



PDA Global Headquarters

Bethesda Towers
4350 East West Highway
Suite 200
Bethesda, MD 20814 USA

Tel: +1 (301) 656-5900

Fax: +1 (301) 986-0296

www.pda.org

OFFICERS

Chair:

John Shabushnig, PhD
Pfizer Inc

Chair-Elect:

Maik Jornitz
Sartorius Stedim Biotech

Secretary:

Rebecca Devine, PhD
Regulatory Consultant

Treasurer:

Anders Vinther, PhD
Genentech, Inc.

Immediate Past Chair:

Vincent Anicetti
Genentech, Inc.

President:

Robert Myers

DIRECTORS

Harold Baseman
ValSource LLC

Véronique Davoust, PhD
Pfizer Inc

Lothar Hartmann, PhD
Hoffmann-La Roche

Yoshihito Hashimoto
Chiyoda Corporation

Louise Johnson
Aptuit

Stefan Köhler
AstraZeneca

Steven Mendivil
Amgen

Michael Sadowski
Baxter Healthcare Corporation

Amy Scott-Billman
GlaxoSmithKline

Gail Sofer
GE Healthcare

Laura Thoma, PharmD
University of Tennessee

Martin Van Trieste
Amgen, Inc.

General Counsel:

Jerome Schaefer, Esq.
O'Brien, Butler, McConihe &
Schaefer, P.L.L.C.

Editor, *PDA Journal of
Pharmaceutical Science
and Technology*:

Lee Kirsch, PhD
University of Iowa

February 15, 2008

Division of Docket Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

**Reference: Amendment to the Current Good Manufacturing Practice
Regulations for Finished Pharmaceuticals; FR Notice December 4, 2007; Vol.
72, No. 232; Legacy Docket No. 2007N-0280; Federal Dockets Management
System Docket FDA-2007-0614**

Dear Sir/Madam,

PDA is pleased to offer comments on the FDA's proposed changes to the GMP requirements defined in 21 CFR § 210 and § 211, as outlined in the Direct Final and Proposed Final Rules published in the Federal Register of December 4, 2007. PDA is a non-profit international association of more than 10,000 individual member scientists having an interest in the fields of pharmaceutical, biological and device manufacturing and quality. Our comments were prepared by a global workgroup of our members representing our Regulatory Affairs and Quality Committee and our Science Advisory Board. PDA appreciates the opportunity to offer comments on these proposed changes and wishes to thank the FDA for the opportunity to do so.

PDA endorses the need to update the current regulations as well as continuation of the approach and motivation stated in the Amendment's Background section. PDA also agrees that since the breadth and complexity of updating all aspects of pharmaceutical CGMP regulations may be impractical and too lengthy to perform at one time, the incremental approach taken by FDA is appropriate.

With regard to the proposed changes themselves, PDA believes that as presently written, the proposed 211.68(c) presents several concerns:

- In Supplementary Information Section II. D. Verification by Second Individual, the sections cited in the Final Rule do not adequately represent the intention of the statement "*Rather, in these situations, only one person is needed to verify that the automated equipment is functioning adequately. In cases where there is an operator for the automated equipment, the verifying individual may be, but is not required to be, the operator.*" FDA's proposed language does not seem to permit automated equipment operation where a check is performed by the operator of proper functioning of the equipment at the beginning of a shift, or acceptance of the validation of the calculation algorithm. Rather, it would seem that each component addition would need to be witnessed/verified, or that the calculation of the yield would need to be performed by hand following calculation by the system.
- It may hinder the adoption of PAT. For example, in instances where components are charged in a fully automated manner per a validated algorithm, there would not appear to be any value added in a manual verification of that component addition.
- Many current biotech processes include component additions and deletions in a continuous or periodic manner over long periods of time. Again, it would not seem to be value added to have a manual verification of this component management scheme in a fully automated scenario.

PDA believes that validated automated systems which include real-time alarms to warn of malfunctions and do not require any human intervention should not require human verification with each use. In addition, as outlined in our more detailed comments, when human verification is needed, the level required should be consistent with the level of automation used. When properly qualified and validated fully automated systems or equipment are used, a single check of proper functioning at the beginning of the shift should suffice. In a similar manner, validation of a calculation algorithm should suffice as verification that calculations are performed appropriately and obviate the need for an independent human verification of calculations. These concepts are applicable to proposed 211.68(c), 211.101(c)(3), 211.101(d), 211.103 and 211.188(b)(11).

Our detailed comments on these proposed changes and on the proposed changes to 211.94(c), 211.113(b) and 211.48 are provided in the accompanying spreadsheet and include suggested new wording for several of the proposed changes. We have also included the rationale for our comments and recommendations.

Again, PDA appreciates the opportunity to comment and offers these suggestions for your consideration. We believe that these comments will serve to clarify and strengthen the proposed regulations and will create the opportunity to better serve the needs of both regulators and industry.

If appropriate, we would be happy to participate in a public discussion of these and other comments which FDA may receive on the proposed Amendment, and would be happy to discuss the details of such a meeting and contribute to the planning process, should you wish to pursue that concept.

If you need further clarification, please do not hesitate to contact me.

Sincerely,

A handwritten signature in cursive script that reads "Robert Myers".

Robert B. Myers
President, PDA

Enc: Detailed Comment Spreadsheet

GMP Changes Cover Letter v 5; 2-15-08

PDA Comments; Final Rule Changes to FDA 21 CFR 210 & 21 CFR 211
February 2008

Section	Current Regulation	FDA Proposed Revision	PDA Suggested Revision
Human checks on automated systems and equipment			
211.68(c) Automatic, mechanical and electronic equipment	There is a new sub-section	“Such automated equipment used for performance of operations addressed by Sec. 211.101(c) or (d), 211.103, 211.182, or 211.188(b)(11) can satisfy the requirements included in those sections relating to the performance of an operation by one person and checking by another person if such equipment is used in conformity with this section and one person verified that the operations addressed in those sections are performed accurately by such equipment.”	“Automated equipment used in conformance with this section can satisfy the requirements for verification of proper operations addressed by Sec. 211.101(c) or (d), 211.103, 211.182, or 211.188(b)(11), as follows: i) if such unit operation is fully automated, then no manual verification is necessary, or ii) if there is an operator for the automated equipment, then the verifying individual may be, but is not required to be, the operator.”
<p>Rationale: The rationale for PDA’s recommendation is multi-faceted;</p> <ol style="list-style-type: none"> 1) Automated, validated systems equipped with real time alarms that do not require any human intervention should not require human verification with each use, as section 211.68(a) currently and adequately addresses the maintenance and verification of automated systems performance. 2) The need and type of verification required should be consistent with the level of automation used: <ol style="list-style-type: none"> a. Fully automated and alarmed operations using systems compliant with CGMP qualification, maintenance, and data trail requirements should require no additional human verification. (Of course, the data trail of performance would be subject to the Quality Unit’s review prior to product release.) b. Operations which are not fully automated using systems that meet CGMP expectations (per above) but require operator participation may serve as verification of the operator’s activities, replacing the current second human verification requirement. c. Fully manual operations would continue to require a second human verification. 3) As written, the proposed regulation may hinder the adoption of PAT. For example, in instances when components are charged in a fully automated manner per a validated algorithm, there would not appear to be any value added by a manual verification of that component addition. 			

PDA Comments; Final Rule Changes to FDA 21 CFR 210 & 21 CFR 211
February 2008

Section	Current Regulation	FDA Proposed Revision	PDA Suggested Revision
211.101(c)(3) Charge-in of components	No existing rule.	If the weighing, measuring, or subdividing operations are performed by automated equipment under Sec. 211.68, only one person is needed to assure paragraphs (c)(1), (c)(2), and (c)(3) of this section have been met.	“If the weighing, measuring, or subdividing operations are performed by automated equipment, then verification that paragraphs (c)(1), (c)(2), and (c)(3) of this section have been met shall be in accordance with section 211.68(c).”
Rationale: Please refer to the comments on the proposed revision to section 211.68(c).			

211.101(d) Charge-in of components	“Each component shall be added to the batch by one person verified by a second person.”	“Each component shall either be added to the batch by one person and verified by a second person or, if the components are added by automated equipment under Sec. 211.68, only verified by one person.	“Each component shall either be added to the batch by one person and verified by a second person or, if added by automated equipment, verified in accordance with section 211.68(c).”
Rationale: Please refer to the comments on the proposed revision to section 211.68(c).			

PDA Comments; Final Rule Changes to FDA 21 CFR 210 & 21 CFR 211
February 2008

Section	Current Regulation	FDA Proposed Revision	PDA Suggested Revision
211.103 Calculation of yield	“Actual yields and percentages of theoretical yield shall be determined at the conclusion of each appropriate phase of manufacturing, processing, packaging, or holding of the drug product. Such calculations shall be performed by one person and independently verified by a second person.”	“Actual yields and percentages of theoretical yield shall be determined at the conclusion of each appropriate phase of manufacturing, processing, packaging, or holding of the drug product. Such calculations shall either be performed by one person and independently verified by a second person or, if the yield is calculated by automated equipment under Section 211.68, be independently verified by one person.”	“Actual yields and percentages of theoretical yield shall be determined at the conclusion of each appropriate phase of manufacturing, processing, packaging, or holding of the drug product. Such calculations shall either be performed by one person and independently verified by a second person or, if calculated by automated equipment, verified in accordance with section 211.68(c).”
Rationale: Please refer to the comments on the proposed revision to section 211.68(c).			
211.188(b)(11) Batch production and control records	“Identification of the persons performing and directly supervising or checking each significant step in the operation.”	“Identification of the persons performing and directly supervising or checking each significant step in the operation, or if a significant step in the operation is performed by automated equipment under Sec. 211.68, the identification of the person checking the significant step performed by the automated equipment.”	“Identification of the person(s) and/or automated systems performing or checking each significant step in the operation.” The proposed PDA revision is predicated upon FDA accepting the PDA-proposed revision to 211.68.
Rationale: Please refer to the comments on the proposed revision to section 211.68(c).			

PDA Comments; Final Rule Changes to FDA 21 CFR 210 & 21 CFR 211
February 2008

Section	Current Regulation	FDA Proposed Revision	PDA Suggested Revision
211.94(c) Drug product containers and closures	“Drug product containers and closures shall be clean and, where indicated by the nature of the drug, sterilized and processed to remove pyrogenic properties to assure that they are suitable for their intended use.”	“Drug product containers and closures shall be clean and, where indicated by the nature of the drug, sterilized and processed to remove pyrogenic properties to assure that they are suitable for their intended use. Such depyrogenation processes shall be validated.	“Drug product containers and closures shall be clean and, where indicated by the nature of the drug and its manufacturing process, sterile and non-pyrogenic to assure they are suitable for their intended use. Where containers and closures are actively rendered non-pyrogenic by a designated depyrogenation process, the depyrogenation process shall be validated.”
<p>Rationale: It is important to note that currently not all containers and closures for sterile drug products are actively treated/processed to reduce/remove pyrogens. The supplementary information for this proposed rule (Part II.B. <i>Aseptic Processing</i>, Section 211.94(c)) appears to presume that all containers and closures are actively depyrogenated: “To assure that certain products are suitable for their intended use, drug product containers and closures are required to be sterilized and depyrogenated to remove microbial contamination and pyrogens or endotoxin.”</p> <p>Some containers and closures are non-pyrogenic by nature and/or design of their manufacturing process(es) or have been qualified not to require active depyrogenation. Handling procedures are also designed and controlled (e.g., bulk packaging, incoming parts control, storage, personnel control, etc.) to minimize the risk of pyrogen contamination during finished product manufacturing.</p>			

PDA Comments; Final Rule Changes to FDA 21 CFR 210 & 21 CFR 211
February 2008

Section	Current Regulation	FDA Proposed Revision	PDA Suggested Revision
Control of Aseptic Processing			
211.113(b) Control of microbiological contamination	“Appropriate written procedures, designed to prevent microbiological contamination of drug products purporting to be sterile, shall be established and followed. Such procedures shall include validation of all sterilization processes.”	“Appropriate written procedures, designed to prevent microbiological contamination of drug products purporting to be sterile, shall be established and followed. Such procedures shall include validation of all aseptic and sterilization processes.”	PDA proposes that this section not be revised from the current regulation.
<p>Rationale: We feel that the statements in the preamble accompanying the proposed GMP changes [“Even before 1987, when the Guideline for Sterile Drug Products Produced by Aseptic Processing was issued, industry routinely conducted validation studies that substituted microbiological media for the actual product to demonstrate that its aseptic processes were validated. These parts of validation studies are often referred to as media fills. (Federal Register/Volume 72, No. 232, page 68066)] could lead the reader to incorrectly conclude that only media fills are required to validate an aseptic process.</p> <p>PDA believes that a well controlled, robust process is required for aseptic processes. A highly defined system of risk evaluation and management, engineering and manufacturing controls, maintenance, quality systems, employee training, written procedures, environmental monitoring, strict adherence to aseptic technique, and minimal personnel intervention, can establish a state of control, ensuring that the aseptically produced product consistently meets its pre-determined specifications and quality attributes. Once the state of control has been established, process simulations (media fills) can be useful in confirming the state of control.</p> <p>So, unless the new preamble can be modified, we recommend this section not be revised from the current regulation. The current regulation, and the accompanying preamble, which states, “The Commissioner believes this paragraph, as written, can apply to both sterile fill process and terminal sterilization process. In both instances there must be validation of the process used to show that it produces a sterile product” provide sufficient regulatory authority for the agency to assure that firms demonstrate a state of control for aseptic processing.</p>			

PDA Comments; Final Rule Changes to FDA 21 CFR 210 & 21 CFR 211
February 2008

Section	Current Regulation	FDA Proposed Revision	PDA Suggested Revision
211.48 Plumbing	“Potable water shall be supplied under continuous positive pressure in a plumbing system free of defects that could contribute contamination to any drug product. Potable water shall meet the standards prescribed in the Environmental Protection Agency's Primary Drinking Water Regulations set forth in 40 CFR part 141. Water not meeting such standards shall not be permitted in the potable water system.”	“Water supplied by the plumbing system of the facility must be safe for human consumption. This water shall be supplied under continuous positive pressure in a plumbing system free of defects that could contribute contamination to any drug product.”	“Potable water supplied by the plumbing system of the facility must be safe for human consumption per applicable public health standards. This water shall be supplied under continuous positive pressure in a plumbing system free of defects that could contribute contamination to any drug product.”
<p>Rationale: By removing the reference to “Potable,” the language proposed by FDA is not specific regarding the water systems affected by this regulation and could be misinterpreted to include all water distribution systems in the facility. In addition, PDA believes the term “safe for human consumption” is not sufficiently prescriptive and not consistent with the agency’s initiative to be more standards-based. In order to clarify the expectation to meet an appropriate standard, we have suggested terminology that incorporates the following CDC definition for potable water:</p> <p style="text-align: center;">“Potable (drinking) Water: water suitable for drinking per applicable public health standards.”</p>			