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June 27, 2011

Dockets Management Branch (HFA-305)
Food and Drug Administration
5600 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2011-N-0259: Periodic Review of Existing Regulations; Retrospective Review under Executive Order 13563

Dear Sir/Madam:

The Biotechnology Industry Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on the Agency's "Periodic Review of Existing Regulations; Retrospective Review under Executive Order 13563." BIO represents more than 1,100 biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial and environmental biotechnology products.

America leads the world in biotechnology innovation and our industry holds great potential for advancement of the next generation of new cures and therapies for patients, as well as future economic growth and job creation. Over the last 20 years, biotechnology has created more than 250 new therapies to help extend and improve the quality of life for more than 325 million patients suffering from serious and cruel diseases such as cancer, Parkinson's disease, Alzheimer's disease, HIV/AIDS and multiple sclerosis. Today, biotechnology companies have more than 600 new biologic medicines in development and biotechnology is behind about two-thirds of the new medicines in development. However, continued advancement in biotechnology and the life sciences requires an efficient and effective regulatory environment that supports innovation, keeps pace with modern science, and promotes the public health, while not impeding robust economic growth and job creation.

I. *The Appropriate Balance of Benefits and Risks in FDA Regulations:*

FDA's regulatory paradigm for drugs and biologics has been guided by the principle that the regulations must be flexible to account for emerging science and technological innovations. This flexibility has largely served FDA, industry and patients well over the last 30 years. However, this flexibility also poses considerable challenges when the regulations are interpreted in a manner inconsistent with FDA's mission to promote the public health and support the development of innovative medical products that can advance public health.

Because of their inherent flexibility, there are few examples of particular FDA regulations that are egregiously outmoded, ineffective, insufficient, or excessively burdensome. However, BIO is particularly concerned by how the existing regulations have been incrementally re-interpreted in recent years in a manner that has positioned the Agency as being more risk-averse and has increased the regulatory burden on industry. These re-interpretations are often not made through new regulation or formal amendments to existing regulations, but through Guidances, new precedent set through product approvals or enforcement action, or through advisory committee opinion. Prior to changing a historical precedent, FDA should at a minimum publically disclose the new requirement, rather than incrementally introducing a new requirement on a case-by-case situation.

By definition, prescription drugs and biologics carry both benefits and risks that must be carefully balanced in the context of disease severity. Excessive regulation that overemphasizes risk over benefit may have the direct impact of decreasing the likelihood that patients are exposed to potentially dangerous drugs, but also has considerable indirect impact to society as a whole by limiting patient access to new treatments that can reduce mortality and reduce patient suffering. This indirect impact on patients waiting for new cures must be a driving determinate in FDA's benefit/risk assessment and regulatory policies.

Additionally, risk averse regulation can have a deleterious effect on research and development of new treatments for key public health priorities. Historically, FDA's regulatory posture has not taken into account the key linkage between regulation and its impact on the investment-product development cycle. U.S. biotech companies invest more than $30 billion annually in research and development. In fact, 98% of the industry's funding comes from the private sector and almost ninety percent of BIO's membership is comprised of small, emerging biotechnology companies that rely on venture capital funding and private investment to support R&D and clinical research programs. Recent history has demonstrated that investors will take flight and refuse to finance research into high priority disease areas, such as diabetes or certain cancers, if FDA's demands for clinical data are excessive or if the standards for approving new drugs are uncertain and unpredictable. Ultimately, a risk averse regulatory posture can have immeasurable harm on the ability of the life sciences to innovate and deliver new treatments to patients.

BIO supports a balanced approach to benefit/risk evaluation that takes into account the societal impact of regulation on innovation in the life sciences and the public health. We are pleased to offer the following recommendations regarding specific regulations to evaluate as part of the Administration's retrospective regulatory review, but we believe that this exercise should be

accompanied by a broader public discussion or the appropriate balance of benefits and risks, and the impact of regulation on society.

II. *FDA Should Exercise Greater Flexibility and Discretion under the "Substantial Evidence" Standard for Key Public Health Priorities*

An example of the significant latitude granted in FDA statute and regulations is FDA's "substantial evidence" standard for drug and biologic approvals. The Food, Drug, and Cosmetic Act (FDCA) requires that the FDA approve applications for new drugs when they have been demonstrated to be safe and effective under the intended conditions of use. Under Section 505(d), effectiveness is established when FDA is satisfied that there is "substantial evidence" that the new drug has the intended effect that it is purported to have. Although not detailed in statute, FDA has interpreted this standard to generally require two "adequate and well controlled" studies meeting the statistical standard of $p < 0.05$ with respect to pre-determined endpoints. However, Section 505(d) also states that "If the Secretary determines, based on relevant science, that data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation) are sufficient to establish effectiveness, the Secretary may consider such data and evidence to constitute substantial evidence for purposes of the preceding sentence."

Under the law and existing FDA regulation, the Agency has significant discretion to approve drugs or biologics based upon a single trial and to take into account the broader weight of evidence around the product's safety and efficacy. However, FDA rarely exercises this flexibility. While all products must be demonstrated to be safe and effective and provide adequate evidence that the benefits of the product outweigh its risks, an excessively rigid approach to approval standards can lead to longer clinical development times, decreased investment in biomedical research, and reduced access to new therapies for patients with no therapeutic alternatives. For dire and unmet medical needs, rare diseases, and other public health priorities, BIO encourages FDA on a case-by-case basis to utilize the significant discretion and flexibility in its approval standards to help advance the development of new lifesaving and life enhancing medical products.

III. *Clarification of the Treatment of Therapeutic Biologics under Drug and Biologics Regulations*

BIO also believes that the current regulations should further clarify how therapeutic biologics are treated under both drug-focused regulations (Parts 200 and 300) and biologics-focused regulations (Parts 600). Traditionally, biologics are regulated under the Public Health Service Act while small molecule drugs are regulated under the FDCA. However, biologics are also considered to be drugs and many drug-related regulatory provisions have been applied to biologics over time. Consequently, it can be difficult for Sponsors to ascertain whether the drug regulations apply to therapeutic biologics and under what circumstances since the regulations lack sufficient detail and differences in the way the same topics are handled under Parts 600s vs. the 200 and 300s.

Adding to the confusion is that in practice, the Center for Drug Evaluation and Research (CDER) applies many expectations that are based in the New Drug Application (NDA) regulations to the biologics that they review. Specific examples include:

- Content/requirements for New Drug Applications (NDAs)/Biologics License Applications (BLAs)
- 4-month safety updates
- Carton/container labeling
- Periodic reporting for marketed products (annual reports, distribution reporting, Post-marketing Requirement/Commitment (PMR/PMC) /pediatric study reporting)

We suggest that FDA could 1) clarify which of the Part 200 and Part 300 regulations also apply to therapeutic biologics, or 2) update the Part 600 regulations to be more detailed and relevant to therapeutic biologics.

IV. *The Regulatory Burden of Guidances should also be Evaluated:*

Industry believes that equally, or perhaps more important than the need for public comment on regulations, is the need for review of the burden of related Guidances for Industry. These guidance documents provide implementation details and are often helpful, but can also impose more burden than the actual regulations represent. This approach would ensure a more holistic approach to ensuring that there is an open exchange of ideas. Therefore, we recommend that the Agency includes a review of guidance in addition to regulation policy when developing its plan to respond to Executive Order 13563.

V. *HHS Proposed Regulatory Revisions:*

We thank the Department of Health and Human Services (HHS) and FDA for releasing a list of proposed revisions to the existing regulations and BIO agrees in principle with many of the FDA-related proposals. We applaud efforts to move the regulatory environment into the world of electronic communication and data handling and changes to improve flexibility and to global harmonization. The HHS/FDA/CDER initiatives appear to be moving in this direction with proposals for electronic submission requirements for postmarketing safety reports, clinical data submissions, and product registration and listing and their proposals regarding current Good Manufacturing Practices (cGMPs). All these changes have the potential to result in efficiencies across the industry and, ultimately, improvements in the public health. Clarifying post-marketing safety requirements for combination products is timely as science and technological advancement is creating a favorable environment for combination products.

The proposed amendments to the regulations as currently drafted are quite brief and provide little of the detail necessary to fully evaluate them. BIO looks forward to participating in a public process, including technical workshops, and the notice-and-comment rulemaking process as FDA elaborates upon these proposals.

VI. *Economic Impact and Cost Analysis*

With respect to the following specific recommendations, BIO was unable to provide supporting economic or cost data in most instances. However, we have every reason to believe that streamlining and updating regulatory processes will result in savings in the long term. BIO's recommendations focus on eliminating redundancies, harmonizing with international standards or other competent authorities, and revisions intended to incorporate modern communication and data management tools into the regulatory process. Achieving these goals should result in resource savings for both the government and industry.

VII. *Prospective Evaluation of Existing FDA Regulation*

Regarding prospective evaluation of FDA regulations, BIO suggests that the FDA utilize their inspection trend analysis, which identifies incidences of common noncompliance (483) observations, and conduct further evaluation of such, to determine if the root cause of high incidences is a result of unclear regulations and/or regulations which have no bearing on ultimate patient safety. An example of such would be relative to inspections conducted under the Bioresearch Monitoring Program for nonclinical studies, and the relative increase of inspection observations associated with 21 CFR 58.185 (a)(12). There appears to be a high expenditure of reactive effort on the part of the agency as well as the industry perhaps due to confusion of the regulation and agency expectations with little relativity to patient safety.

CONCLUSION:

BIO appreciates this opportunity to comment on "Periodic Review of Existing Regulations; Retrospective Review under Executive Order 13563." More specific regulatory recommendations are included in the following pages. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/S/

Andrew J. Emmett
Managing Director, Science and Regulatory Affairs
Biotechnology Industry Organization (BIO)

SPECIFIC REGULATORY RECOMMENDATIONS:
(In order of CFR Number)

PART 00-99

21 CFR 54.2: Financial Disclosure by Clinical Investigators, Definitions

- *Product Type:* Drugs and Biologics
- *Brief Description of Problem:* 21 CFR Part 54 was last amended more than a decade ago. With a changing economy, regulations addressing monetary values should be periodically reviewed and updated to reflect amounts commensurate with current costs and fair market values.
- *Available Data on Cost or Economic Impact:* N/A
- *Proposed Solution:* Provide current appropriate values wherever specific dollar amounts are provided in regulations.

21 CFR 58: Good Laboratory Practice for Non-Clinical Laboratory Studies

- *Product Type:* Drugs and Biologics
- *Brief Description of Problem:* BIO supports FDA's initiative to revise the Good Laboratory Practice (GLP) regulations to more completely address how nonclinical studies are currently conducted, particularly in light of the fact that the regulations have not been substantially revised since the late 1970's. BIO supports a quality systems approach to GLP to ensure continual improvement and high quality lab studies, which is embodied in the current GLP regulation. Wherever possible, we also encourage alignment with international standards and principles governing the conduct of nonclinical studies.[1]
- *Available Data on Cost or Economic Impact:* N/A
- *Proposed Solution:*

    1. Clarify the GLP regulations (*e.g.* 21 CFR Part 58.105) to indicate that it would be acceptable to generate test and control article characterization data in compliance with Current Good Manufacturing (cGMP) regulations. A Certificate of Analysis

[1] BIO comments on *Good Laboratory Practice for Nonclinical Laboratory Studies*, Docket No. FDA–2010–N–0548, February 22, 2011, http://www.bio.org/reg/20110222.pdf

should be provided to the study director including the purity, identity, and retest date prior to finalization of the study report.

2. Additionally, compliance with Organisation for Economic Co-operation and Development (OECD) GLPs or US GLPs should be acceptable even for US based companies/studies even where there are differences in US GLPs and the OECD guidance. Some examples of areas for consideration follow:

   - Consider revising 21 CFR Part 58 for alignment with global standards for GLPs thereby supporting ease of compliance by global organizations and of enforcement by different countries health authorities. Consistency with OECD GLP Consensus Guidance Documents would be a valuable revision to 21 CFR Part 58. Aligning 21 CFR Part 58.3 and 58.33 with OECD consensus documents #8 and #13 would retain the current 21 CFR Part 58 study director responsibilities as well as add clarity to the conduct, roles and responsibilities of GLP studies and study personnel at multiple sites. Further clarification of distinction between a test facility and test site would be helpful. Studies conducted at multiple sites, which are under single management control with harmonized SOPs, and in which the study director has adequate access to study data in accord with OECD GLP guidance, should not be considered multisite studies.

   - Consider adding clarification to 21 CFR Part 58 allowing flexibility of study directors to be located at the sponsor site for multi-site studies. It is understood that collaboration between sponsor, study director and CRO scientists is critical to ensure appropriate exchange of scientific information, which may impact accurate assessment of study conclusions by the study director. The sponsor and sponsor study directors often have crucial knowledge, experience, and expertise regarding the test article being evaluated. Applying this information and experience to study data interpretation and reporting may often result in the drawing of significantly more accurate conclusions.

21 CFR 58.15(a): Inspection of a Testing Facility

- *Product Type:* Drugs and Biologics

- *Brief Description of Problem:* Some of the information routinely requested by the agency per Bioresearch Monitoring Compliance Manual could be supplied prior to the agency presenting themselves at a firm's site.

- *Available Data on Cost or Economic Impact:* This has the potential to reduce agency costs as well.

- *Proposed Solution:* Consider updating 21 CFR Part 58.15(a) to allow advance notice of routine surveillance inspections by the FDA in the U.S. This approach would further

enhance sponsor's facilitation of inspections and align the U.S. with global inspectional approaches.

PART 200

21 CFR 201: Labeling

- *Product Type:* Drugs and Biologics

- *Brief Description of Problem:* Paper labeling (package insert and patient labeling) materials are currently required to be distributed with the product container. Outdated paper labeling may exist in the distribution system for an extended time limiting availability of new safety information. Paper labeling is not user-friendly (small print, large paper sizes folded and often glued to container) nor environmentally friendly, and is often discarded without use.

- *Available Data on Cost or Economic Impact:*
    - Manufacturers: Elimination of considerable manufacturer costs associated with preparing, printing, inspecting, storing, controlling, revising, purchasing materials, and destroying out-of-date paper inserts. Also eliminates costs associated with exceeding the capacity of available packaging equipment when the size of labeling documents increases with the implementation of the Physician's Labeling Rule.

    - Distributors: Elimination of costs associated with the challenges of handling paper inserts. Reduced shipping costs due to weight/bulk of paper inserts.

- *Proposed Solution:* Change the regulation as soon as possible to allow electronic distribution of US package inserts for human drug and biological prescription products to dispensing sites instead of current requirement for shipment of paper labeling.

21 CFR 202: Advertising

- *Product Type:* Drugs and Biologics

- *Brief Description of Problem:* The definition of advertising and regulations governing promotion are outdated and do not address modern communications systems available through internet such as websites, social media and twitter. This leads to confusion in the industry as to whether or not modern communication systems squarely fit into the definition and what the requirements are for advertising in such media.

- *Available Data on Cost or Economic Impact*: N/A

- *Proposed Solution:* BIO believes that--in addition to rulemaking--FDA should also issue guidance for industry on the use of the Internet and social media to promote and communicate about regulated medical products. BIO members are concerned about the current lack of clarity in this area, and while regulations are warranted, guidance would also be useful, either on an interim basis while regulations are in development, or to clarify how the regulations will apply to specific technologies."

21 CFR 203 Subpart D: Samples

- *Product Type:* Drugs and Biologics

- *Brief Description of Problem:* To ensure consistency and clarity with the current samples requirements, particularly 21 CFR 203.33 sample forms, 203.34 policies and procedures, subpart D of 21 CFR 203 should be amended to reflect new requirements in section 6004 of ACA.

- *Available Data on Cost or Economic Impact:* N/A

- *Proposed Solution:* Require only aggregate sample information in the annual report (under ACA). Confirm that existing forms and policies in 203.33 and 203.34 are sufficient for the reporting requirements in ACA.

21 CFR 210: Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs; General;

21 CFR 211: Current Good Manufacturing Practice for Finished Pharmaceuticals

- *Product Type:* Drugs and Biologics

- *Brief Description of Problem:* FDA and industry increasingly face challenges due to the globalization of drug development and manufacturing, so BIO members strive to achieve a level of quality assurance that often exceeds FDA's regulatory requirements. The changing world has required both FDA and industry to devise and evaluate more complex risk scenarios and apply more sophisticated technologies to screen and evaluate prescription drugs and biologics entering the U.S. to ensure their quality. Given the highly technical and evolving nature of testing requirements, FDA rulemaking is an appropriate process for improving product characterization beyond that provided for under current cGMPs. Rulemaking is how changes to the GMPs have been handled since the publication of the original GMP regulations, and can most efficiently and effectively further the goals at hand. Further, revisions to the cGMPs can further harmonize

international requirements among international regulatory authorities and incorporate best practices identified in ICH guidance.

- *Available Data on Cost or Economic Impact:* N/A

- *Proposed Solution:* The GMP regulations should be reviewed to align with the layout of the Rest of World (ROW) GMP regulations (EU, Canada, Japan, etc.).

PART 300

21 CFR 312.33: Annual Reports

- *Product Type:* Drugs and Biologics

- *Brief Description of Problem:* The International Conference of Harmonisation (ICH) has released Guidance E2F – Note for Guidance on Development Safety Update Reports (DSUR). This guidance is being required to be met in many of the EU regions and hence products are starting to convert to these reports. In the U.S., people are getting permission from FDA to replace the Annual Report requirement of 312.33 with the more content rich report requirements defined in E2F. This report now provides a health authority reviewer an understanding of what is truly going on with the product from a safety perspective as opposed to just a snapshot of the IND activity for the year.

- *Available Data on Cost or Economic Impact:* N/A

- *Proposed Solution:* Update U.S. regulations to reflect what is actually happening in practice and to make it more reflective of the language associated with that in ICH E2F.

21 CFR 312.6: Labeling of an Investigational New Drug

- *Product Type:* Drugs and Biologics

- *Brief Description of Problem:* FDA provides text for clinical label that states "Caution: New Drug – Limited by Federal (or United States) law to investigational use." It is our understanding now that most studies are international and companies have changed the wording slightly to accommodate other countries so the text in quotes is not adhered to.

- *Available Data on Cost or Economic Impact:* N/A

- *Proposed Solution:* We suggest modifying the language of the regulation to reflect actual practice.

21 CFR 312.110: Import and Export Requirements

- *Product Type:* Drugs and Biologics
- *Brief Description of Problem:* Active Pharmaceutical Ingredients (APIs) used in development are more than adequately controlled through the regulatory documents and should not need to be occurring at the border. This portion of the regulation adds a hurdle to the research efforts (and thus jobs) in the United States when producing the API outside of the United States.
- *Available Data on Cost or Economic Impact:* N/A
- *Proposed Solution:* Revise the regulations indicating the need to have an IND in place for API importation.

21 CFR 312.32(b)(2): Telephone and facsimile transmission safety reports

- *Product Type:* Drugs and Biologics
- *Brief Description of Problem:* Facsimile transmission may not be as reliable as email with respect to delivery to recipient due to printing, paper, or other errors.
- *Available Data on Cost or Economic Impact:* N/A
- *Proposed Solution:* Include "or electronic" whenever facsimile transmission is mentioned.

21 CFR 312.42(c): Clinical holds and requests for modification; Discussion of deficiency

- *Product Type:* Drugs and Biologics
- *Brief Description of Problem:* This regulation is not followed consistently by the FDA and, therefore, needs expansion. The current requirement that, "…FDA will, unless patients are exposed to immediate and serious risks, attempt to discuss and satisfactorily resolve the matter with the sponsor before issuing the clinical hold order," is not adhered to because there is no consequence to FDA and the regulation is insufficient to achieve its intent. Improving adherence to this regulation would allow sponsors to make changes to INDs so that important therapeutic investigations could continue without costly study stops and resumptions, while protecting patients. To improve this regulation, revise to

include an incentive or specific deadline for FDA to communicate, or a consequence for not discussing and attempting to resolve the deficiency.

- *Available Data on Cost or Economic Impact:* N/A

- *Proposed Solution:* Modify the regulation to state, "…FDA will, unless patients are exposed to immediate and serious risks, ~~attempt~~ contact the sponsor no later than 5 days prior to imposition of a clinical hold to discuss and attempt to satisfactorily resolve the matter with the sponsor before issuing the clinical hold order." Provide guidance to explain how FDA would attempt to resolve the matter with the sponsor.

21 CFR 314.70 and 601.12: Supplements and Other Changes to Approved Applications

- *Product Type:* Drugs and Biologics

- *Brief Description of Problem:* Regulations are too restrictive and are a burden to FDA and the industry for submitting unnecessary, low-risk, post approval CMC changes. FDA held a public meeting in 2007 to seek feedback from stakeholder on reclassification of manufacturing changes based on science and risk based approaches and has taken no action to revise the regulations.

- *Available Data on Cost or Economic Impact:* N/A

- *Proposed Solution:* FDA should revise regulations to limit the number of supplement types to Prior Approval Supplements, Changes-Being-Effected 30 days, and annual report changes. Prior approval supplements should be limited to changes that result in a broadening of filed specifications or directly impacts safety or efficacy of the product.

21 CFR 314.50: Content and Format of an Application

- *Product Type:* Drugs and Biologics

- *Brief Description of Problem:* Since passage of the FDA Amendments Acts of 2007, Risk Evaluation and Mitigation Strategies have become an important component of the content and format of an application if a REMS is required to ensure the benefits of the product outweigh the risks. However, the REMS requirements are not cross-referenced in the regulations.

- *Available Data on Cost or Economic Impact:* N/A

- *Proposed Solution:* This regulation should be modified to reflect inclusion of section(s) to address risk management (e.g., REMS) content and format requirements.

21 CFR 314.520 and 601.42: Approval with Restrictions to Assure Safe Use

- *Product Type:* Drugs and Biologics

- *Brief Description of Problem:* This provision is redundant with the statute. Section 505-1 (Risk Evaluation and Mitigation Strategies) of the Food Drug and Cosmetic Act provides FDA with the same authority to impose elements to assure safe use under §314.520. The same rationale applies to the biologics regulations in § 600 Subpart E regarding restrictions to assure safe use.

- *Available Data on Cost or Economic Impact:* N/A

- *Proposed Solution:* Delete 21 CFR 314.520. Delete reference to §314.520 in §314.530(a), (b) and §314.560. Delete to § 601.42. Delete reference to § 601.42 in §601.43(a), (b) and §601.46.

21 CFR 314.55: Pediatric Use Information

- *Product Type:* Drugs and Biologics

- *Brief Description of Problem:* 314.55 was promulgated as the "Pediatric Rule" and published in the Federal Register on December 2, 1998 (63 FR 66670). A suit was filed against the rule in December 2000 by The Competitive Enterprise Institute, The Association of American Physicians and Surgeons, and Consumer Alert. The Federal District Court overturned the Pediatric Rule on October 18, 2002. In its ruling, the court found that FDA lacked authority under FDCA to mandate pediatric studies. Congress subsequently passed the Pediatric Research Equity Act (PREA) in December 2003 but the statute did not exactly match all provisions of the "Pediatric Rule." In addition, Congress included a 5-year "sunset" clause in the law. PREA was re-authorized by Congress in 2007 under Title IV of the Food and Drug Administration Amendments Act (FDAAA), with further changes compared with the original "Pediatric Rule." FDA has not promulgated regulations reflecting the provisions of PREA. 21 CFR 314.55 is obsolete and, therefore, leads to confusion regarding requirements for pediatric drug development.

- *Available Data on Cost or Economic Impact:* N/A

- *Proposed Solution:* Please remove this section from 21 CFR.

CFR 316.30: Annual Reports of Holder of Orphan Drug Designation

- *Product Type:* Drugs and Biologics

- *Brief Description of Problem:* We suggest that there should be a way to incorporate the requirements of this section into those of the NDA Annual Report, and if the IND or NDA holder does not have orphan status, then the Sponsor would indicate such in the NDA Annual Report. This may fulfill the content requirements to understand the status of the orphan drug status while minimizing burden on both the IND or NDA holder and the FDA reviewers as they could have information via one report.

- *Available Data on Cost or Economic Impact:* N/A

- *Proposed Solution:* Incorporate orphan drug designation status into a single report under the NDA Annual reporting requirements if the IND or NDA holder does not have orphan status.

PART 600

21 CFR 600.14: Reporting of Biological Product Deviations by Licensed Manufacturers

- *Product Type:* Biologics

- *Brief Description of Problem:* The requirements for reporting all deviations from cGMP, and applicable regulations and standards is too broad and fails to consider the manufacturer's risk management and quality systems designed to assess impact of such deviations on product safety, purity and potency.

- *Available Data on Cost or Economic Impact:* N/A

- *Proposed Solution:* This regulation should be revised to address only deviations that are shown through appropriate risk management and internal quality investigation to cause potential risk to product safety, purity or potency.

21 CFR 600.81: Distribution Reports

- *Product Type:* Biologics

- *Brief Description of Problem:* We believe this requirement to submit to FDA 6-monthly distribution reports for biologics is inconsistent with other regulations and should be removed.

- *Available Data on Cost or Economic Impact:* N/A

- *Proposed Solution:* Please remove.

21 CFR 610.12: Sterility

- *Product Type:* Biologics

- *Brief Description of Problem:* The sterility test of bulk material is not applicable to therapeutic proteins regulated by CDER, nor should it be applicable to recombinant therapeutic proteins and monoclonal antibodies regulated by 610.12. This rule was put into place prior to the development of recombinant biotechnology products and does not reflect how these products are manufactured. Briefly, this product type does not routinely include a "sterile bulk" stage and attempts to create / sample bulk product post sterile filtration is often at risk of contaminating product. Many companies have, with concurrence from FDA, taken the first several units from the aseptic filling line and identified these as samples that constitute the "sterile bulk".

- *Available Data on Cost or Economic Impact:* The work-around of defining early units from the aseptic filling line as the sterile bulk results in unnecessary, costly testing. Final product is tested for sterility and testing as described in 21 CFR 610.12 represents unnecessary duplicative testing that does not provide any additional protection to public health, or assurance of product quality.

- *Proposed Solution:* Remove the requirement for performing the bulk sterility test for recombinant therapeutic proteins and monoclonal antibody products. The requirement for a bulk sterility test should only be applied for those bulk materials that cannot be filtered through one or more sterilizing filters prior to filling. Remove the sterility test specified in 610.12 and refer instead to the relevant compendia test for sterility.

21 CFR 610.14(b): Test for Pyrogenic Substances

- *Product Type:* Biologics

- *Brief Description of Problem:* This test is outdated, a burden to conduct, and has been replaced by more sensitive and reproducible in vitro test methods that do not involve the use of animals.

- *Available Data on Cost or Economic Impact:* N/A

- *Proposed Solution:* Replace with requirement for performing appropriate in vitro analytical test methods.

21 CFR 610.15(a): Constituent Materials- Ingredients, preservatives, diluents, adjuvants

- *Product Type:* Biologics

- *Brief Description of Problem:* The current regulation states, "An adjuvant shall not be introduced into a product unless there is satisfactory evidence that it does not affect adversely the safety or potency of the product." This regulation was written when only products mixed in a vaccine could be conceived of as adjuvants, for example aluminum. However, there are many immune-modulating compounds, some oral or administered not in suspension with the vaccine, that are possible today. The definition of an adjuvant and a claim that a product is an adjuvant must be revised to current science to promote further development in immune-regulatory interventions. This change will foster innovation in immunotherapies. Availability of adjuvants as separate products could address public health emergency needs, such as permitting various adjuvants to be used with various preventive influenza vaccines to avert vaccine shortages.

- *Available Data on Cost or Economic Impact:* N/A

- *Proposed Solution:* Remove "adjuvant" related language, including aluminum specifications, from §610.15, Constituent Material, to a separate regulation on adjuvants that does not limit adjuvants to only products introduced into the vaccine. Allow adjuvants that are new drugs, having effect on structure and function of the immune response, to be approved under section 505 of the Food Drug and Cosmetic Act.