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Data Integrity Key to GMP Compliance

FDA demands accurate manufacturing and test information to ensure product quality.

Sep 02, 2014
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Pharmaceutical Technology
Volume 38, Issue 8

It may seem to some members of the biopharmaceutical manufacturing community that incomplete records and faulty documentation are much less serious than contaminated facilities and unsafe products. But to FDA officials, data that are not valid and trustworthy is a sign that an entire operation or facility is out of control and cannot assure the quality of its medicines. As FDA struggles to devise a more targeted, risk-based approach to overseeing the vast, global network of pharmaceutical ingredient suppliers and manufacturers, agency officials find themselves hampered by unreliable industry information.

New mandates to attain parity in inspection of foreign and domestic facilities further complicates the picture by expanding FDA oversight to many firms less familiar with US standards. As erroneous and fraudulent records continue to surface during plant inspections and in submissions filed with the agency--despite years of warning letters criticizing such infractions--FDA leaders are ramping up the rhetoric to compel manufacturers to clean up data operations.

A lack of data integrity often is “just fraud,” says Howard Sklamberg, FDA deputy commissioner for global regulatory operations and policy. FDA relies on company information documenting adherence to cGMPs, he explained at a July conference on “Understanding cGMPs” sponsored by the Food and Drug Law Institute (FDLI). Yet almost all recent warning letters cite evidence of altered and falsified records. If data are “knowingly incorrect, we take that very seriously,” Sklamberg stated, expressing dismay that some manufacturers still fail to remedy record-keeping problems despite repeated warnings from the agency.

Sklamberg anticipates more prosecution of data integrity issues to deter violative behavior. FDA aims to make biopharmaceutical companies that hide manufacturing data discrepancies and that display a lack of integrity in regulatory programs and policies “increasingly uncomfortable,” said Thomas Cosgrove, acting director of the Office of Manufacturing and Project Quality (OMPQ) in the Office of Compliance (OC), Center for Drug Evaluation and Research (CDER). In addition to warning letters, inaccurate and unreliable data can expose a firm to product seizures, import alerts, and broader injunctions, he explained at the FDLI conference.

The most serious data breaches are handled by FDA’s Office of Criminal Investigation (OCI) in the Office of Regulatory Affairs (ORA), which manages the agency’s 1800 investigators and some 200 OCI special agents. FDA will perform extensive audits and impose penalties, which can be more expensive to a firm than “getting it right the first time,” Cosgrove observed.

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High quality data also are “a very big issue” related to medical product imports, which are rising exponentially, commented Douglas Stearn, director of enforcement and import policy at ORA. He noted that dealing with poor data slows down FDA operations and thus imposes a visible cost on the agency. “We’re looking at that very closely,” he said.

Not just India

Data integrity issues have always existed, but now FDA is doing more to uncover the evidence of such problems, acknowledged Carmelo Rosa, director of OMPQ’s Division of International Drug Quality. FDA is training investigators to better detect signs of data problems and is looking more closely at international facilities for signs of altered and doctored records.

But it’s “not only India” that is experiencing these problems, said Rosa; data integrity issues have surfaced in all regions. A July 2014 warning letter, for example, cited Italian API producer Trifarma S.p.A. for deleting key test data and failing to establish systems to identify how and when changes are made in manufacturing records. Tianjin Zhogan Pharmaceutical Co. in China received a warning letter in June citing inadequate records of manufacturing and cleaning operations (1).

Certainly, many of the most egregious data integrity transgressions have surfaced at Indian API facilities. From mid-2013 to mid-2014, seven Indian manufacturers received warning letters referencing the integrity of their records, procedures, and interactions with FDA investigators, according to a report by International Pharmaceutical Quality (IPQ) (2). Wockhardt Ltd. was cited in July 2013 for multiple GMP violations, including

efforts to cover up faulty and incomplete anti-microbial studies, stability protocols, and batch testing. Ranbaxy Laboratories recently was hit by an import ban on two facilities in India, culminating in a series of enforcement actions following the discovery of widespread falsification of data and test results more than five years ago.

Drug makers should not look to contract manufacturers to reduce their responsibility for data accuracy and reliability, Rosa noted at the July CMC Workshop on “Effective Management of Contract Organizations” sponsored by CASSS. Some biopharma companies regard contract testing and production operations as one way to alleviate their involvement in inspections and dealings with regulatory authorities. But Rosa emphasized that the licensed manufacturer remains responsible for products meeting all quality standards and noted that FDA and other authorities are looking closely at all facilities, including CMOs.

To document that manufacturing processes comply with GMPs, biopharmaceutical companies are required to retain complete and accurate production information and to make that available to FDA inspectors, explained OMPQ branch chief Alicia Mozzachio at the FDLI conference. She observed, however, that agency investigators continue to uncover multiple data integrity issues: failure to record activities contemporaneously; document back-dating; copying existing data as new information; re-running samples to obtain better results; and fabricating or discarding data. Parexel Vice-President David Elder cited recent FDA warnings letters that refer to “unofficial testing” and “trial” analysis of samples until the data come out right and evidence that records are signed by company personnel absent from work that day.

Rosa added that field inspectors encounter employees who admit to falsification of records and that certain operations were not performed as recorded. When FDA uncovers such discrepancies at one company site, Mozzachio said, that becomes a “red flag” for FDA to look closely at records and practices at a firm’s other manufacturing facilities.

Key indicators

Data integrity matters because properly recorded information is the basis for manufacturers to assure product identity, strength, purity, and safety, Elder pointed out. Frances Zipp, president of Lachman Consultants, observed that data integrity has become a main focus of FDA inspections, as agency audits aim to determine how well company management monitors sites and ensures the “rigor and effectiveness” of global compliance. Evidence of misrepresented data or problems with batch records found during a preapproval inspection is a prime factor leading to delays in market approval.

Inaccurate manufacturing data, moreover, threatens to undermine FDA efforts to streamline regulatory processes, which is of particular concern to agency leaders. Cosgrove explained that FDA is working hard to establish systems for targeting inspections to more high-risk products and operations. The aim is to focus agency resources on the greatest sources of risk to patients, while also reducing oversight of firms with “robust quality systems,” which, he said, then may benefit from “less interference from FDA.”

But for such a strategy to work, the data that FDA receives “must be real,” he stated. Cosgrove voiced particular dismay over company executives and attorneys who “shade the facts” and that resulting integrity issues can “have consequences.”

References

1. Warning Letter to Tianjin Zhogan Pharmaceutical Co [5]., WL: 320-14-09 (June 10, 2014),
2. International Pharmaceutical Quality [6], Apr. 28, 2014. PT

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