PDA
Parenteral Drug Association

Connecting People, Science and Regulation®

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13 April 2018

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Reference: Review of Existing Center for Drug Evaluation and Research Regulatory and Information Collection Requirements
Docket No. FDA-2017-N-5101

Dear Sir/Madam:

PDA appreciates the opportunity to provide comments to this federal register request to identify existing regulations and related paperwork requirements that could be modified, repealed, or replaced. PDA's mission is to advance biopharmaceutical manufacturing science and regulation so members can better serve patients. PDA proposals below are aligned with FDA's vision on implementing risk-based approaches and focus on three areas where there are significant opportunities to repeal, modify, or replace existing regulatory requirements to incorporate such concepts.

- Validation data submitted in eCTD
- Annual review of quality standards
- Annual reports

PDA is a non-profit international professional 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 committee of experts in regulatory affairs including members of the PDA Board of Directors and the Regulatory Affairs and Quality Advisory Board.

If there are any questions, please do not hesitate to contact me.

Sincerely,

Richard M. Johnson

Richard Johnson
President, PDA

Cc: christine.kirk@fda.hhs.gov; Denyse Baker, PDA

PDA's comments to FDA's Federal Register "Review of Existing Center for Drug Evaluation and Research Regulatory and Information Collection Requirements"

Questions	Information/ Justification
Name of Regulation	**Validation data submitted in BLA;** ICH Q11 section VII for DS validation
Type of product or FDA Center regulating the product.	Drugs and biologics
Citation to Code of Federal Regulations and statutory citation (as applicable)	**21 C.F.R. § 601.2(a)** and FDA guidance document entitled "Q11 Development and Manufacture of Drug Substances,")
Approved information collection and OMB Control Number (as applicable)	
Brief description of concern	With each Biological License Application, there is a requirement to submit drug substance validation data and associated production/commercial stability data. Typically, the manufacture of three drug substance lots are required for the validation. This is extremely burdensome to industry, extending the drug development process significantly prior to BLA submission.
Available data on cost or economic impact	Shifting the drug substance validation review from the BLA review process to the pre-approval inspection will save industry significant time (6-12 months) prior to regulatory filing and enable industry's ability to bring new products to the market faster. Making this change would also promote efficiency from regulator so that validation assessment can be done effectively on site during the inspection.
Proposed solution	Records and data should be subject of FDA inspectional review (i.e. pre-approval inspections; and not part of the regulatory filing). Remove the application requirement and instead manage process validation as a cGMP requirement. This approach would enable speed to market, and also facilitate submissions for products designated as Breakthrough Therapies.

Questions	Information/ Justification
Name of Regulation	**Annual Review of Quality Standards**
Type of product or FDA Center regulating the product.	Drugs and Biologics
Citation to Code of Federal Regulations and statutory citation (as applicable)	**21 CFR 211.180(e)**
Approved information collection and OMB Control Number (as applicable)	
Brief description of concern	Annual review of quality standards are overly burdensome and companies already update these specifications and related documents as needed. Per ICH Q10, regulatory approaches for a specific product or manufacturing facility should be commensurate with the level of product and process understanding, the results of quality risk management, and the effectiveness of the pharmaceutical quality system. Senior management have the responsibilities to ensure that quality management systems in place are robust and ensure that all quality standards are kept up to date. Industry should have the ability and flexibility to determine the frequency, the annual review requirements add record keeping and administrative obligations without any corresponding benefit.
Available data on cost or economic impact	The cost associated with employees performing annual reviews and its documentation of all specifications, procedures and master batch records is high. Estimated number of documents can range from 100's to 1000's per site depending on the number of products manufactured.
Proposed solution	Regulations requiring annual review of all quality standards, drug product specifications, and manufacturing or control procedures should be eliminated. Industry should be adopting ICH Q10 principles to ensure that quality management systems and standards are effective.

Questions	Information/ Justification
Name of Regulation	**Annual Reports**
Type of product or FDA Center regulating the product.	Drugs and Biologics/CDER, CBER
Citation to Code of Federal Regulations and statutory citation (as applicable)	21 CFR. 314.70 (d) 21 CFR. 314.80(c)(2) 21 CFR. 600.80(c)(2) 21 CFR. 314.80(b) 21 CFR. 600.80(b) 21 CFR 314.81(b) (NDA annual report), 21 CFR 601.70 (annual progress reports of postmarketing studies for biologics.)
Approved information collection and OMB Control Number (as applicable)	
Brief description of concern	In the past, the reports submitted under these regulations have exhibited wide variability from firm to firm, and at times the information submitted has been inconclusive or insufficient. FDA regulations require that sponsors of Investigational New Drug applications (INDs) and New Drug Applications (NDAs) to submit an annual report regarding the status of the clinical investigation and information obtained during the previous year's clinical and nonclinical investigations as well as for marketed products: 21 CFR.312.33 and 21 CFR 314.70 (d). Other regulators, such as the European Medicines Agency or Health Canada, require similar annual or periodic reports for clinical trials as well as manufacturing changes. Thus, sponsors of global clinical trials are subject to overlapping, but not identical, reporting requirements. FDA has adopted the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline for the content and format of development safety update reports (DSUR). In that guidance, FDA stated that it will consider a DSUR consistent with the E2F guidance to meet the requirement for the IND annual report. However, FDA has not revised the IND annual report regulation to reflect the agency's adoption of the ICH guideline. Therefore, there exists a lack of clarity as to the application of the E2F guidance and how sponsors are required to comply with 21 CFR. 312.33 and 314.70 (d). Further, the usefulness of submitting the Annual Reports is questioned as all the information provided here is maintained in-house in the company (through the pharmaceutical quality system and pharmacovigilance system) and could be subject to inspections, as necessary. It is also not clear if the Agency does review or has the necessary resources to review this

	information submitted by multiple companies for multiple products on a routine basis.
Available data on cost or economic impact	Reduction in regulatory burden for preparation and submission of the Annual Reports. Compilation of these annual reports requires a lot of resources in the company and the value of this AR to the Agency is unknown or cannot be fully understood.
Proposed solution	PDA recommends removing the requirement for submission of IND and NDA Annual Reports, unless it is required to include CMC changes made during the year that have low impact on the quality, safety or efficacy of the clinical or marketed product to be reported. Other CMC changes that have moderate or high impact on the quality, safety or efficacy of the clinical or marketed product are routinely submitted to the Agency through Prior Approval Supplements or CBE supplements.