

Trends in FDA Good Manufacturing Practice Warning Letters

Recent US Food and Drug Administration warning letters provide clues to pharmaceutical companies about how they can enhance their quality systems, improve their manufacturing processes and more effectively manage future FDA establishment inspections, say *Rob Church* and *Steve Mahoney*.

In the past 12 months, the US Food and Drug Administration has issued more than 25 warning letters to manufacturers of finished pharmaceuticals and active pharmaceutical ingredients for violations of the current good manufacturing practice regulations. A detailed review of these letters provides a number of useful insights into where the FDA is currently focusing its limited GMP enforcement resources, and where the agency may start to place greater emphasis in the future.

Some key messages from the GMP warning letters include the following:

- the FDA issued the large majority of GMP warning letters (approximately 80%) to domestic facilities, notwithstanding the many concerns that have been raised in the past year about the increasingly global nature of pharmaceutical manufacturing;
- the FDA issued a similarly large majority of GMP warning letters to finished product manufacturers – rather than API manufacturers – again highlighting the fact that the FDA is still primarily focused on final production instead of the global supply chain for pharmaceutical manufacturing;
- several GMP warning letters incorporated other compliance issues, including allegations of unapproved new drugs, misbranded drugs¹, promotional issues^{2,3} and pharmacy compounding⁴, which demonstrates that the FDA is taking a more holistic approach to enforcement when it identifies violative conduct;
- the letters that we reviewed show that the FDA is taking a more systemic and risk-based approach to assessing GMP compliance and paying particularly close attention to such areas as the quality control unit, manufacturing process validation and laboratory out of specification (OOS) test results and investigations. Recent FDA guidance also reflects this regulatory focus⁵⁻⁸; and
- virtually all GMP warning letters address the inadequacies of the company's reaction to inspectional observations, which serves as an important reminder of the necessity for a company to submit a high quality response to the FDA that demonstrates its commitment to implement aggressive corrective action in response to the inspectional observations.

The FDA has issued more than 25 warning letters for cGMP violations in the past 12 months

The FDA is taking a more systemic and risk-based approach to assessing GMP compliance

We believe that pharmaceutical companies, by carefully assessing FDA GMP warning letters from the past year, can enhance their quality systems and improve their manufacturing processes, and, therefore, more effectively manage future FDA establishment inspections.

Background on the FDA's GMP regulations

Although the FDA finalised the GMP regulations for finished pharmaceuticals over 30 years ago, the agency requires the pharmaceutical industry to produce human drug products using current manufacturing standards, specifications and technologies⁹.

Rather than explicitly codifying its current GMP expectations into regulations, which would require frequent amendments to those rules, the FDA relies on a number of less formal communications to publicly disseminate its evolving expectations, including guidance documents and warning letters¹⁰. Consequently, when trying to achieve sustainable manufacturing compliance, a company should routinely evaluate recent guidance documents and warning letters to understand the agency's current thinking on GMP.

Based on our review, we believe that the following areas of GMP compliance merit special attention by pharmaceutical manufacturers.

The FDA relies on less formal communications to disseminate its expectations on GMP

Global supply chain and vendor qualification

Notwithstanding the fact that in the past year the FDA's GMP enforcement was still primarily directed at US-based manufacturers of finished pharmaceuticals, we believe that this trend will start changing in the near future and that the agency will dedicate a larger portion of its resources to international inspections.

Robert Church is a partner at the international law firm Hogan & Hartson; he works out of the Los Angeles and San Francisco offices. **Stephen Mahoney** is an associate at Hogan & Hartson, based in Washington, DC. Mr Church is a former FDA associate chief counsel for drugs and Mr Mahoney is a former compliance officer in the FDA's Center for Drug Evaluation and Research.

It is expected that the FDA will scrutinise how domestic manufacturers qualify international suppliers

In fact, the FDA has already announced that, as part of its "Beyond Our Borders" initiative, it will establish offices overseas in countries like China, where the agency believes that closer working relationships with its counterpart regulators will be beneficial¹¹.

Recognising that the FDA will have limited resources to devote to international inspections even with inspectors based overseas, we anticipate that the agency will more carefully scrutinise how domestic manufacturers qualify their international suppliers. The following observation from a 2008 warning letter¹² serves as an example:

Your vendor qualification program should provide adequate evidence that the manufacturer can consistently provide reliable and safe materials. Suppliers should be monitored and regularly scrutinised to assure ongoing reliability. It is your responsibility to ensure that raw materials received are suitable and approved by the quality unit prior to use.

More recently, the FDA warned a Chinese API manufacturer and its subcontractor about the inadequate systems they had in place to ensure the safety of raw materials used in their manufacturing of heparin sodium^{13,14}. As a result of these GMP deficiencies, and broad concerns with the reliability of information generated at each facility, the FDA placed materials imported from each facility on import alert, thereby refusing those materials admission into the US¹⁵.

Bundling GMP enforcement with other violations

As noted above, the FDA appears to have become more aggressive in its use of GMP warning letters to notify drug companies about violative conduct in other areas of their business. In some cases, the agency has alerted companies that some of their products lack the necessary FDA approvals. In others, the agency has raised concerns about a company's promotional activities. In other cases still, the FDA has notified companies that they are violating FDA's pharmacy compounding rules.

We fully expect this trend to continue in the future. As the agency continues to face an increasingly large number of enforcement priorities with limited resources, we believe that this "bundling" approach to enforcement will become more common. In addition to the areas of enforcement listed above, we think it is extremely likely that the FDA will focus on pharmacovigilance systems and adverse event reporting during future GMP inspections. This is especially true in light of the agency's heightened sensitivity to drug safety.

The "bundling" approach to enforcement is likely to become more common

Quality systems

We identified references to deficient quality systems in virtually every GMP warning letter that we reviewed. The following quotations from recent warning letters illustrate the FDA's concern in this area.

[The observed GMP deficiencies are] indicative of your quality control unit not fulfilling its responsibility to assure the identity, strength, quality and purity of your manufactured product¹⁶.

Please explain why your firm's Quality Control Unit (QCU) did not detect and document these deficiencies during their batch production and control and what actions will be taken to assure these deficiencies do not extend to other batches of the same or other drug product¹⁷.

Failure to conduct investigations in a timely manner and to extend the investigations to other drug products that may have been impacted by the same failure while investigations of confirmed cross-contamination (without a probable root cause identified) were ongoing demonstrate the failure of your QCU to provide adequate oversight and ensure procedures are followed¹⁸.

These passages underscore the critical role that quality control units play in pharmaceutical manufacturing and how closely the FDA monitors their performance.

Effective regulatory management

Virtually all GMP letters address the inadequacies of the company's inspection response

As noted above, virtually all GMP warning letters from the past year address the inadequacies of the company's inspection response. While there are a variety of acceptable ways to respond to an inspection observation, we have seen many examples of inspection and warning letter responses that fail to adequately address the FDA's concerns.

Given the potentially significant consequences of GMP non-compliance, we strongly encourage our clients to make every effort to ensure that their written responses demonstrate a commitment to manufacture high-quality drug products and to implement aggressive corrective action as part of a robust pharmaceutical quality system.

This article was originally published in Hogan & Hartson's Pharmaceutical and Biotechnology Update, 22 April 2009.

References

1. FDA warning letter to Deltex Pharmaceuticals Inc, 31 October 2008, www.fda.gov/ICECI/EnforcementActions/WarningLetters/2008/ucm1048079.htm
2. FDA warning letter to Cascadia Manufacturing, Inc, 6 August 2008, www.fda.gov/ICECI/EnforcementActions/WarningLetters/2008/ucm1048190.htm
3. FDA warning letter to Omega Tech Labs, 21 October 2008, www.fda.gov/ICECI/EnforcementActions/WarningLetters/2008/ucm1048091.htm
4. FDA warning letter to Civic Center Pharmacy, 16 December 2008, www.fda.gov/ICECI/EnforcementActions/WarningLetters/2008/ucm1048048.htm
5. FDA Guidance for Industry – Q10 Pharmaceutical Quality System, April 2009, www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073517.pdf
6. FDA Guidance to Industry: Quality Systems Approach to Pharmaceutical CGMP Regulations, September 2006, www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070337.pdf
7. FDA Guidance for Industry – Process Validation: General Principles and Practices, November 2008, www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070336.pdf
8. FDA Guidance for Industry: Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production, October 2006, www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070287.pdf
9. See 21 U.S.C. 351 and 21 C.F.R. 210-211.
10. FDA website, www.fda.gov
11. FDA Consumer Health Information, FDA Beyond Our Borders, 9 December 2008, www.fda.gov/consumer/updates/beyondborders120908.pdf
12. FDA warning letter to Changzhou SPL, China, 23 April 2008, www.fda.gov/ICECI/EnforcementActions/WarningLetters/2008/ucm1048332.htm
13. FDA warning letter to Qingdao Jiulong Biopharmaceuticals Co. Ltd, China, 14 April 2009, www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm136670.htm
14. FDA warning letter to Shanghai No. 1 Biochemical & Pharmaceutical Co. Ltd., China, 14 April 2009, www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm136668.htm
15. See 21 U.S.C. 381(a)
16. FDA warning letter to Catalent Pharma, 28 March 2008, www.fda.gov/ICECI/EnforcementActions/WarningLetters/2008/ucm1048356.htm
17. FDA warning letter to Ranbaxy Laboratories, India, 16 September 2008, www.fda.gov/ICECI/EnforcementActions/WarningLetters/2008/ucm1048133.htm
18. FDA warning letter to Caraco Pharmaceutical Laboratories, 31 October 2008, www.fda.gov/ICECI/EnforcementActions/WarningLetters/2008/ucm1048080.htm

Copyright

Under internationally accepted copyright legislation, the subscriber is not allowed to copy copyright materials, such as *The Regulatory Affairs Journal – Pharma*, except in certain circumstances, e.g. you may make a single copy of one article per periodical issue for research or private study. If you photocopy the whole or part of an issue of *The Regulatory Affairs Journal – Pharma* in order to avoid subscription fees, for example, the subscriber is in breach of the law and could be successfully prosecuted. Please contact the publisher for details of fees to cover your copying needs. Alternatively, you may obtain a licence from the Copyright Licensing Agency (90 Tottenham Court Road, London W1P 9HE, UK), or from rights organisations in other countries, which will enable you to make limited numbers of copies for business purposes.

Reprints

Reprints of articles published in *The Regulatory Affairs Journal – Pharma* are available for use as training and promotional materials, inserts for direct mail, public relations literature and sales support materials. Discounts are available for bulk orders.

For details, contact **Advertising Sales, Regulatory Affairs Journals**, Informa Healthcare (Tel: +44 (0)20 7017 6785, E-mail: advertise@informa.com).

Circulation

The subscriber is reminded that it is a condition of sale of *The Regulatory Affairs Journal – Pharma* that you circulate it only to members of staff working at the site to which it is sent. Please contact the publisher for details of special arrangements for purchasing multiple copies for domestic and international circulation.

The Publisher

