dear Sir/Madam:

On behalf of the Board of Directors and membership of PDA, I am pleased to submit comments regarding FDA's proposed rule, "Current Good Manufacturing Practice; Proposed Amendment of Certain Requirements for Finished Pharmaceuticals", 61 FR 20103, May 3, 1996.

PDA is an international non-profit association with a worldwide membership of over 7,500 scientists. PDA members are involved in pharmaceutical development, manufacturing, quality control and regulatory affairs, and will be affected by any change that occurs in CGMP regulations. These comments represent the consensus views of PDA volunteer members representing diverse sectors of our membership. Our Japan and European chapters have also reviewed the proposed changes, providing recommendations consistent with our U.S.A. based working group. All PDA's comments have been consolidated into this letter.

PDA understands it is the intent of FDA to clarify requirements in certain GMP areas that have been the subject of recent enforcement actions. However, in at least three major areas -- process validation, blend uniformity testing and contamination control -- the proposed regulations impose substantial new requirements that do not contribute to the quality or safety of drug products. We urge FDA to limit additional CGMP requirements to those that are "both feasible and

valuable in assuring drug quality", which was the standard used in promulgating the existing CGMP regulations (43 FR 45018, 1978).

FDA's estimate of \$60 to \$600 per establishment, per year to implement the additional process validation, blend uniformity testing, contamination control and other requirements in these proposed rules is grossly low (Preamble, VII. Analysis of Impacts, p. 20112). This view surfaced repeatedly and emphatically as our members prepared these comments. We strongly urge FDA not to impose, or informally enforce through inspections, practices that are not valuable toward assuring drug quality.

The proposed provisions, particularly those regarding process validation, in-process testing and investigation of discrepancies cannot be applied literally to investigational new drugs (clinical supplies) as they would be to commercial batches. Clinical supplies may consist of a single batch, where data is insufficient to establish pre-determined specifications, and where process validation cannot be conducted in accordance with the proposed provisions. We recommend that the preamble to any Final Order make it clear that for investigational new drugs, manufacturers may use flexibility and alternative approaches to validation and in-process testing in order to achieve the intended purpose.

We request the opportunity to arrange a public meeting for our members and other scientists to speak with FDA officials regarding these comments. Because the May 3 announcement was the first notice to industry of the specific proposals, the notice-and-comment process is not adequate for industry experts to communicate concerns to FDA.

Our specific technical comments follow. The first four areas, process validation, blend uniformity testing, control of contaminants and definitions, are particularly critical to industry scientists and are identified in Section A, below. Other comments are in Section B.

A. Major Technical Issues and Proposed Changes

211.220 Process validation

Discussion : Process validation has emerged over the past two decades as a valuable, but resource-intensive activity. The pharmaceutical industry has invested enormous resources in implementing process validation, guided by FDA's "Guideline on General Principles of Process Validation" (May 1987), and a wealth of published scientific literature by industry and FDA

experts. Proposed Subpart L and the associated proposed terms introduce definitions that are similar to those used in the FDA guideline and in the industry, but which differ in significant respects. FDA must realize the significant impact on company operations of revising definitions in such an important area, and the confusion that can be caused when definitions are changed. We urge FDA to consult carefully with industry working groups on any new guidance regarding process validation, before changes are implemented.

Proposed change : In paragraph 211.220(a), the first sentence should be changed to eliminate the requirement that *all* manufacturing processes must be validated, regardless of relationship to product quality. We suggest the following wording for 211.220(a):

"The manufacturer shall validate all drug product manufacturing and control processes which determine whether a product will consistently meet its predetermined specifications."

We propose deletion of the second sentence which lists processes to be validated.

Rationale : As written, the proposed rule would require unnecessary validation of *all* drug product manufacturing processes, regardless of the impact on product quality. In addition, it would require validation of procedures or steps which do not lend themselves to validation, and which are already double checked, monitored and controlled per CGMP requirements; e.g. manual weighing and labeling operations.

Incorporating a list of processes to be validated is not necessary and will be misleading, as evidenced by the inconsistencies between the lists in the proposed definition of "manufacturing process" in 210.3(b)(30) and the proposed list of manufacturing processes to be validated in 211.220(a).

Validation of *all* manufacturing processes goes far beyond current industry practice, will introduce costly new requirements with no corresponding increase in the quality of the product, and will be of little value to the patient. It has been and should remain the responsibility of the manufacturer, who best understands the process, to determine the critical steps which require validation.

We estimate that requiring *all* processes to be validated, regardless of benefit to product quality, could increase validation costs by 20% to 50%. Reliable figures on the cost of validation are not available, but are substantial. One expert

estimated that validation constitutes about 20% of the current cost of producing pharmaceuticals, or as much as \$1 billion per year. A 20% increase in validation requirements will substantially exceed the estimates cited in Section VII. Analysis of Impacts. (Anisfeld, M. H. "Validation - How Much Can the World Afford? Are We Getting Value for Money?", J. Pharm. Science and Technology, Vol. 48, No. 1, 1994)

Proposed change : Paragraph (b) should be changed to read,

"Validation protocols shall be developed and approved. The protocol shall specify a sufficient number of replicate process runs to demonstrate reproducibility of the process. The manufacturer shall document execution of the protocol and test results obtained."

Rationale : Validation protocols are defined in 210.3 and the details need not be repeated here. It is not industry practice to include variability assessment as part of process validation, nor is it described in FDA's own definitions ("Guideline on General Principles of Process Validation", May 1987). Variability assessment is inappropriate within the limits of a validation program; rather, it is the subject of ongoing post-validation reviews, e.g. annual product reviews.

Proposed change : Reword paragraph (c) to read,

"The manufacturer shall design or select equipment and processes that are capable of producing product that meets predetermined specifications. The manufacturer's determination of equipment qualification shall include testing to verify that the equipment is capable of performing satisfactorily within the operating limits as required by the process. Parts of the process which may affect the ability of the product to meet specifications shall be tested."

Rationale : The terms process suitability and equipment suitability have been removed (see proposed changes under 210.3(b)). In place we suggest the term qualification which is widely used and understood validation terminology. As rewritten, this section is now consistent with current industry practice and FDA guidance.

Proposed change : Reword paragraph (d) to read,

"There shall be a system through which changes, deviations and reprocessing are assessed for their impact on product quality and a course of action determined. This may include revalidation, but does not require it in all situations."

Rationale: Not all changes, deviations or reprocessing require revalidation. Product effectiveness is inappropriate for inclusion in this section as CGMPs address safety, identity, strength, purity and quality.

211.110 Sampling and testing of in-process materials and drug products

Proposed change: Paragraph (d) should be deleted.

Rationale: Recent literature indicates that small samples are not true indicators of homogeneity or lack thereof, but add significant bias to the results (refer to the enclosed bibliography). Sample size should not be specified in the GMP regulations, but should be determined and justified by scientific principles. PDA held a special scientific forum in January 1996, with FDA participation, at which no scientific support for small samples emerged. We suggest FDA set forth its scientific information justifying the necessity of small samples.

Imposition of this requirement will require pharmaceutical manufacturers to divert significant resources to the study of sampling techniques. Costs per establishment to develop these techniques will significantly exceed FDA's estimates.

Paragraph (d), when read together with the preamble statements (p. 20109) imply that blend uniformity testing is considered to be a requirement for most, if not all routine production batches. However, blend uniformity testing is not current practice for routine production batches. Process validation means establishing "...a high degree of assurance that a specific process will consistently produce a product that meets its predetermined specifications and quality characteristics." Once a validated state has been established, determination of appropriate in-process testing should be the responsibility of each drug product manufacturer.

One of FDA's expert consultants, Robert Gerraughty, Ph.D. is among the many experts who have advised PDA that blend uniformity testing for routine production batches is unnecessary and wasteful.

Since routine in-process blend homogeneity testing is not current practice in the industry, imposition of this requirement for ordinary production batches would significantly increase costs over FDA's estimate of \$60 to \$600 per establishment.

In addition, the requirement for blend testing for validation batches is already addressed in proposed 211.220(a). Accordingly,

this section of proposed 211.110(d) is redundant.

211.240 Control of chemical and physical contaminants

Proposed change : In (b), change "or" to "and," delete the phrase "such as penicillin," and insert the phrase "to appropriate levels" to read,

"(b) Dedicated production, which.....where contaminants pose a special danger to either human or animal health and if there are no reasonable methods for the cleaning and removal to appropriate levels of drug substances and/or...."

Rationale : Dedicated production should be employed only when there is a combination of "special danger" and lack of effective cleaning methods. A dedicated production facility is not required when an "appropriate level" of contaminant can be determined and cleaning to below that level can be achieved.

The preamble implies that all drugs in the categories of penicillin, cephalosporins, cytotoxic anti-cancer drugs, and infectious agents require dedicated facilities. In fact, this is not current industry practice. There are facilities currently safely manufacturing drugs in some of these categories (cytotoxics) in multiproduct facilities. If the current wording in the preamble and this section remain unchanged FDA's cost estimates (\$60 - 600 per facility) for implementing these revisions have been grossly understated.

Production of non-penicillin *animal drugs* in the same facility as penicillin poses no special danger to animal health, thus the recommended deletion of the reference to penicillin. Such production is currently accepted practice and should remain so. As stated above, if such change is actually required, the costs of implementing these revisions have been considerably understated.

Proposed change : Reword (c) to read,

"(c) If a reasonable possibility exists that a drug has been exposed to *objectionable* cross-contamination, the manufacturer..."

Rationale : Consistency with wording in 211.240(a).

210.3(b) Definitions

(25) Methods validation

Proposed change : The definition should be changed to be harmonize

with wording in USP 23, <1225> *Validation of Compendial Methods*; or, the final ICH harmonized guideline "Validation of Analytical Procedures: Definitions and Terminology" (Q2A):

USP 23, <1225> p.1982 (excerpt)

"Methods validation means the process by which it is established, by laboratory studies, that the performance characteristics of the method meet the requirements for the intended analytical applications."

- or -

ICH (Q2A), 60 FR 11260, March 1, 1995 (excerpt)

"The objective of validation of an analytical procedure is to demonstrate that it is suitable for its intended purpose."

Rationale: Harmonization with a currently accepted and equivalent definition is preferable to creation of a new definition specific to the CGMPs. Considerable confusion can be created when important definitions in widespread use are changed.

(26) Equipment suitability

(27) Process suitability

Proposed change: Delete both of these definitions.

Rationale: As stated above, there is potential for a high degree of confusion resulting from the adoption of new terms that are defined differently than the widely accepted and similar terms "performance qualification" and "installation qualification" defined in FDA's "Guideline on General Principles of Process Validation" (May 1987). There is no explanation in the preamble of why new definitions are needed, or how they relate to the more commonly recognized validation terms. Further, the terms are only used in new Subpart L, *Validation*, and we do not believe they need further definition.

(28) Out-of-specification

Proposed change: Change this term to *Out-of-specification result*, and reword the definition by replacing "preestablished criteria" with "regulatory specification", and including the following statement in the preamble discussion for this section

"Regulatory specifications in the context of this definition include compendial requirements, specifications in applications (NDAs, ANDAs, etc.), OTC monographs, CFR, etc. They do not include internal control limits such as alert limits, machine adjustment limits, etc."

Rationale: The term *specifications* is used widely in the industry to describe a variety of limits, results and outcomes of testing and measuring activities in the industrial environment. PDA agrees with FDA, as suggested in this definition, that specifications be related directly to the attributes of "identity, strength, purity and quality" as described in 211.160(b). As such, results related to in-process limits, for example, are not truly related to specifications, regardless of the terminology used by the manufacturer, and thus cannot be subject to the definition of *out-of-specification result*.

The proposed change is consistent with the preamble statements, "The agency also recognizes that the industry may impose additional criteria beyond those required to ensure identity, strength, quality, and purityThe agency encourages such internal controls. Under such circumstances, a manufacturer could have test results that violate internal standards although they would not be out-of-specification, as defined in these regulations." (See O. Section 211.192, p.20110)

(29) Reprocessing

Proposed change: Add the following sentence to the end of the definition:

"The normal repetition of one step (e.g., refiltering a liquid or reblending a granulation) once, in the sequence of processing, without changes in the composition range is not considered to be reprocessing."

Rationale: The above wording reflects current industry practice, and is consistent with the draft FDA guidance document, *Guidance for Industry: Content and Format for Submission of Drug Products for Investigational New Drug Applications (INDs), New Drug Applications (NDAs), Abbreviated New Drug Applications (ANDAs), and Abbreviated Antibiotic New Drug Applications (AANDAs)*, February, 1996; p.14.

(30) Manufacturing process

Proposed change: Change the phrase "finished product" to "drug product" both places that it appears in this definition, and make the listing of manufacturing and storage steps at the end of this definition consistent with the steps listed in the preamble, IV. Description of the Proposed Rule (p.20107).

Rationale: Consistency. "Drug product" is already defined in 210, and is consistent with the intent of this definition.

B. Additional Technical Issues and Proposed Changes

211.22 Responsibilities of the Quality Control Unit

Proposed change : The preamble discussion of the proposed change to 211.22(a) should clarify that, as stated in the preamble to the existing CGMP regulations (43 FR 45033, 1978), it is intended that the quality control unit should be responsible for ensuring that controls are implemented that assure drug product quality, not that the quality control unit perform each one of the duties.

211.46(d) Ventilation, air filtration, air heating and cooling

Proposed change : Delete this section

Rationale : While this section was not proposed for revision by FDA, it is specific to penicillin and deletion is consistent with FDA's proposal to delete 211.42(d)

211.84 Testing and approval or rejection of components, drug product containers and closures

Proposed change : In proposed (c)(1), restore words "where necessary" after the word cleaning, and replace "raw material" with "components." The revised section will read,

"The containers of components selected shall be cleaned, where necessary, in a manner to prevent introduction of contaminants into the component."

Rationale : The purpose of this section is to protect the components from which the sample is drawn. The existing regulation provides for exceptions in cases where cleaning of the component container is not necessary, e.g., intermediate wrapping or packaging. This exception should be preserved for situations where cleaning of the container is not necessary. The term "raw material" is not defined while "components" is. This change will make the regulation internally consistent.

211.101 Charge-in of components

Proposed change : Reword proposed (c)(4) to read,

"The components are those specified in the batch record for the intended drug product."

Rationale : Determining conformity to quality specifications is a responsibility of Quality Control [see 211.160(b)(1) and

211.165(a)]. As proposed, the statement implies that, additionally, the personnel responsible for charge in of components must examine the product test specification and laboratory records prior to using a component. This is not current industry practice and is unnecessarily redundant.

211.103 Calculation of yield

Proposed change : Delete the proposed added sentence.

Rationale : The addition of this sentence is redundant with the requirement in proposed 211.192, which requires a written procedure for investigating discrepancies (including a percentage of theoretical yield exceeding the maximum or minimum percentages established in master production and control records).

211.111 Time limitations on production

Proposed change : Reword this section to delete the word "maximum" and replace words "each phase" with "affected phases."

Rationale : While we agree with the intent of this section, not every drug manufacturing process or processing phase is time sensitive. The revised wording recognizes only affected phases require time limits and not all time limits are maximums.]

211.166 Stability testing

Proposed change : In the first sentence of (c), change "ensure" to "confirm", and delete the second sentence.

Rationale :

- The testing program does not ensure stability, it confirms it.
- Some products are not manufactured each year.
- There are other applicable documents, such as the ICH Guideline entitled "Stability Testing of New Drug Substances and Products" (Q1A), published in the FR September 22, 1994. This guideline more comprehensively addresses the specific requirements of a stability testing program, including selection of representative batches for ongoing stability testing. Although the ICH Guideline was written for a different purpose, it represents consensus on stability issues among worldwide industry and regulatory scientists. The CGMP regulations should not establish different requirements where there is no scientific justification.

211.180 General requirements

Proposed change : Reword (a) to read,

"Any production, control or distribution record that is required to be maintained in compliance with this part and is specifically associated with a batch of a drug product shall be retained for at least one year after the expiration date of the batch, or in the case of certain OTC drug products lacking an expiration date because they meet the criteria for exemption under 211.137, three years after distribution of the batch. Validation records, including the validation protocol, production and control records for validation batches, data and the study report, shall be retained for at least one year after the expiration date of all batches associated with that validated process."

Rationale : As proposed this section would require retention of all batch records, including production, control and distribution records, until one year after the expiration date of the last batch *made with that validated process*. According to the preamble (p. 20114) it is intended only that validation records be retained for such a long period. PDA's proposed change separates validation records from other records and brings the requirements of the regulation into agreement with the intent as stated in the preamble.

211.192 Production, control and laboratory record review and investigation of discrepancies

Proposed change : In (b), Delete the phrase "Such procedures shall include" and delete the following items (1) through (7).

Rationale : This level of detail is not appropriate for a regulation and is overly restrictive. The requirements for an investigation into an out-of-specification result are addressed in section (c). Procedures and criteria must be specific for the type of test and cannot be adequately addressed in this general fashion.

Proposed change : Add to (c)(4) the following phrase,

"Such justification may include the use of statistically appropriate outlier tests in the analysis of microbiological and chemical test results."

Rationale : It is recognized by experts that there are circumstances where it is appropriate to apply statistically sound tests to identify outliers. Relevant information appears,

for example, in USP/NF 23, General Information, p.9, *Tests Results, Statistics, and Standards*, which references AOAC guidelines for data handling. It is not possible in this brief comment period to develop more specific proposals. Recent experience with FDA's enforcement actions, however, indicates that unless FDA recognizes the validity of sound outlier tests, there will be unnecessary investigations and even unnecessary rejection of good batches.

Proposed change : Delete item (c)(8).

Rationale : The inclusion of a requirement for signatures in this list would result in unnecessary creation of an additional record. Section 211.192(a) already requires review and approval of all batch records by the quality control unit, and existing 211.188 requires inclusion of investigation reports in the batch records.

211.222 Methods Validation

Proposed change : Change "test methods" to "analytical methods" and revise wording (e.g. reproducibility) in harmony with the ICH harmonized guideline "Validation of Analytical Procedures: Definitions and Terminology"(Q2A), 60 FR 11260, March 1, 1995.

Rationale : These changes will result in consistency with definition in 210.3. The referenced ICH guideline does not list reproducibility as a characteristic of analytical procedures, and includes many others (detection limit, quantification limit, range, linearity, robustness) which are not referenced in the proposed revision to this section.

We appreciate this opportunity to provide comments, and look forward to dialog with FDA on the evolution of these proposed changes. PDA will be happy to assist with the organization of meetings or other forums where these issues can be discussed and clarified.

Sincerely,

Edmund M. Fry
President

Enclosure: Literature Review - Sampling Technology

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LITERATURE REVIEW SAMPLING TECHNOLOGY

Current Good Manufacturing Practice; Proposed Amendment of Certain Requirements for Finished Pharmaceuticals

Proposed 21 CFR 211.110 Sampling and testing of in-process materials and drug products

61 FR 20114

PDA Solid Dosage Form Validation Committee June 1996

The proposed rule is predicated on the assumption that current technology provides a means to collect minute, unbiased samples from a static powder bed that may be over seven orders of magnitude greater in size. These samples, presumably representative of the bulk material, must then be held to a very high standard. Unfortunately, according to the scientific literature, sampling technology has not changed since the CGMPs were originally promulgated in 1963. The sampling spear or thief still represents state-of-the-art in sample collection technology.

It is generally recognized that a thief is far from an ideal sampling device [1-15], particularly when used to collect samples of very small volume as is suggested by proposed §211.110(d). As it is inserted into a static powder, a thief will distort the bed by carrying material from the upper layers of the mixture downward towards the lower layers [1, 3-8]. The force necessary to insert a long thief through a large powder bed can be appreciable; this can lead to compaction, particle attrition and further distortion of the bed [7-8]. If the blend has a wide particle size, distribution percolation of fines through the coarser material can result in samples that are not representative of the bulk [7,9].

Additionally, when a thief is used to sample a uniform mixture consisting of powders with different flow characteristics, the more freely flowing powder will preferentially collect in the thief chamber resulting in a biased sample [3-5, 8]. The static pressure of the bulk powder, which forces material into the sample chamber of the thief, is significantly greater at the bottom of a large container than in the middle or near the top. It has been demonstrated [15] that one thief can extract samples of significantly different particle size from the bottom and top of a static powder bed. Furthermore, a single thief inserted in a vertical orientation can extract samples of different particle size than one that is inserted into a bed at an acute angle as is often required when sampling from a commercial scale V-blender [15].

The design of the chamber openings of a thief can also affect the sample that is collected. Two thieves of different design have been shown to bias samples, collected from the same pharmaceutical blend under identical conditions, in significantly different ways [15]; in this example, one thief provided a "friendlier" result than a second thief. There are studies reported in the pharmaceutical literature [11, 12, 14, 15] that demonstrate the propensity of a thief to extract biased (near) unit dose samples from blends of actual pharmaceutical products. Unfortunately,

there are even more examples of this problem that have not made their way to the open literature.

It is recognized by the scientific community [1-15] that a sample thief is prone to extract a biased sample from a static powder bed. In general, the potential for sampling bias increases as the size of the sample and/or the concentration of drug in the formulation decreases [10,14]; however, in practice, each product and each thief is different. The utility of the sample thief was summarized by Terence Allen in his classic treatise on particle measurement [9, page 18].

'The accuracy (or inaccuracy) of the sampling spear is comparable to the accuracy of scoop sampling and, on the whole, its use is to be deprecated.'

In summary, according to the scientific literature, existing technology does not provide a means to accurately collect small, unbiased samples from a large static powder bed.

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