Abstract: 52340

Preventing Shortages of Biologic Medicines

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INTRODUCTION

Drug Shortages Are a Growing Global Concern

- As of May 15, 2013, the US Food and Drug Administration (FDA) identified >130 ongoing drug shortages[1]
- Shortages may result in
  - Use of alternative medications/suppliers[2-5]
  - Drug rationing[4]
  - Delays of critical treatments[2-5]
  - Substitution with less efficacious and/or more expensive medications[3]
- Drug shortages and manufacturing quality are linked[6]
- The majority of current drug shortages are with generic small-molecule sterile injectable drugs[6]
  - Chemotherapy drugs
  - Anesthetics
  - Intravenous (IV) electrolytes
- The FDA lists ongoing shortages for several drugs including biologics[7]
  - Past biologic shortages have included essential medicines, such as factor VIII[8]

"Not every production disruption turns into a shortage, but virtually all shortages are preceded by disruptions in production." (p 170)

—Woodcock J, et al. *Clin Pharmacol Ther.* 2013;93:170-176

Could factors that contribute to shortages of small-molecule sterile injectable drugs also affect biologics?

OBJECTIVES

- To explore the root causes of reported manufacturing-related drug shortages
  - To relate these reports to the manufacture of highly complex biologic medicines
  - To discuss the quality systems required to avoid such shortages

METHODS

- Published reports in the US were reviewed to identify manufacturing-related issues that repeatedly led to drug shortages
- Manufacturing practices shared by small-molecule drugs and biologic medicines were analyzed
- Quality systems required to produce both drugs and biologics consistently were assessed
- Additional factors that may be important drivers for shortages in other jurisdictions were not analyzed

RESULTS

Drug Shortages: What is the Root of the Problem?

- Primary reasons identified for drug shortages
  - Repeated violations of current good manufacturing practice (cGMP) that led to at least 1 regulatory warning letter
  - Major failures in quality systems affecting raw materials, production, packing, and labeling that were observed either during an inspection or as a result of a major safety event

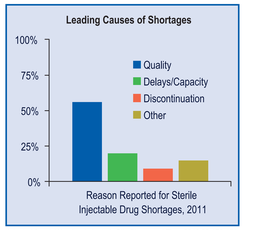
"…the fundamental problem is insufficient market reward for quality (including reliability of production) stemming from the buyers' inability to observe it. This in turn gives manufacturers strong incentives to minimize quality system investments…" (p 175)

—Woodcock J, et al. *Clin Pharmacol Ther.* 2013;93:170-176

Shortages of Injectable Drugs

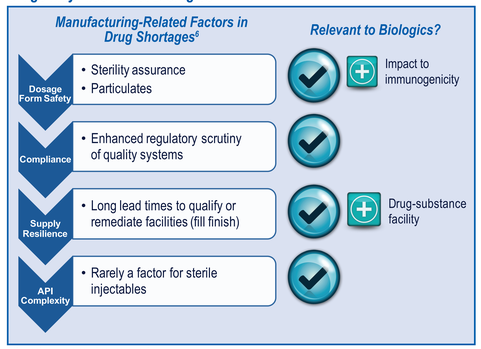
- A large proportion of shortages occur for generic sterile injectable drugs[6]
- Injectable drugs are especially susceptible to quality disruptions
  - Sensitive to contamination with adventitious agents or particulates
  - cGMP compliance inspections focus primarily on sterile formulation step

Shutdowns of manufacturing facilities by the FDA for noncompliance with cGMP have played a central role in shortages of injectable drugs.



Adapted from[6]: Woodcock J, et al. *Clin Pharmacol Ther.* 2013;93:170-176

Factors That Contribute to Shortages of Small-Molecule Sterile Injectable Drugs May Also Affect Biologics

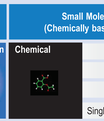


API = active pharmaceutical ingredient

Differences Between Small-Molecule Drugs and Biologics Increase Risks to Product Quality

- Biologics are more complex than small-molecule drugs[9-11]

		Biologics (Protein-based drugs)	Small Molecules (Chemically based drugs)
Properties	Size	Large	Small
	Structure	Complex	Simple
	Degradation Mechanism	Complex degradation	Precise and known
	Variability	Heterogeneous product	Single, defined structure
Manufacturing		Unique bank of living cells Unlikely to achieve identical copy	Predictable chemical & reagent reaction Identical copy can be made
Characterization		Many products well-characterized Correlation of structure-function elusive	Easy to fully characterize
Stability		Sensitive to storage and handling conditions	More stable
Immunogenicity		Higher potential	Lower potential



Manifestation of Manufacturing-Related Drug Shortages

- Escalation of FDA enforcement
  - Warning letter or untitled letter
    "You failed to establish adequate written procedures describing the handling of all written and oral complaints regarding a drug product"[12] —Montemurro A. PDA Chapter Meeting, May 2009
  - Consent decree and license revocation
    "Because this company continued to violate current good manufacturing practice regulations and falsify information on drug applications…"[14] —FDA News Release. January 25, 2012

Escalation of regulatory enforcement

Warning Signs of Manufacturing-Related Drug Shortages: The Regulatory Inspection Report

- Numerous and repeated regulatory observations are manifestations of an organization with reduced commitment to quality

Company	Inspection year	Number of observations found	Outcome
[redacted]	1997	139	Consent decree with FDA[a]
	1997	96	No regulatory action
	1997	107[b]	No regulatory action
	1996	87	Consent decree with FDA

[a]A consent decree of permanent injunction is a court-ordered action against a firm or individual, which either mandates corrective actions that must be taken or which prohibits the operation of the firm unless and until such actions are taken. [b]Thirty observations were found at [redacted] facility; 77 were found at its [redacted] facility.

From[13]: General Accounting Office. Blood Plasma Safety. GAO/HEHS-98-205. 1998; p 27

Regulatory observations of high severity

Bloomberg

[redacted] Drug Plant Shut by U.S. on Quality Issues

Drugs produced by [redacted] have been withdrawn about 40 times since 2002, reflecting "a continuing pattern of significant deviations from current good manufacturing practices," the U.S. Justice Department said in a statement. Among the medicines was [redacted] leukemia therapy, pulled in February 2012 because it may not have been sterile.

From[15]: Lopatto E. Bloomberg.com. January 31, 2013

Repeat regulatory observations

Biologics Quality in the Biosimilar Era

- Biosimilars will offer patients and providers additional treatment options[16]
  - May reduce the cost of therapy for off-patent biologics
  - Represent an opportunity to better manage factors that contribute to shortages of generic injectable products

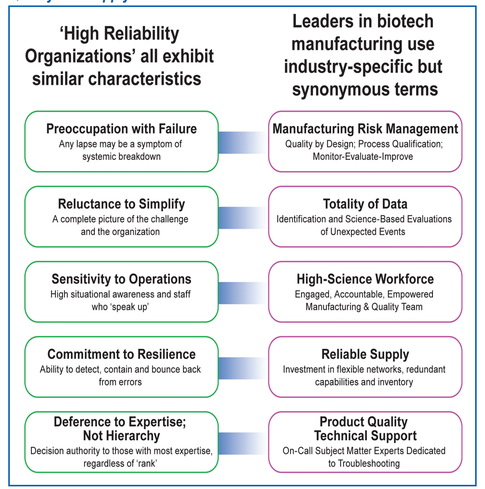
Manufacturers that can reliably produce safe biological drugs, including biosimilars, will be critical in ensuring continuous drug availability and uninterrupted patient treatment.

A Comprehensive Approach for Preventing Drug Shortages

Prevention	Technology	Inventory	Diversification
• Compliance with cGMP and a robust quality management system • Operational excellence – Right first time • Supply-chain security • Infrastructure investments • Business continuity planning	• Enhance product and process robustness • Greater focus on characterization • Investment in technology – NMR – High-temperature, short-time sterilization – Isolators	• Quantity of material • Stage of manufacturing • Storage location	• Implement backup manufacturing capabilities (diversification) • Enhance existing contract manufacturing capabilities

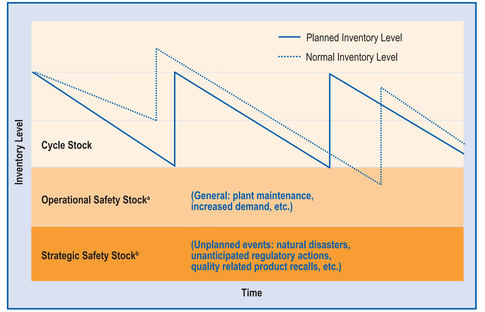
These 4 approaches are not mutually exclusive, and each has an impact on risk, cost, and flexibility.

High Reliability Organizations Manage Unexpected Events to Reduce Quality and Supply Risks[17]



From[17]: Grampp G, et al. *BioDrugs.* 2013:[Epub ahead of print].

Leading Biologics Manufacturers Maintain Sufficient Stock to Mitigate Shortages, Including Those Resulting from Unplanned Events

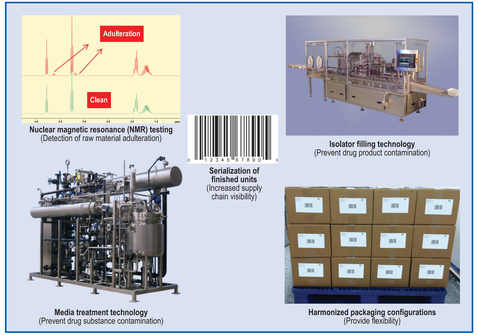


[a]American Production and Inventory Control Society industry standard methodology[18] was used to calculate appropriate level of operational safety stock using a 99.99% customer service level

[b]Strategic safety stock levels are set based on product supply risk assessment result (single vs dual-sourced, raw material supplier risks, etc)

From[18]: Mica A, et al. 17th Congress of the European Association of Hospital Pharmacists. 2012

Leverage Technology to Improve Robustness of Operations



Inventory Management as a Component of a Risk-Mitigation Strategy

- Inventory can be managed to prevent drug shortages in 2 primary ways
  - Better management of supply-and-demand variability (operational inventory)
  - Better management of a significant production interruption (strategic inventory)
    Just-in-time manufacturing leaves little margin of error to prevent drug shortages
- Product-specific standard operating procedures define inventory policy by stage of manufacturing
- Regular management reviews

Inventory targets should be set for each step in the supply chain.

CONCLUSIONS

- Shortages often result from violations of cGMP and failures in quality systems affecting raw materials, production, packing, and labeling
- Current market dynamics may not reward higher quality,[6] contributing to
  - Underinvestment in facilities and quality oversight by some generics manufacturers
  - cGMP deficiencies
  - Drug shortages
- To prevent similar shortages of biologics, manufacturers should
  - Implement adequate quality systems
  - Establish reliable supply chains, from raw materials to finished drug products
  - Focus on continuous improvements, including investments in technology
- Drug quality information could assist payers and prescribers as they assess manufacturers' ability to supply high-quality biologics reliably

Effective prevention of drug shortages requires a holistic and multifaceted risk management strategy.

ACKNOWLEDGMENT AND DISCLOSURES

- The authors acknowledge James Balwit, MS, whose work was funded by Amgen Inc., for assistance in preparing this poster
- Sundar Ramanan and Gustavo Grampp are employed by and own stock in Amgen Inc.

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