"REGULATORY CHALLENGES AND TRENDS IN FINISHED DOSAGE MANUFACTURING: A CMO PERSPECTIVE"

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President – Oso Biopharmaceutical Manufacturing LLC
INFORMEX 2013 - Anaheim, CA
Overview

- Outsourcing of all phases of pharmaceutical/biological development and manufacturing is on the rise
- The number of Official Actions (as measured by Warning Letters) have dramatically increased in the last 3-4 years
- The agency states the Application Holder is ultimately responsible for development and manufacturing of their product....
- However, a review of Form 483 observations and Warning Letters suggest there is not a clear delineation of responsibilities and expectations between Contract Providers and Application Holders as each have been accountable for the other’s actions
- There is a definite concentration by the Agency on the Drug Sponsor/CMO relationship with a focus on;
  - Clear communication of both expectations and activities between contract providers and application holders with formal feedback loops
  - Clear Quality Agreements
  - An understanding that .....“they” are “you,” and “you” are ultimately responsible for product quality
OUTSOURCING OF ALL PHASES OF PHARMA/BIOPHARMA DEVELOPMENT AND MANUFACTURING IS ON THE RISE
Macro CMO Market Trends

The U.S. pharmaceutical contract manufacturing market is growing at a 10% rate

Total U.S. Pharmaceutical CMO market is $10+ billion, growing at 10% per annum split 50/50 between:

- 1st market focused on API manufacturing; and
- 2nd market focused on finished dosage form development services and end-product manufacturing

Continued adoption of drug development and manufacturing outsourcing strategies:

- Reduce time to market in an efficient and cost-effective manner
- Adoption of virtual pharma model by the biotech and specialty pharma players
- Growing pressures on big pharma to shift away from R&D and manufacturing activities
- Smaller scale personalized medicines (including orphan drugs) less suited to large, in-house manufacturing facilities

Drug development pipelines are shifting toward those requiring more complex and specialized CMO capabilities (e.g., biologics, biosimilars, cytotoxics)

Increasing Importance of Biologics, Biosimilars and Vaccines

Ethical biopharmaceutical drug development spend is expected to outpace that of traditional small molecules

**Focus on Biologics R&D Spend**

**Leading Ethical Biologics Market**

<table>
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<tr>
<th>Product</th>
<th>Indication</th>
<th>Company</th>
<th>2008 Sales</th>
<th>Approval</th>
<th>Patent Expiry</th>
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<tr>
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<td>2004</td>
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<td>Breast Cancer</td>
<td>Roche</td>
<td>$5,048</td>
<td>1998</td>
<td>2019</td>
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Source: Industry research

Informex 2013
Cytotoxics/Oncology

The injectable oncology therapeutic market is large and growing rapidly

Market Size

- Injectables oncology therapeutics market projected to grow from $25.6 billion in 2010 to $42.3 billion by 2015 (11% CAGR)

Trends

- Increasing complexity in cytotoxic manufacturing is driven by several key trends:
  - Low volume runs for smaller patient populations
  - High costs associated with building and maintaining high-potency molecule containment facilities
  - Significant safety precautions and stringent regulatory requirements
  - High economic risks associated with cytotoxic drug development
  - 60% of investigational cytotoxics expected to be outsourced to contract manufacturing organizations (CMOs), vs. 30% of non-cytotoxic products

Source: Datamonitor 2010, Press Releases, Expert Interviews, M&M Analysis
ContractPharma Annual Outsourcing Survey
2008 - 2012

Outsourcing is up and trend is toward preferred suppliers

Comments from 2012 Survey from respondents that outsource at least 50% of their commercial manufacturing . . .

• 61% report that they expect to increase their outsourcing spending in the next year
• 59% work at companies that employ a “preferred provider” model
• 63% said that more than half of their outsourcing dollars go to preferred providers
• 55% use CMOs for secondary supply for commercial products
• 40% report that they will probably or definitely outsource a project to an Asia-based providers in the next year
• 57% describe their outsourcing as strategic (as opposed to tactical)
• 60% outsource because their company is virtual, while 25% do so to focus on core competencies
THE NUMBER OF OFFICIAL ACTIONS (AS MEASURED BY WARNING LETTERS) HAVE DRAMATICALLY INCREASED IN THE LAST 3-4 YEARS
## Inspection Outcomes

<table>
<thead>
<tr>
<th>NAI</th>
<th>VAI</th>
<th>OAI</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Action Indicated</td>
<td>Voluntary Action Indicated</td>
<td>Official Action Indicated</td>
</tr>
</tbody>
</table>

- **NAI (No Action Indicated)**
  - No Findings or 483’s.
  - May include recommended actions

- **VAI (Voluntary Action Indicated)**
  - 483’s but no product impact.
  - Products approved
  - Export lic granted
  - EIR issued with VAI statement

- **OAI (Official Action Indicated)**
  - Withhold Application
  - Regulatory Meeting
  - Untitled Letter
  - Warning Letter
  - Seizure
  - Injunction
  - Prosecution

Official Actions up to a Warning Letter are designed to initiate Voluntary Action on the part of the inspected party. Official Actions become enforcement activities if companies do not voluntarily remedy noted issues.
Dramatic Rise in Official Action

**Why the rise in Official Actions?....Initiatives and money.**

“When the FDA finds that a firm is significantly out of compliance, we expect a prompt response to our findings. Once the FDA provides inspection findings identifying a serious problem, the firm will generally have no more than fifteen working days in which to respond before the FDA moves ahead with a warning letter or enforcement action. This will help FDA issue warning letters on a timely basis and facilitate prompt corrective action. . . . [T]he FDA will take responsible steps to speed the issuance of warning letters. . . . The FDA is fortunate to have received significant funding increases for the current and next fiscal year that will be devoted to additional inspection and compliance activities that will support the elements of an effective enforcement strategy that I have outlined.”

http://www.fda.gov/newsevents/speeches/ucm175983.htm
• The FDA will set post-inspection deadlines. When the FDA finds that a firm is significantly out of compliance, we expect a prompt response to our findings. Once the FDA provides inspection findings identifying a serious problem, the firm will generally have no more than fifteen working days in which to respond before the FDA moves ahead with a warning letter or enforcement action.

• The FDA will take responsible steps to speed the issuance of warning letters. I have approved a new policy brought forward by the FDA’s Chief Counsel to limit warning letter review to significant legal issues. As a result, most enforcement letters will be able to move forward through a more streamlined process.

• The FDA will prioritize enforcement follow-up. After a warning letter is issued or a major product recall occurs, we will make it a priority to follow up promptly with appropriate action, such as an inspection or investigation to assess whether or not a company has made required changes in its practices.

• The FDA will be prepared to act swiftly and aggressively to protect the public. The FDA will no longer issue multiple warning letters to noncompliant firms before taking enforcement action. If we find that we must move quickly to address significant health concerns or egregious violations, we will consider immediate action – even before we have issued a formal warning letter.

Excerpts from remarks by Margaret A. Hamburg, M.D. Commissioner of Food and Drugs on "Effective Enforcement and Benefits to Public Health" at Food and Drug Law Institute August 6, 2009
• Of America’s five largest manufacturers of generic injectable drugs—APP, Hospira, Teva, Bedford, and Sandoz—the latter four were effectively forced to simultaneously take significant production off-line in order to deal with FDA warnings.
• Production of generic injectables declined by 30 percent, contributing to a massive shortage.
• Of the 219 drugs listed on the American Society of Health System Pharmacists (ASHSP) shortage list as of February 21, 2012, at least 128 – 58% of the drugs on the shortage list – were produced by at least one facility undergoing FDA remediation
• Even though the House Oversight committee postulated the Official Actions had a large role in drug shortages, there has been no policy change

A review of recent 483’s and WL’s and FDA’s stated expectations

WHO IS ULTIMATELY ACCOUNTABLE FOR PRODUCT QUALITY?  CONTRACT PROVIDER OR DRUG SPONSOR
Biochem Laboratories
CMO responsible for sponsor’s inadequate validation package

• **Warning Letter issued** February 17, 2012
• Excerpt;
  
  – *b. Your firm failed to validate the specificity of the test procedures used to analyze finished product stability samples to ensure that the methods are stability-indicating. For example, your firm determined the content of salicylic acid in *(b)(4)* stability samples by titration. Your firm has not demonstrated the specificity of the method for degradation products. The method may not allow you to detect the presence of degradation products that may indicate deterioration of the drug product.*

  – *In your response, you state that you have informed your clients on the importance of validating the methods, but they have chosen not to validate the methods. In addition, you state that you will inform them again in writing. Your response, however, is inadequate because you do not provide your firm's planned corrective actions for this CGMP violation. **You are responsible for ensuring that the test methods used by your firm are validated.***

http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2012/ucm292891.htm
Increased Scrutiny Equals Increased Activities, Equals Increased Costs. Who Pays?

- **Application Holder Perspective**
  - Unlikely to abdicate responsibility for their product control strategy
  - Based on the Warning Letter to Biochem, regulatory risk appears to be more with the contract lab
  - Cost pressure, especially for generic products can be a primary concern
  - What is the incentive to support a more thorough method development and validation plan?

- **CMO Perspective**
  - Most common mistake by drug sponsor is limited development runs to control cost while still expecting successful scale up. ("Bio Data Points" 2012 Life Science Leader CMO Leadership Awards supplement)
  - If client disagrees, choices are limited
    - Hard line may mean loss of current and potential revenue
    - Proceeding at risk may question cGMP compliance and bring increased scrutiny to other projects
    - Absorbing costs and remediating the validation yourself will likely be done with little support from your client. May be precedent setting.

- **Expectations are evolving and accountability spread**
  - No longer is the risk solely with the application holder for non-approval
  - It is clear that the FDA expects the location doing the work to retain accountability for all aspects of their own cGMP compliance while holding the sponsor for overall quality of the drug product.
  - The costs are real and if not shared, service providers will ultimately walk away from clients unwilling to cover the additional costs.

http://www.contractpharma.com/issues/2012-05/view_bio-news-amp-views/the-fda-says-you-are-responsible
River’s Edge, a pharmaceutical company specializing in dermatological products, received a warning letter in May 2010, after an inspection of one of its contract manufacturers resulted in a form 483 and a subsequent inspection at River’s Edge.

Excerpts from the WL.....Your quality control unit has not fulfilled its responsibility nor exercised its authority to approve or reject all drug products manufactured, processed, packed or held under contract by another company [21 C.F.R. § 211.22(a)].

- …. we are concerned about your firm's fundamental understanding of what is required by your QCD and the regulatory expectations for a firm that enters into agreements with contract manufacturers to manufacture all drug products.
- Although you have agreements with other firms that may delineate specific responsibilities to each party (e.g., quality control responsibilities), you are ultimately responsible for the quality of your products.
- Regardless of who manufactures your products or the agreements in place, you are required to ensure that these products meet predefined specifications prior to distribution and are manufactured in accordance with the Act and its implementing regulations, including CGMP regulations for Finished Pharmaceuticals, Title 21, Code of Federal Regulations, Part 211.

http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm220315.htm
River’s Edge
“They” are “you” and “you” are responsible......;

- At the PDA/FDA conference, DMPQ’s Rick Friedman replied in a Q&A session that FDA’s practice is to copy the CMO or the sponsor when either receives a warning letter, or to mutually notify them when compliance issues arise through other means.
  - In the case of River’s Edge, he noted, problems were found initially at the CMO resulting in a 483. “Then we went back to the product owner, which we are not always doing” and informed them that “you are responsible for these products – your name is on them.”

- It was also noted the agency is seeing “more and more” situations where sponsors are “virtual owners” who need to take responsibility for assuring that the CMO “manufactures the product in a safe and effective way – every day, every dose.” The CMO is required to ensure that its operations meet GMPs, but ultimately “the owner of the product has to take responsibility.”

http://www.ipqpubs.com/cmo-story/
• The Warning Letter, issued to the CMO on November 1, 2010, specifically mentions the affected applicant holders without redaction. Most experts agree this is a new development as client/distributor names associated with the problem products are usually not mentioned, or at the very least have been redacted before being posted.

• Another interesting feature of this Warning Letter that it is fairly direct in stating what the FDA expects to see in Claris’ response. For each observation, there was a paragraph that began with: “In your response to this letter, include...”

• For example, FDA requested:
  – Explain your failure to initiate the complaint investigation promptly.
  – Explain the discrepancy between finding fungi in the IV bag as well as the overwrap and reporting that no leak or contamination was found.
  – Explain why defective parts were being used and how the supplier of these defective parts was qualified.
  – Explain how and when Claris identified and informed all customers affected by your IV bag manufacturing problems.
  – Explain why other products filled in the same packaging line, with the same bags and printing process, were not affected or contaminated.

• “In conclusion,” wrote the FDA, “you are under FDA Import Alert so we will refuse admission of your products into the U.S...”

• This last statement broadcast the potential delivery issues the applicant holders would have

PharmPro Dec 6, 2010 “FDA to Claris: ...and in conclusion...”
Product had a history of reconstitution issues when administered in home health care settings. Investigations and documents to file by the Drug Sponsor attributed the phenomenon to not following insert instructions.

- **483 Observation:** Since ........, your firm has received 28 complaints regarding incomplete reconstitution of product and lack of vacuum in the product for XXXXX . Your firm does not have documented scientific data to support that correctly following the product insert would eliminate cases of incomplete reconstitution of the product and lack of vacuum in the product.

- **Response (excerpted & redacted):**
  - The scientific evidence needed to support the information in the product insert is the responsibility of the license holder.
  - As a preventative action, CMO will require a formal closure for field complaints of any type from the customer. SOP STA-QBR-0002, *Product Customer Complaint Quality System*, will be revised to document such closure. Follow Up PR#162484 will track the revision to SOP STA-QBR-0002, with a target completion date of 06-08-12.
  - Upon receipt of the product complaints each one was investigated and a historical trend analysis was performed for all product .......... An investigation was completed and documented for each complaint per SOP........

- Due to this observation, CMO performed a global review of all complaints received for products manufactured by CMO within expiry. There were no complaints received for any product, on any filling line for reconstitution issues related to the product and/or no vial vacuum.

District indicated response was inadequate. After a meeting to clarify 483 responses, changes to the Quality Agreement and implementation of formal feedback loops were accepted as remediation of the observation.
agency trends and expectations

IN THEIR OWN WORDS...
FDA is putting industry on notice that relationships between sponsors and contract manufacturing organizations (CMOs) will be receiving close attention during upcoming agency inspections.

Comments at the 2011 PDA/FDA conference from CDER Office of Compliance Division of Manufacturing and Product Quality (DMPQ) Director Richard Friedman.

- As a result of the “undoubtable trend toward outsourcing,” FDA is paying closer attention to contract relationships, Friedman stressed, and sponsors “should expect to hear questions during inspections about how their companies are making sure that their CMOs are actually being monitored.”

Friedman also noted that quality agreements and communication mechanisms would garner more scrutiny – for example, notifications from CMOs to sponsor firms when an out-of-specification (OOS) result occurs.

In these “shared manufacturing agreements,” the DMPQ director emphasized, issues discovered at a CMO have been leading to subsequent inspections and enforcement actions at the sponsor firm.

http://www.ipqpubs.com/cmo-story/
Whose Responsibility? - Agency Expectations

• Agreeing with the statement “the owner of the product has to take responsibility”, Center for Devices and Radiological Health (CDRH) Office of Compliance official Steven Silverman stressed that his center has the same view.

• This is an “integrated responsibility.” In the case of specification developers and contract manufacturers, Silverman emphasized, “finger-pointing...is unacceptable.”

• However in the answer to the question “Short of discontinuing sale of a product, what is the expectation then on the license holder in terms of CMO or third party oversight?”

• Friedman responded that the issue is a “tough” one because ‘the person in plant’ is not the panacea. I think everybody has found that out over the years.” He explained that ultimately it is the CMO’s responsibility to put in place a quality management system that is robust and that would “actually be able to address these issues within their site.”

• Answer: Ultimately YOU are responsible for the quality of YOUR product, whether that product is the drug product, drug substance or contract service that produced such.

http://www.ipqpubs.com/cmo-story/
FDA Expects Greater Transparency Between Contract Providers and Drug Sponsors on GMP Status

- Comments from Kathleen Culver (FDA Cincinnati District Investigator and Preapproval Manager) at the Global Outsourcing Conference at Xavier University, June 14, 2010.
  
  - FDA investigators will be looking for more transparency between a sponsor and its contract sites regarding the sponsor’s drug application commitments and the contractor’s plant-wide GMP status.
  
  - **Applicant Holder Responsibility:** Drug firms that outsource services should share the appropriate sections of their drug applications with the contract firms to avoid misunderstandings, facilitate site compliance with the commitments in the application and aid review and pre-approval inspections, Culver emphasized. “I am looking for this when I do the pre-approval inspection to assure there are no misunderstandings and that we will not end up with adulterated or misbranded drug product,” she explained.
  
  - **CMO Responsibility:** In turn, where the contract firm manufactures for multiple clients, it is important that the sponsor have access to other client’s audit findings and records that shed light on the contractor’s overall quality system, Culver stressed. “How can you really thoroughly audit a GMP system when you cannot review all the deviations, investigations or data generated in that system?”
• FDA acknowledges the reality of contract operations in the drug manufacturing community
• FDA has to deal with and manage the complexity contract operations brings to the FDA evaluation process before and after drug application approval.
• Often times, the partnerships between sponsors and contract manufacturers and testers produce a high quality drug product.
• BUT, what happens when a commercial drug product produced by a contract firm under the sponsor’s oversight is found to be non-GMP compliant and adulterated/misbranded?
• Aren’t both parties, the sponsor and the contract site, RESPONSIBLE for assuring the drug product is made under GMP control and meets all legal specifications?
• **If the contract manufacturing site gets a Warning Letter because the drug product is adulterated or misbranded, shouldn’t the sponsor also be held accountable by FDA?**

A CMO perspective

AS THE REGULATORY CLIMATE IN THE ERA OF INCREASED OUTSOURCING IS EVOLVING, WHERE SHOULD WE FOCUS?
The continuing lesson for FDA-regulated companies is that the FDA is fully-engaged, and highly-focused, on enforcement activities. Movement from 483 to Warning Letter and beyond is much swifter than in past years. For these companies an FDA inspection is in your future – it is a matter of when, not if, FDA will walk through your doors. The costs of remediating compliance after the fact far exceeds the incremental spend for personnel, systems remediation and consultants in an ongoing manner. Understanding the environment suggests non compliance has a huge negative impact on your business’ bottom line.

(http://www.compliancearchitects.com/2012/01/fda-warning-letters-increase-155-from-2010-levels/)
CMO Perspective – Our Observations

• Trends/observations from Global Inspections & Regulatory Meetings (EMA/CDER/CBER/PDMA/MOH)
  – A strong emphasis on Quality Agreements
  – Requests for specific communication plans, especially for deviations, OOS, and 483 observations
  – Expectations for stronger feedback loops and closeouts for market complaints, field events and adverse reaction.
  – Communication plans in the Quality Agreement have to be in synch with Sponsor requirements for event notification
  – Global focus on systems
  – Documentation, Documentation, Documentation (7 of top 10 483 issues were related to documentation)
  – Making drug sponsor representative available during inspection, especially for PAI’s
  – Where there are issues or lack of expertise, an expectation that outside expertise will be utilized
Example Communication Plan – constant and fluid

(Formal responsibilities should be defined in the Quality Agreement)

- Contract provider only dispositions product and provides documents and data to Sponsor for review (i.e. electronic portal)
- Sponsor releases product for shipment and to market
- Sponsor should not release to market without review of all complaints, deviations, investigations, etc.
- Process is reviewed, as much as possible, in real time through final release(s)
- Overall process is reviewed afterwards for trends, field complaints, AE, etc.

Informex 2013
Necessary Actions – *What the CMO should Expect*

**From Inspectors:**
- Global review of all Quality Agreements
  - Necessary updates
  - Adherence
  - Strong Communication plans
- Utilization of client audits for gap analysis and vulnerabilities
- Matrix of client filing actions to predict and prepare for PAI audits
- Retention of outside expertise for specific areas of focus
- Excellent Documentation
- Ability to show knowledge of client product (i.e. copy of drug application)

**From Clients:**
- Greater & immediate transparency in all areas
- Immediate notification of issues
- Participation in closeout of investigations
- Negotiations regarding “Who Pays?”
• As Outsourcing of Pharma/BioPharma development and manufacturing is on the rise regulatory agencies are focusing on the relationship between the Contract Provider and Drug Sponsor
• This focus and heightened enforcement actions are changing the traditional relationship of “ours” and “theirs” to “OURS”
• The agency states the Application Holder is ultimately responsible for development and manufacturing of their product...however contract providers are also being held responsible for transparency and deliverables from the sponsor
• Quality Agreements and evidence of strong communication channels are being scrutinized
• The cost of non compliance is high
  – Delays to market for drug sponsors
  – Decreased inflow of projects for contract providers
• From a Contract Provider perspective we must accept the dual expectation;
  – we are responsible for our site compliance AND
  – regarding clients; our quality is their quality
Q&A Session

THANK YOU