A Total Systems Meltdown Leads to Drug Shortages

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Worldwide, healthcare professionals and patients are experiencing shortages of oncogenic and other drugs. According to the United States Government Accountability Office, there were shortages of 220 finished drug products in 2011 (1). The US Food and Drug Administration’s coordinator of the Agency’s drug shortage program said that in 2010 54% of the shortages were due to quality or manufacturing issues (2). Drug shortages directly affect the patients who rely on these products. What has led to this potential crisis?

In the United States, closure of Ben Venue Laboratories’ (BVL) Bedford, Ohio facility is likely to exacerbate a shortage of Johnson and Johnson’s (J&J) Doxil that has persisted since the summer and has cut off treatment for many cancer patients. Approximately 2,700 people are on a J&J waiting list to receive the drug, which is used to treat ovarian cancer, multiple myeloma, and other cancers (3).

National Regulatory Agency (NRA) inspections performed at BVL’s Bedford facilities during 2011 resulted in the British and French authorities withdrawing product licenses (P/L) from several companies that used BVL as their contract-manufacturing source. BVL has been in business for more than 70 years as a contract manufacturing organization (CMO). Its Bedford facility specialized in the aseptic manufacture of many drugs, especially oncogenic drugs. BVL’s clients range from the largest multi-nationals to the smallest start-ups needing someone to make small batches of Phase II clinical trial supplies. BVL product was distributed and trialed and marketed by BVL clients around the world (4).

Examining what caused the closure of BVL’s Bedford facility and the apparent lack of good manufacturing practices (GMPs) followed by industry might give some insight on how the current drug shortage situation may have developed.

Timeline
A timeline of 2011 regulatory inspections at BVL shows that current company “troubles” began with a joint British Medicines and Healthcare Products Regulatory Agency (MHRA) and French Agence Francaise de Securite Sanitaire des Produits de Sante (AFSSAPS) inspection in January and February of 2011. This inspection found many points of concern with basic GMP compliance and serious issues involving aseptic product manufacture (in regards to EU GMPs–Annex 1; a document equivalent to FDA’s Guidance on Aseptic Processing [5]). The agencies advised BVL of their concerns, and through the FDA and MHRA Memorandum of Understanding, their inspection findings were shared with FDA. This gave FDA qualms about the quality of product made at the Bedford facility. Between May 2 and May 25, 2011, an FDA team inspected the facility performing an in-depth GMP compliance investigation. This investigation resulted in a 33-page FD-483 listing of inspectional observations, containing 46 different areas of concern about BVL’s aseptic process operations issued to the company’s president and CEO (6).

Problems
Areas of concern cited during this May 2011 inspection included the following:

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• Failure to identify the root cause, or implement corrective actions, involving the presence of stainless steel particles, in BVL products. FDA notes eight different client complaints on this matter covering 17 batches of products.
• Repeated failures to meet BVL’s own aseptic media fill (process simulation) criteria. One failure includes a BVL deviation report noting that “the media fill batch size is less than the batch size noted in the validation protocol,” but despite this notation the media fill was passed and deemed acceptable.
• BVL’s validation master plan specified the frequency of performing media fills, but the firm was not compliant with this frequency.
• Cleanroom qualifications did not include assessment of airflow patterns under conditions of room usage.
• The sites of environmental monitoring used by BVL did not reflect BVL’s own procedures and failed to reflect actual operational conditions of clean room usage.
• Some sterility test failures were attributed to contamination by anaerobes, but the environmental monitoring program did not include testing for anaerobic contaminants.
• Over a 15-month period BVL had recovered at least 1,171 microbial contaminants, of which 1,047 organisms were gram-positive. BVL failed to identify the root cause or implement corrective actions to address the contaminations.
• No trending of microbial contaminations had been performed, nor had contaminants been identified to species and genus levels.
• Despite the company having limits for non-viable contamination in cleanrooms, these were exceeded 112 times during a five-month period. Even though BVL required filling activities to halt if the automated system detected an out-of-specification non-viable particle count, the remediation procedure employed did not include sanitizing the filling lines.
• BVL did not keep records of pressure differentials of cleanrooms and surrounding areas.
• Temperature and humidity of the sterile storage was not monitored, including during the occasions when rainwater leaked from the roof through the HEPA plenum and into the sterile storage area.
• Visual observation of cleanroom activities from the outside area was difficult in that door windows did not provide a full view of clean room operations.
• The computer-controlled stopper washer and depyrogenation tunnel is deficient in that there is no documentation of which individuals have access to which levels of password control. Additionally, alarm reports for various out of limits tunnel operations are not reviewed or trended.

It seems that the authorities gave BVL time to clean up their act, literally, but in November 2011 a three-week joint inspection by FDA (four inspectors including Mr. Thomas Arista, FDA’s national expert on sterile product manufacture) and inspectors from AFSSAPS and MHRA returned to review remediation progress after the earlier inspections. The inspectors were in a quandary—BVL was the only manufacturer for many anti-cancer products; if they stopped the company manufacturing these products, patient therapy and safety were at risk. Should the authorities allow product onto the market with potentially lethal quality problems, or shut the facility and deprive patients of desperately needed anti-cancer therapy?

The FD-483 issued to BVL’s new president and CEO following the November 2011 inspection comprises 11 pages and cites 10 areas of concern with each area having multiple sub-items of concern—many of them issues that had not been corrected from the six-month previous May inspection.

In mid-November the British and French withdrew the product licenses from several BVL-manufactured products with a recommendation to the European Medicines Agency (EMA) that this be a Euro-wide ban. Canada, Hong Kong, and other countries have instituted similar action (4). In the US, FDA convinced Ben Venue Laboratories to engage in a voluntary shutdown. The ripples of these regulatory product withdrawals have had worldwide reach.

Responsibility
There seems to have been a chain of ineptitude in many spheres surrounding this entire issue at local, national, and international levels, resulting in potential risk to patients.

At the local level, where was BVL’s own quality assurance (QA) group and Boehringer-Ingelheim’s (Bl) (the parent company) corporate QA? Didn’t their internal audits reveal these defects, and if so, why were the deficiencies found by FDA in 2011 allowed to remain unresolved? Surely these auditors had no constraints as to where in the factory they could audit. It appears that cleanroom operations could not be viewed without gowning and entering the work area,
which BVL consistently refused entry to client auditors and NRA inspectors (7).

The 2011 quality concerns are not an epiphany regarding the BVL’s quality and GMP compliance concerns. BVL’s problems can be traced back over three decades since the 1980s with the MHRA (and its prior incarnations—DHSS and MCA) and the EMA, having over a 30-year period pulled several P/Ls from companies where BVL was the CMO. Each time BVL, the world’s largest manufacturer of oncogenic injectable drug products, committed to make improvements and the need for these products resulted in a restoration of the P/L. In hindsight, remediation was always slow and often incomplete, but patient needs trumped GMP compliance—such is the risk-to-benefit equation.

How did BVL come to this quagmire? In BVL’s own words they are “the oldest and most experienced manufacturer of lyophilized products in the United States” (8). If BVL has these problems, what is the Quality/GMP profile of other less experienced companies? Is it coincidental that when the GMP compliance problems came to light during these AFSSAPS, FDA, and MHRA inspections, that German parent company Boehringer-Ingelheim, who had owned BVL since 1997, announced that they would divest themselves of BVL to quote “concentrate on their core business”—which is what, pray tell, if it is not pharmaceutical manufacture?

Why did it take an overseas inspection by MHRA and AFSSAPS in the US to shed light on these severe GMP deficiencies before FDA went storming into the facility? Why had FDA’s much lauded risk management approach to GMP inspections not resulted in more frequent and tougher inspections? Seems that the regulators need to provide some answers.

Product Recalls
At the end of 2011, EMA recalled all batches of Busilvex (Pierre Fabre Médicament), Ecalta (Pfizer Limited), Luminity (Lantheus MI UK Ltd), Velcade (Janssen-Cilag International NV), Vidaza (Celgene Europe Ltd), and Vistide (Gilead Sciences International Ltd.) manufactured at Ben Venue (9). EMA also asked healthcare professionals to visually examine vials of Caelyx (Janssen-Cilag International), Ceplene (Epicept GmbH), and Torisel (Pfizer Limited) for the presence of metal particles—these last three products were not recalled.

Why Were Audits Ineffective?
Why is it that the GMP inspections by these authorities revealed a plethora of GMP failings while the routine audits and inspections by many company QA groups obviously did not find compelling reasons to cease sourcing their product from Ben Venue Laboratories? The following potential reasons might be at play:

- BVL did not allow QA groups in-depth access to data that the regulatory authorities were able to access.
- The QA group’s inspection was not sufficiently rigorous to evaluate the true state of the contract manufacture’s GMP compliance profile. Consider how deep a GMP compliance assessment by one experienced corporate QA auditor for two days—the typical time allotted to such audits—compared to what can be gleaned by 14 experienced government inspectors on-site for three weeks.
- Contract-giver GMP compliance assessments are biased in favor of finding nothing critical and little of consequence during an audit, thus continuing the contract giver-contract receiver relationship. When registering a drug, the drug applicant states the name of the CMO, and all submitted stability and process validation data are based on the CMO’s involvement. If a QA audit reveals significant GMP failures, then severing the contract giver/contract receiver relationship requires effectively being off the market for one to two years while an alternate CMO is found, stability and validation data generated and submitted to the authorities, and waiting for approval of the site change from the authorities. We are talking major money in making a decision to sever a relationship with a CMO. Many colleagues have told me of situations where they have been required by their company to significantly tone down their report. A QA audit is inherently biased to continue the contract giver/receiver relationship such that contract giver’s sales and profits are not jeopardized; rarely do thoughts of patient safety enter the discussion, let alone appear in minutes of meetings to discuss whether to continue the CMO relationship.

Where are We Headed?
Looking back, 2011 has been an annus horribilis in GMP compliance for the US pharmaceutical industry. What with the Johnson and Johnson’s Tylenol (acetaminophen/paracetamol) debacle and the almost complete removal of all Tylenol products from the US market (10); the $750 million fine paid by GlaxoSmithKline for GMP non-compliance issues (11); and now the BVL experience—we should all be deeply concerned. Is all this a consequence of globalization, or the worldwide economic malaise and the need to
cut company quality oversight programs, or a move to ever leaner lower and middle management?
Perhaps like the US meat processing industry where for at least 50 years a US Department of Agriculture inspector is permanently based in each factory, are we headed for an age where an FDA inspector is permanently based in factories manufacturing critical pharmaceutical products?

REFERENCES
7. Personal communication from ex-FDA/MHRA inspectors