What’s New in GCP? Group’s Transparency Proposals for FDA Include Release of Trial Data

A Blueprint for Transparency at the FDA, which was published online March 13 by JAMA, includes several recommendations involving clinical trial data.

An academic working group with members from Johns Hopkins, Harvard and Yale developed the Blueprint. Invited patient advocacy organizations, consumer groups, clinicians, legal scholars, practitioners and industry representatives provided comment on early drafts of the document and the FDA provided technical comments.

The report made 18 recommendations in five areas:

- information about key application milestones;
- the agency’s analysis and decision-making;
- data from scientific studies to enhance understanding of medical products;
- misleading information in the market; and
- generic drugs and biosimilars’ application and review process.

The group noted that all the “recommendations, by design, can be implemented by the agency under existing statutes without additional action by Congress. Under existing statutory authority, FDA has broad discretion to define much of what is considered confidential by amending its regulations and refining policy.”

Recommendations Call for CSR Release

The Blueprint recommended the FDA disclose Clinical Study Reports (CSR) that have been submitted in support of a marketing application and, to the extent possible, the agency should harmonize standards on CSR release with the European Medicines Agency.

The group said the FDA should disclose CSRs after the approval of a marketing application, after the issuance of a Complete Response Letter, or upon the withdrawal or abandonment of the application. The disclosure should include the applicable ClinicalTrials.gov numbers.

The recommendation added that the FDA should consider using a data repository, such as the National Institutes of Health Biologic Specimen and Data Repository Information Coordinating Center, as an intermediary to protect patient privacy. The group noted “there are important privacy concerns that must be addressed” regarding data sets with individual patient data.

The group also recommended the FDA release the final reports that fulfill Postmarketing Requirements and Postmarketing Commitments, including CSRs of Phase 4 studies and other post-approval reports, when the agency considers the sponsor’s obligation to conduct a study to be fulfilled. These disclosures also should include the applicable ClinicalTrials.gov numbers, if any.

In addition, “when there are clinical trial data, including patient-level data, that were submitted to FDA in support of a marketing application but that are not reasonably available to independent investigators through industry-sponsored websites, FDA should make data available, such as through the National Institutes of Health Biologic Specimen and Data Repository Information Coordinating Center, with policies on de-identification to protect patient privacy,” the group recommended.
“In recent years, there has been an important evolution in thinking about access to data from clinical trials,” the report said. “The sharing of clinical trial data will advance innovation, improve clinical study design, and avoid exposing humans to trials of products that have already failed to meet prespecified endpoints or caused harm. In the case of observational post-approval studies, while some are published, a policy of transparency will improve the assessment and surveillance of the known and unexpected serious risks to patients related to the use of the drug, biologic or device,” the group said.

The group also recommended the FDA:

- Adopt the 2010 FDA Transparency Task Force draft proposals on investigational applications, marketing applications, and the existence of clinical holds. “These proposals would make the basic information in these filings broadly available,” the report said.
- Include in disclosures of investigational applications and marketing applications the class of medication and mechanism of action, if known.
- Include in disclosures of investigational applications and new applications the National Clinical Trial numbers for all trials conducted for marketing approval.
- Release the text of Special Protocol Assessments relevant to safety and efficacy after the study is completed.
- Release a summary of reasons for a clinical hold related to safety or efficacy within 10 days.
- Disclose whether a marketing application has been designated for an expedited development or review program and, if so, the scientific basis for that designation. For orphan-designated drugs, in addition to disclosing the name of the drug and its proposed indication, the group recommended the FDA disclose the name of the sponsor and the epidemiologic basis for the designation.
- Disclose written requests for pediatric studies under the Best Pharmaceuticals for Children Act at the time such requests are made, as well as other documents indicating agreement on changes to the initial request.
- Make public its clinical and statistical reviews pertaining to products that are not approved or for which the marketing applications are abandoned or withdrawn. The group added the agency should issue guidance on the definition of abandonment.
- Make its pooled data sets, masked and de-identified as appropriate, and the FDA’s analyses of the data sets, available to the medical and research community through clinical data repositories, such as the National Institutes of Health Biologic Specimen and Data Repository Information Coordinating Center.

**Correcting ‘Misleading’ Information**

The report also said the FDA should correct misleading information that is released in the market. The working group noted “the problem of misleading or inaccurate claims made by manufacturers may grow worse as a result of a recent appellate court decision that used the First Amendment protection of commercial speech as a justification for giving broader deference to companies to make statements about non-FDA-approved uses of available products.”

The report added, “Companies have wide latitude to characterize data submitted to FDA or their engagement with the FDA without the risk that FDA will correct the record. Under current regulations, FDA has the authority to correct such misconceptions only when doing so allows the agency ‘to pursue its regulatory activities without disruption.’ In practice, FDA rarely takes such action.”
The Blueprint recommended the FDA establish a standard for correcting misleading information “where there is the potential for substantial confusion about the safety and efficacy of the medical product for both approved and unapproved uses. The agency should retain the ability to provide disclosures under additional circumstances vital to public health. To the extent feasible, FDA should provide advance notice to companies. FDA should also disclose the scientific basis for its concerns, where possible,” the report said.

The working group noted there were three relevant policy questions regarding the FDA’s ability to correct misinformation.

“The first is whether the agency should adopt a basic set of standards for when to correct misinformation in the market. The advantage of doing so is to facilitate agency engagement when needed, without the worry of potential precedent set by each case. The agency might consider adopting a standard based on whether the information has the potential to cause significant confusion in the medical community and among patients about the safety or efficacy of a medical product for approved or unapproved uses. Even with such a standard, FDA should retain the authority to release information under other circumstances vital to public health,” the group said.

The second question is whether the FDA should give advance notice to the company regarding any concerns. “While this is reasonable as a matter of practice, FDA must remain able to move quickly to protect patients in response to urgent public health needs. An opportunity to provide advance notice should not lead to unnecessary delay,” the group said.

The third question is whether the FDA should disclose the scientific information that is the basis of its concern about misinformation in the market. “Doing so would facilitate greater understanding of the agency’s position,” the group concluded.

**Concerns Raised**

The working group noted that one objection to the recommendations is that greater transparency will undermine the business case for innovation. “The concern is that if information or analysis related to one company’s products is available to help competitors, there is less likelihood that the company will proceed in the first place,” the report said. The group contended that “basic information about the regulatory process is already broadly available through proprietary databases; FDA disclosure will create a level playing field and improve access to information for the public. Greater disclosure of FDA analysis and decision-making will help inform companies about what it takes to be successful with the agency.”

In addition, the report said “targeted disclosures to correct misinformation are necessary to avoid market confusion. In other recommendations, we have paid special attention to the nature and timing of disclosures to minimize the risk that may be of greatest concern to manufacturers. For example, we recommend releasing only information about clinical holds and Special Protocol Assessment provisions on safety and efficacy, not other topics that are more likely to touch on actual trade secrets. Our recommendation on release of scientific data submitted by companies for clinical studies focuses on those where sponsors have not already made their data available by other means.”

The group added a related objection concerning the potential disclosure of non-approval documents, such as Complete Response Letters. “Companies that fail once but plan to try again may consider release to be premature. Yet at this early stage, for innovator drugs, patent and data exclusivity protections still apply. The release of the letter serves to inform patients, doctors, investors and others of the regulatory status of the product and to help
researchers understand the potential limitations that need to be overcome in creating safe and effective alternative products,” the report said.

Transparency Could Be Costly

The group also noted that “transparency can be costly, and, if misapplied, can unnecessarily slow down regulatory decision-making. Most of our recommendations regarding transparency involve public dissemination of products that FDA has already created and that clearly do not involve trade secrets or data that can lead to identification of patients (such as complete response letters or de-identified secondary databases), or basic information about regulatory milestones that should involve minimal resources.”

However, some of the recommendations would require more effort and resources on the part of the FDA. “The most challenging are those that involve disclosure of large amounts of scientific data from clinical trials. These files are extremely large, and special care must be taken to protect patient privacy. In addition, based on comments submitted to FDA to date, it is likely the agency would face legal challenges from manufacturers to such disclosures. While our view is that such challenges would not have legal merit, the legal process could be burdensome on the agency,” the report said.

“If the FDA agrees to take up these costlier recommendations, it should move forward with sufficient funding and with the legal support of the Administration and Department of Justice,” the report said.

Another concern is that the FDA “would go beyond our recommendations and disclose too much information. Our recommendations are for the agency to set clear policies in these areas, and not make ad hoc transparency determinations.”

There is also concern about patient privacy. “Patient privacy objections are most salient in the context of datasets with patient-level information and Clinical Study Reports. The report recommends that FDA permit the online release of redacted Clinical Study Reports, similar to the redacted Clinical Study Reports that are produced in response to Freedom of Information Act requests,” the report said. Redacted Clinical Study Reports remove any identifying information about specific patients, including the part of the ID number that would reveal the site of the study.”

The group also noted the report recommends the FDA release redacted data sets using National Institutes of Health guidelines and publish them through an existing federal repository. “Any repository adopted for this purpose should employ safeguards to promote the sharing of clinical research data to advance science and improve public health and healthcare; promote the responsible conduct of research; ensure good stewardship of clinical research data; and protect the rights of research participants. For instance, before releasing data, the repository should verify the research proposed would advance science or improve public health and healthcare, check institutional status, and create legally enforceable agreements that ensure applicants will not compromise patient identity,” the report said.


Other Recent Developments in the Guide to Good Clinical Practice

European Group Recommends Changes to Trial Regulations

U.K. Gives Guidance on Common Application Errors
ASCO Issues Five Recommendations to Enhance Utility of Observational Cancer Research