

Pharmaceutical Outsourcing: Maintaining Quality, Reducing Risk

Approximately 80 percent of drugs sold in the United States are produced wholly or in part in India and China. This increasing globalization of the drug industry has lowered ingredient prices for pharmaceutical and biotechnology firms. However, inconsistencies in the quality of imported materials, especially with respect to the active pharmaceutical ingredients (APIs) that produce a medication's desired medicinal effect, have raised public and governmental concern. (For more information about the background and scope of pharmaceutical outsourcing, see Patricia Van Arnum's "The Anatomy of the Changing Supply Chain," cited on page 6.)

The growing utilization of imported materials and products – some of which may not meet agreed-upon specifications – has significantly complicated supply chain management for domestic manufacturers and increased the risk of contamination, mislabeling and substitution. Problems with imported pharmaceuticals have been documented by a variety of reliable sources.

The following well-publicized events exemplify the quality control problems involving outsourced ingredients that have emerged in recent years:

- **2008:** Heparin manufactured in China for the U.S. market was contaminated with over-sulfated chondroitin sulfate (OSCS), causing allergic reactions, elevated blood pressure and death.
- **2007:** Chinese-made toothpaste sold in the U.S. contained diethylene glycol (DEG), a toxic substance used in antifreeze that can cause death.
- **2006:** Cold medicine sold in Panama and manufactured in China contained DEG.

Although the need for quality control of overseas pharmaceuticals and ingredients is increasing, the U.S. Food and Drug Administration (FDA) has acknowledged it can no longer be relied upon to ensure adherence to U.S. quality requirements. (See "Changing Regulatory Strategies," this page.) In view of the limited FDA resources available for global oversight, the pharmaceutical industry must be prepared to adopt best practices aimed at monitoring the safety and quality of imported products and materials.

This issue of *ALERT Bulletin* offers suggestions for improving quality control and decreasing risk exposures for companies that import APIs. In addition to presenting regulatory and legal requirements, it offers ways to minimize risk by examining and refining policies and procedures in such areas as due diligence, on-site management, contracts and quality control.

The recommendations noted herein are drawn from a review of expert opinions in this area, as well as identified resources. They are designed to help you improve your overall risk posture by effectively managing your company's compliance with published good manufacturing practices (GMPs), good distribution practices (GDPs) and good supply practices (GSPs).

Changing Regulatory Strategies

Historically, U.S. authorities have primarily relied on border intervention for interception of unsafe goods. However, recent scandals have revealed the limitations of this approach when applied to the burgeoning market for imported pharmaceutical materials. In 2007, the federal government established the Interagency Working Group on Import Safety to develop new protective strategies and tactics. In November 2007, the group issued its "Action Plan for Import Safety," followed by a 2008 update. (See citations, page 5.)

The steps outlined in the "Action Plan Update" illustrate a major shift in the U.S. government's approach to import safety. The new, more proactive strategy calls for regular and vigorous contact with trading partners to ensure that quality control processes are built into every step of a product's life cycle. It seeks to focus regulatory attention and resources upon critical points in the manufacturing process, where the risk level is highest.

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Regulatory Framework and Resources

Reducing product liability risks associated with outsourced API and other materials requires consistent, documented adherence to best practices, which are developed by recognized experts and subject to peer review. Prior to working with overseas manufacturers, review the reports and guidelines published by the European Chemical Industry Council (CEFIC), the FDA and other U.S. regulatory entities, and the World Health Organization (WHO).

Important CEFIC practice and guidance documents (available at <http://apic.cefic.org/publications/publications.html>) include

- "Good Manufacturing Practices for Active Ingredients Manufacturers," 1996
- "Quality Management System for Active Pharmaceutical Ingredients: Integrating GMP into ISO 9001," 1997
- "Manufacture of Sterile Active Pharmaceutical Ingredients," 1999
- "Cleaning Validation in Active Pharmaceutical Ingredient Manufacturing Plants," 1999
- "GMP in Active Pharmaceutical Ingredients Development," 1999
- "Guidance on Aspects of Cleaning Validation in Active Pharmaceutical Ingredient Plants," 2000
- "Quality Management System (QMS) for APIs," 2005
- "GMPs for APIs: 'How to Do' Document, Interpretation of the ICH Q7a Guide, Version 5," 2006
- "The Audit Programme," 2008
- "Auditing Guide," 2008

U.S. regulatory and guidance documents include, among others:

- "Guidance for Industry: Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients," 2001. Published by the FDA under the auspices of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (abbreviated as ICH). Available at www.fda.gov/cder/guidance/4286fnl.htm. (Last accessed 11/18/2008.)
- "Q3A: Impurities in New Drug Substances," 2008. Published by the FDA and ICH. Available at <http://www.fda.gov/cber/gdlns/ichq3a.htm>. (Last accessed 11/18/2008.)
- "Questions and Answers on Current Good Manufacturing Practices, Good Guidance Practices, Level 2 Guidance, Production and Process Controls," updated 2008. Published by the FDA. Available at <http://www.fda.gov/cder/guidance/cGMPs/production.htm>. (Last accessed 11/18/2008.)
- "Amendments to the Current Good Manufacturing Practice Regulations for Finished Pharmaceuticals," 2008. Available at <http://www.fda.gov/OHRMS/DOCKETS/98fr/E8-20709.pdf>. (Last accessed 11/18/2008.)
- "Good Storage and Shipping Practices." *Pharmacopeial Forum*, Volume 30(6), pg. 2118. Available at http://www.pharmacopoeia.com.cn/v29240/usp29nf24s0_c1079.html. (Last accessed 12/10/2008.)

Pertinent WHO documents include

- "Good Distribution Practices for Pharmaceutical Products." The Fortieth WHO Expert Committee on Specifications for Pharmaceutical Preparations, Geneva. WHO Technical Report Series, Number 937, Annex 5, 2006. Available at http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf#page=191. (Last accessed 11/18/2008.)
- "Good Distribution Practices for Pharmaceutical Products Including Measures Against Penetration of Counterfeits into the Legitimate Supply Chain." Proposal for Revision of WHO Version 9, December 13, 2007, Geneva. WHO Working Document QAS/08.252, January 2008. Available at http://www.who.int/medicines/services/expertcommittees/pharm_prep/GDP_counterfeits_QAS08_252_11012008.pdf. (Last accessed 11/18/2008.)

Establishing a Working Relationship

U.S. pharmaceutical corporations are held accountable under U.S. law for the quality and effectiveness of their end products, irrespective of ingredient provenance. Therefore, quality standards and processes of foreign companies must comply with both FDA and country of origin requirements, as well as applicable industry guidelines.

Prior to establishing any relationships with foreign suppliers, it is essential to have a company representative visit manufacturers in the country under consideration and review their operations. Then, begin the task of creating an international risk and quality control framework by retaining the services of a regulatory compliance consultant with extensive work experience who is from the country of origin.

To be most effective, this business partner, at a minimum, should

- **reside in the manufacturing country** and be fluent in its language
- **possess an understanding and appreciation of the culture** of the country of origin
- **operate independently, objectively and freely** in the manufacturing country
- **willingly verify his or her references** to your organization and be interviewed in person

Significant legal issues to address when creating relationships with international suppliers include

- **identifying pertinent international regulatory filing requirements**, which may differ from the GMPs and GDPs as defined by Q7A (See citation, this page.)
- **requiring that suppliers of APIs and outsourced materials have current foreign certification**, as required by local law
- **ensuring that national and international regulatory filing requirements are current** and accurately reflect recent operational changes

By preparing partners to maintain a state of continuous and perpetual readiness for FDA inspections, you can help ensure quality and assuage regulatory concerns. This involves

- **establishing a stability sample testing program** at predefined intervals and maintaining complete records of related data
- **proactively identifying, addressing and documenting possible solutions for potential deficiencies** related to storage and inventory management processes
- **verifying cleaning records** for equipment used in manufacturing operations
- **confirming “real-time” presence of overseas employees** who sign testing verification logs

Due Diligence

Misrepresentations by foreign suppliers have been a recurring issue. Examples may include a trading company falsely claiming to operate its own factory, and a chemical company posing as a pharmaceutical manufacturer, operating under less stringent standards. To counteract these risks, due diligence must be conducted before entering into relationships with overseas vendors. Allocate sufficient time and resources to the process, which may involve the following steps:

- **Develop the Request for Proposal**, including essential elements to be verified, such as
 - compliance expectations regarding applicable regulations and designated guidelines
 - proof of financial responsibility for potential liabilities associated with the goods or services to be provided
 - certificate of valid and collectable product liability insurance, underwritten by a company carrying an AM Best rating of A- or better
 - copies of inspection reports by local and FDA inspectors for the last three years, indicating whether such inspections have been conducted on a regular basis
 - applicable certifications from licensed testing agencies
 - verifiable vendor references
 - listing of alternative suppliers to prevent shortages in the event of a business interruption
- **Determine if potential partners are certified** by both the FDA and comparable agencies in the country of origin.
- **Question and evaluate overseas manufacturer representatives about their understanding of U.S. regulatory requirements** and basic quality control measures.
- **Review manufacturing, distribution and storage standard operating policies (SOPs)** in light of regulatory requirements.
- **Inquire about staff turnover** to ascertain vendors' ability to fulfill regulatory and performance expectations.
- **Assess whether the overseas manufacturers' leadership team and quality control staff can present and articulate their actions and intent in a constructive manner** if the organization becomes subject to regulatory or legal action.

On-site Management

A successful relationship with a foreign supplier depends upon the ability of the U.S. company to conduct business in a manner consistent with prevalent business practices in the foreign country. Assuming that foreign companies will adopt U.S. business practices does not represent a prudent approach.

One of the most important recommendations offered is to station on-site in the overseas operations a loyal, full-time employee of your organization to direct and monitor the manufacturing and logistics of all ingredients and products intended for use in the U.S. This individual should have significant control over operations, be able to work within the culture, and be fluent in the local language and/or dialect. The following additional measures can also help strengthen the supply chain:

- **Minimize and consolidate the use of subcontractors** to enhance accountability and quality.
- **Provide training to suppliers in their native language** about the critical quality control processes required by your organization and U.S. regulatory bodies.
- **Ensure that an employee who is fluent in the local language and English accompanies auditing inspectors** from the FDA and foreign regulatory agencies.

Contract Language

Contracts between companies domiciled in different countries must be sophisticated and sufficiently flexible, recognizing legal and cultural differences. If a written contract is not possible, a written quality agreement must be in force. Often, the basic elements of a U.S. agreement may not comport with the regulations and cultures of other countries. For example, the use of contractual sanctions regarding breach of contract, such as withholding payment or incurring additional charges for delay, may not be effective in countries that place a higher value on rewards.

Significant controls that protect the interests of the U.S. company against liability and potential loss should be incorporated in such agreements. These may include contractual provisions that provide incentives for the overseas company to comply with the terms of the agreement and also impose appropriate consequences and sanctions with respect to breach of contractual terms and conditions. Where feasible, standard U.S. contractual provisions should be included in agreements with international vendors. Clear definitions of services to be provided, performance standards and pricing terms should be expressed.

Contract language should incorporate, at a minimum, the following safeguards:

- Specify your organization's right to perform unlimited, discretionary on-site audits and inspections at suppliers' and subcontractors' plants.
- Impose responsibility on the overseas manufacturer for reporting quality inspection results, infractions, recall notifications and negative evaluations by any regulatory agency if these events involve an ingredient or product to be purchased by your organization.
- Instruct overseas contractors and their subcontractors to include your company as an additional insured on their insurance policies.
- Retain the option to control defense counsel assignment in the event of litigation.
- Specify the jurisdiction in which disputes will be settled.
- Outline the dispute resolution mechanism, either through mediation or arbitration.
- Specify the procedure for supplier participation in product recalls.
- Warrant that overseas contractors' and their subcontractors' ingredients and products are in compliance with current GMP, GDP and GSP and satisfy local laws and regulations.
- Require that contractors and their subcontractors inform the U.S. company of any changes in the production of ingredients, prior to making said changes.
- Require the overseas entity responsible for internal and overseas transport and logistics of the product to provide a copy of an auditable quality control protocol.
- Require implementation of policies and procedures for authorizing procurement of products to ensure that these products meet agreed-upon specifications.
- Require implementation of releasing procedures in order to ensure that products and ingredients are obtained from approved suppliers and distributed by approved entities.
- Ensure that the ingredient manufacturer and its subcontractors and suppliers disclose pre-manufacturing agreements in writing, rather than standard purchase order agreements.
- Stipulate that contractors must notify the U.S. corporation if they are subcontracting any of their manufacturing processes.

Quality Control

Incoming ingredients and materials must be consistently monitored to ensure they are from approved sources, utilize the agreed-upon supply chain and are consistent with applicable GMP and GDP. Company-based effective quality control processes should be implemented scrupulously, especially in the absence of available FDA resources for global oversight. The following quality

control strategies – which may surpass standard guidelines and requirements – should favorably affect the resulting manufacturer's product quality:

- **Determine and document the initial source** of API production.
- **Purchase "raw" ingredients and other materials only from companies certified by the country of origin agency authorized to perform such certification.** Purchasing agreements should incorporate specifications approved by your organization's quality control unit.
- **Actively monitor day-to-day operations** and audit manufacturers randomly and frequently. Apply a "trust but verify" approach to ensure that certifications are current and that quality control practices are followed.
- **Randomly inspect storage areas** throughout the supply and logistics chain for suitability and condition.
- **Retain the right to trace each product and ingredient** and to perform authenticity checks.
- **Implement an obligatory "e-pedigree" program** that traces the ownership of specific batches and any associated transactions. Pedigree records should be accessible to all participants in the distribution chain.
- **Identify incoming materials before mixing them with existing stocks**, such as solvents or stocks in silos.
- **Inspect incoming ingredients and materials on a continuous basis** to ensure they are from approved sources and follow the agreed-upon supply chain.

Rigorous product testing is integral to the quality control process. The following guidelines can help ensure consistent compliance with specifications:

- **Perform complete analyses on at least three batches** before reducing in-house testing. These batch analyses should take place at appropriate intervals, and results should be compared with the certificates of analysis.
- **Audit the GMP compliance of active substance suppliers** on a random, statistically valid basis.
- **Require random batch testing and sampling of as close to 100 percent of the material as possible.** Recognize that regulatory authorities may request further information about a starting material if it is an API, or if it is only one or two manufacturing steps removed from an API.
- **Utilize discriminating analytical techniques**, such as fingerprint technologies and Near Infrared Spectroscopy, to check active ingredients against specifications. For each batch analyzed, look for deviations in manufacturing process and site.
- **Verify certificates of analysis** for reliability at regular intervals.
- **Maintain continuous and fluid quality controls.** Add new criteria regularly to preclude circumvention of traditional testing measures by suppliers.

When the supplier of a critical material is not the manufacturer or is subcontracting with another entity, ensure that the supplier and your organization know the supplier's name and address.

Apply the following quality control measures:

- **Minimize or limit the number of subcontractors** used for critical ingredients or manufacturing steps.
- **Require the contractor to notify you of any subcontracting matters** related to its manufacturing processes.
- **Require the manufacturer to submit evidence to you – such as past quality history and certifications** – that the supplier/subcontractor can consistently meet specifications.
- **Ensure that the name and address of the suppliers/subcontractors are known by the intermediate and/or API manufacturer** whenever the supplier of a critical material is not the manufacturer of that material.
- **Audit active substance suppliers** regarding GMP compliance on a random basis.

The FDA's commitment to targeted oversight of overseas pharmaceutical manufacturing is an encouraging development. Ultimately, effective quality and risk control will depend upon a combination of effective government regulation and efforts taken by domestic manufacturers to ensure compliance on the part of overseas suppliers. For more information about regulation of imported pharmaceutical materials, see the Resources section below.

Resources

Reference Documents

"Amendments to the Current Good Manufacturing Practice Regulations for Finished Pharmaceuticals." *Federal Register*, September 8, 2008, Vol. 73 (174). 21 CFR Parts 210 and 211 [Docket No. FDA-2007-N-0379] (formerly Docket No. 2007N-0280), Food and Drug Administration, Department of Health and Human Services. Action: Final rule. Available at <http://www.fda.gov/OHRMS/DOCKETS/98fr/E8-20709.pdf>. (Last accessed 09/22/2008.)

"Drug Safety: Preliminary Findings Suggest Recent FDA Initiatives Have Potential, But Do Not Fully Address Weaknesses in Its Foreign Drug Inspection Program." GAO Testimony Before the Subcommittee on Oversight and Investigations, Committee on Energy and Commerce, House of Representatives. Statement of Marcia Crosse, Director Health Care, April 22, 2008. Available at <http://www.gao.gov/new.items/d08701t.pdf>. (Last accessed 10/24/2008.)

"Drug Safety: Preliminary Findings Suggest Weaknesses in FDA's Program for Inspecting Foreign Drug Manufacturers." Government Accountability Office (GAO) Testimony Before the Subcommittee on Oversight and Investigations, Committee on Energy and Commerce, House of Representatives. Statement of Marcia Crosse, Director Health Care, November 1, 2007. Available at <http://www.gao.gov/new.items/d08224t.pdf>. (Last accessed 10/24/2008.)

"ICH Q10: Pharmaceutical Quality System." London, England: European Medicines Agency, 2008. Available at <http://www.emea.europa.eu/pdfs/human/ich/21473207en.pdf>. (Last accessed 10/24/2008.)

Statement of Andrew C. von Eschenbach, M.D., Commissioner of Food and Drugs, before Committee on Energy and Commerce Subcommittee on Oversight and Investigations, U.S. House of Representatives, on FDA's Foreign Drug Inspection Program, November 1, 2007. Available at www.fda.gov/ola/2007/foreign_drugs110107.html. (Last accessed 10/24/2008.)

Additional Articles, Reports and Documents

"Action Plan for Import Safety: A Roadmap for Continual Improvement." Report to the President from the Interagency Working Group on Import Safety, November 2007. Available at <http://www.importsafety.gov/report/actionplan.pdf>. See also the Action Plan Update at <http://www.importsafety.gov/report/actionupdate/actionplanupdate.pdf>. (Both last accessed 11/18/2008.)

"Agreement between the Department of Health and Human Services of the United States of America and the State Food and Drug Administration of the People's Republic of China on the Safety of Drugs and Medical Devices." FDA, Office of International Programs, December 11, 2007. Available at http://www.fda.gov/oia/agreements/China_Drugsdevices.htm. (Last accessed 09/23/2008.)

Bogdanich, W. "Chinese Chemicals Flow Unchecked onto World Drug Market." *New York Times*, October 31, 2007. Available at http://www.nytimes.com/2007/10/31/world/asia/31chemical.html?_r=1&oref=slogin. (Last accessed 11/18/2008.)

"The Changing Dynamics of Pharma Outsourcing in Asia: Are You Readjusting Your Sights?" PricewaterhouseCoopers, September 16, 2008. Available at <http://www.pwc.com/>. (Last accessed 09/25/2008.)

"China and the United States Signing Agreement on the Safety of Drugs and Medical Devices." Safe Food and Drug Administration, People's Republic of China, and U.S. Department of Health and Human Services, December 2007. Available at <http://eng.sfda.gov.cn/cmsweb/webportal/W43879541/A64025557.html>. (Last accessed 11/18/2008.)

"Drug Safety: Better Data Management and More Inspections Are Needed to Strengthen FDA's Foreign Drug Inspection Program." Report to Congressional Requesters, GAO-08-970. U.S. Government Accountability Office, September 2008. Available at <http://www.gao.gov/new.items/d08970.pdf>. (Last accessed 11/18/2008.)

"European Commission Plans Far-reaching Changes to GMP and GDP in the Fight Against Counterfeit Medicines." European Compliance Academy, *GMP News*, April 9, 2008. Available at http://www.gmp-compliance.org/eca_news_1147.html. (Last accessed 09/23/2008.)

"FDA Advises Consumers to Avoid Toothpaste from China Containing Harmful Chemical." *FDA News*, June 1, 2007. Available at <http://www.fda.gov/bbs/topics/NEWS/2007/NEW01646.html>. (Last accessed 11/24/2008.)

Gold, J. "Suing Chinese Companies Often Useless: Lawsuits on the Rise But Many Find Winning Damages Impossible." Associated Press, February 6, 2008. Available at <http://www.msnbc.msn.com/id/23034814/>. (Last accessed 09/22/2008.)

H.R. 5839: "Safeguarding America's Pharmaceuticals Act of 2008." Bill referred to the U.S. House of Representatives, Committee on Energy and Commerce, Subcommittee on Health, April 17, 2008. Available at <http://www.govtrack.us/congress/bill.xpd?bill=h110-5839>; (Last accessed 11/30/2008.)

Keitel, S. "A Question of Quality." *World Pharmaceutical Frontiers*, September 2008, pg. 21. Available at http://www.worldpharmaceuticals.net/editorials/014_sept08/WPF014_aquestion.pdf.

"Protecting American Consumers Every Step of the Way: A Strategic Framework for Continual Improvement in Import Safety." A Report to the President, Interagency Working Group on Import Safety, September 10, 2007. Available at <http://www.importsafety.gov/report/report.pdf>. (Last accessed 10/24/2008.)

Regulating Pharmaceuticals in Europe: Striving for Efficiency, Equity and Quality. Mossialos, E., Mrazek, M. and Walley, T., editors. Maidenhead, Berkshire, England: Open University Press, McGraw-Hill Education, 2004. Available online at <http://www.euro.who.int/document/E83015.pdf>. (Last accessed 09/22/2008.)

"Status Quo of Drug Supervision in China." Information Office of the State Council of the People's Republic of China, July 2008. Available at http://news.xinhuanet.com/english/2008-07/18/content_8567067.htm. (Last accessed 11/18/2008.)

Van Arnum, P. "The Anatomy of the Changing Supply Chain." *Pharmaceutical Technology*, August 1, 2008. Available at <http://pharmtech.findpharma.com/pharmtech/Ingredients/The-Anatomy-of-the-Changing-Supply-Chain/ArticleStandard/Article/detail/542000>. (Last accessed 09/22/2008.)

Van Arnum, P. "Outsourcing Practices Scrutinized by Congress." *PTSM: Pharmaceutical Technology Sourcing and Management*, August 6, 2008. Available at <http://pharmtech.findpharma.com/pharmtech/Outsourcing-Practices-Scrutinized-by-Congress/ArticleStandard/Article/detail/533228>. (Last accessed 10/24/2008.)

"WHO Expert Committee on Specifications for Pharmaceutical Preparations: Forty-first Report." WHO Technical Report Series, number 943, 2007. Available at http://whqlibdoc.who.int/trs/WHO_TRS_943_eng.pdf. (Last accessed 09/22/2008.)

Online Resources

European Medicines Agency (EMA) home page, at <http://www.emea.europa.eu>. (Last accessed 09/22/2008.)

FDA Imports and Inspections/International Regulatory Activities page, at <http://www.fda.gov/oia/impinsp.htm>. (Last accessed 09/22/2008.)

FDA International Cooperative Agreements listing, at <http://www.fda.gov/oia/default.htm>. (Last accessed 09/22/2008.)

Texts of Latin American and Caribbean legislation and regulations on pharmaceuticals, at http://www.temasactuales.com/laws_policies/legislation_Ph.html. (Last accessed 10/24/2008.)

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