

"Regulatory challenges and trends in finished dosage manufacturing: A CMO perspective"

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Overview

- At Informex 2013 I presented observations on the relationship between Drug Sponsors & CMO's against the background of increased Outsourcing and a heightened regulatory environment. Research at the time showed
 - Outsourcing of all phases of pharmaceutical/biological development and manufacturing was increasing
 - A dramatic increases in the number of Official Actions (as measured by Warning Letters)
 - A focus by the FDA on the Drug Sponsor/CMO relationship and 483's that held each responsible for the actions of the other
- An update to those observations is presented here and key findings include;
 - Outsourcing continues to grow in almost all sectors
 - The Agency published its guidance document for Quality Agreements, formally defining roles and expectations
 - There is a clear expectation for Quality Agreements between application holders and the CMO
 - The Agency is holding both accountable for the actions of the other

Outsourcing – Now the rule, not the exception

- It is difficult to find a study, article or publication that does not cite the increase of CMO, CRO and CDMO activities across all sectors of the Pharmaceutical and Biopharmaceutical markets. Excerpt examples include;
 - The escalating operation cost for every drug company and the vigorous control of the healthcare costs have forced all drug companies to streamline their internal operations and seek external resources as a core strategy
 - The pressure on R&D to increase its success rates are driving pharmaceutical companies to combinations of internal efforts and external resources.
 - Outsourcing of biopharmaceutical manufacturing has been growing for several years, to the point where contract manufacturing has become a common strategic decision for developers, extending beyond simple non-core activities and into more high-value, technical ones that leverage offerings from contract manufacturing organizations (CMOs) that some developers do not have in-house.
- Similar to recent reports from Pharmtech and BioPlan Associates, a quick search of the topic yields the same summary in various forms;
 - **Outsourcing is growing across all areas of Research, Development, Manufacturing and Regulatory Support.**

FDA Enforcement Initiatives

2009 Statements & Actions

- Budget increase in 2009
- 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
 - The FDA will take responsible steps to speed the issuance of warning letters.
 - Enforcement action considered prior to formal warning letters if for significant health concerns or egregious violations

2015

- Formed Office of Pharmaceutical Quality, creating a single unit dedicated to product quality.
- First published show that in over half of the warning situations and 483s delivered, manufacturing related errors are at the root of the problem.
- Stated focus to gather manufacturing data
- Drug shortage pressures coincided with the reduced number of official actions

Current

- Quality Agreement review a routine part of all inspections

Inspection Outcomes



No Findings or 483's.
May include recommended actions

483's but no product impact.
Products approved
Export lic granted
EIR issued with VAI statement

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.



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.***

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

Challenges

- The top issues for both Owners and Contracted Facilities (as cited in Contract Pharma's Annual Outsourcing Survey – 2015) were:
 - Communication
 - Quality assistance
 - Vendor qualification and selection
 - Documentation
 - Analytical method development
- From the CMO perspective the top challenges cited when working with pharmaceutical companies include
 - Insufficient information
 - Unrealistic deadlines
 - Infrequent communication

http://www.contractpharma.com/contents/view_outsourcing-survey/2015-05-13/2015-annual-outsourcing-survey/#sthash.pOt004dz.dpuf

River's Edge Pharmaceutical

Applicant holder gets warning letter due to CMO issues

- 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.

“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.”

Claris Pharmaceutical

Warning letter to CMO implicates applicant holder by association

- 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..."

Sponsor's Patient Education Data Requested in 483 to CMO

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 Focusing on CMO/Drug Sponsor Relationships

- 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.

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?"

My FDA Crystal Ball

Kathleen Culver (FDA Cincinnati District Investigator and Preapproval Manager)

Presentation at FDA/Xavier Global Outsourcing Conference, June 2010

- 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?**

http://www.ipqpubs.com/wp-content/uploads/2010/06/Culver_GOC_Presentation.pdf

Quality Agreements

Contract Manufacturing Arrangements for Drugs: Quality Agreements Guidance for Industry Draft Guidance—May 2013

- Outlines critical roles played by both product owners and contracted facilities
- Explains how manufacturers should use quality agreements to define, establish, and document their responsibilities
- *This guidance describes FDA's current thinking on defining, establishing, and documenting manufacturing activities of the parties involved in contract drug manufacturing subject to current good manufacturing practice (CGMP) requirements. In particular, we describe how parties involved in contract drug manufacturing can use quality agreements to delineate their manufacturing activities to ensure compliance with CGMP.*

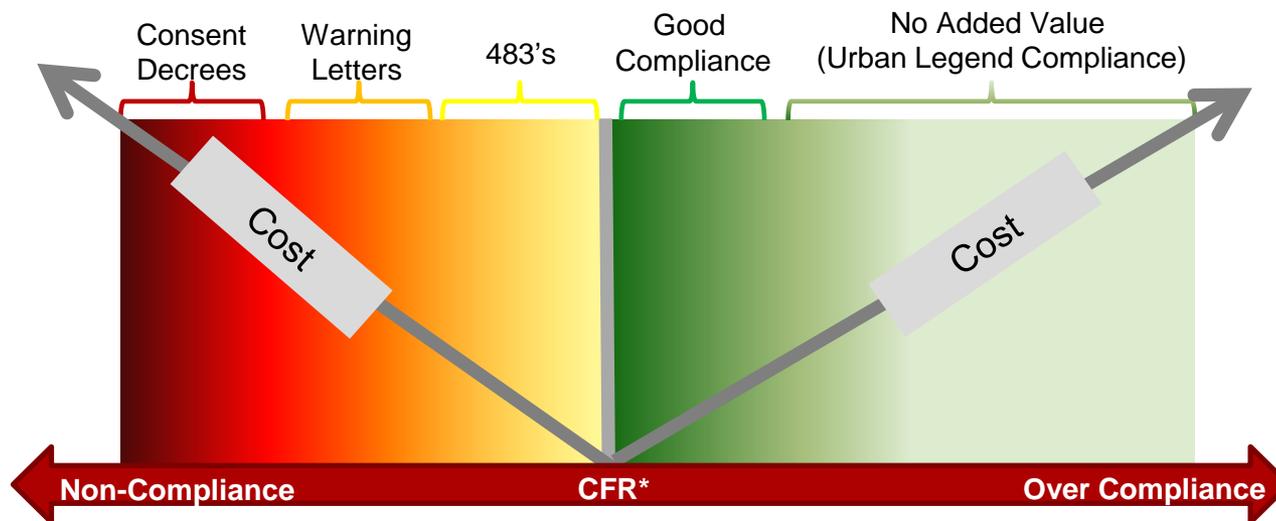
Defining the “WHO” and “WHAT”

- Who
 - Owner or Drug sponsor - FDA refers to the party that introduces (or causes the introduction of) a drug into interstate commerce as the *Owner* of the drug
 - Contracted facilities or CMO – FDA refers to all outside entities performing manufacturing operations for the product Owner as *Contracted Facilities*.
- What
 - Operations Contracted Facilities perform for Owners include
 - Formulation
 - Chemical synthesis
 - Cell culture and fermentation, including biological products
 - Analytical testing and other laboratory services
 - Packaging and labeling.
- Primary responsibilities
 - Owner is responsible for assuring that drugs introduced for interstate commerce are neither adulterated nor misbranded as a result of the actions of their selected Contracted Facilities.
 - Contracted Facilities must assure compliance with applicable cGMP for all services used to make a drug(s) for the Owner.

Elements of a Quality Agreement

- Responsibilities
 - Quality Unit Responsibilities
 - Facilities and Equipment
 - Materials Management
 - Product-Specific Terms Controls
 - Documentation
- Change Control
 - raw materials and starting materials and their suppliers;
 - establishment locations;
 - manufacturing processes;
 - additional products brought into the line, train, or facility:
 - container closure systems; tamper evidence features:
 - Define levels of change
 - Notification
 - Prior review
 - Prior approval

Non Compliance is Costly



*Code of Federal Regulations – establishes what is to be done but not how to do it

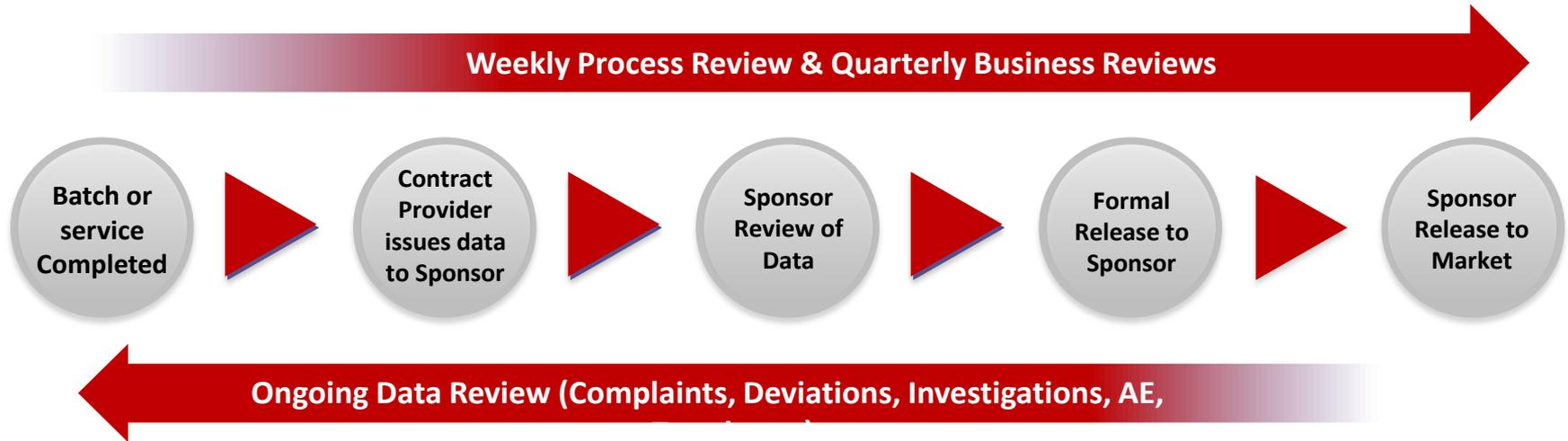
The continuing lesson for FDA-regulated companies is that the FDA is fully-engaged, and highly-focused, on enforcement activities. Movement from 483 to Warning Letter and beyond is much swifter than in past years. For these companies an FDA inspection is in your future – it is a matter of **when**, not **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

- 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*



- 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.

Responsibilities

- Drug Sponsor/Application Holder
 - Release Drug to the Market
 - Final approval or rejection of drug product to the market cannot be delegated to Contracted Facility or via a Quality Agreement
- Contracted facilities
 - Release product to the Sponsor
 - cGMP for all operations performed, including promptly evaluating and addressing manufacturing or quality problems
 - Quality Unit product disposition (e.g., release, reject) decision for each operation it performs
- Both
 - Compliance with all cGMP
 - Product quality
 - Patient safety

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?”

Summary

- 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 both an expectation and are being scrutinized for key responsibilities
- 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

Thank you

Q&A Session

Appendix

Additional Warning Letter examples of
CMO – Drug Sponsor responsibilities
presented at the PDA Outsourcing/CMO
Conference by Paula Katz

WL to Contracted Facilities: Pointing Fingers

- “...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.”
- “Data...generated by an unvalidated method(s)...should not be used for establishment of expiration dates, commercial batch release, or other CGMP decisions.”

WL to Contracted Facilities: Communication

“...you failed to address the impact of the observed method deficiencies on the test results provided to your customers and to indicate whether you will inform your customers of the result of such evaluation.” • “Your response, however, is inadequate because it does not include an evaluation of the data already provided to your clients, which were generated using the unqualified reference standards and unstandardized titrant solutions. Furthermore, your response does not indicate whether you will inform your customers of the result of such evaluation as it relates to their drug product(s).”

WL to Contracted Facilities: Data Integrity

“...Please note that as a contract testing laboratory, it is your responsibility to ensure the integrity of the data generated and that all test results be properly documented, maintained, and reported.” • Failure to investigate OOS: “Please indicate if all your customers were notified of these failures and date of notification.”

WL to Contracted Facility: CC Your Customers!

“You released finished drug products...to your customer without conducting or reviewing release testing to determine if your products conformed to their specifications...FDA laboratory analysis indicated that the drug was sub-potent for both labelled active ingredients...Your written quality agreement with XXXX indicates that XXXX is responsible for final product release to the market. The same agreement also states that [you are] responsible for release of products to the customer, but you did not conduct any laboratory analysis to determine whether your products conformed with specifications prior to releasing them to [your customer].” • Based on FDA’s analysis, Customer recalled all lots in expiry.

WL to Contracted Facility: CC Your Customers! (cont.)

- “Your firm does not have adequate written procedures for production and process controls...[under 211.100(a)] • ...You conducted validation activities for only products X and Y, which you deemed to be the “worst case” products • ...you have not provided a scientific rationale to demonstrate that the mixing studies for X and Y are adequate and fully representative...for the other 118 products • ...Unless you are able to demonstrate that your matrix approach is scientifically sound, all products must be individually validated.” – Copies of WL to CEOs of five of Contracted Facility’s customers.

WL to Product Owner: Disposition

- “Your firm is the owner of this drug product, but did not adequately evaluate whether the CMO..., which is an extension of your operations, can consistently produce product that is suitable for distribution. For example, your quality unit did not evaluate the quality of each batch of drug product produced by the CMO in order to make an appropriate disposition decision (approval or rejection).”
- “Your finished product, XXXX, was not tested for conformance to the labeled amount of active ingredients. Your firm contracted out the XXXX product. Your firm accepted and relied on the Certificate of Analysis (COA) from your contract manufacturer (CMO) and failed to verify the accuracy and completeness of testing results in the COA. For example, XXXX contains six active ingredients. The COA for this lot showed that only identity testing for two of the six active ingredients was conducted. No assay testing was conducted.”

WL to Product Owner: Ultimate Responsibility

- “...we are concerned about your firm’s fundamental understanding of what is required by your QCU and the regulatory expectations for a firm that enters into agreements with contract manufacturers to manufacture 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.”

WL to Product Owner: Ultimate Responsibility “

...We are also concerned about your firm’s fundamental understanding of the overall regulatory expectations for a firm that enters into agreements with contract testing laboratories, including the critical quality unit responsibilities required by 21 CFR 211. Although you have agreements with other firms that may delineate specific responsibilities to each party..., you are ultimately responsible for the quality of your products. The Food and Drug Administration is aware that many manufacturers of pharmaceutical products utilize extramural independent contract facilities...and regards extramural facilities as an extension of the manufacturer's own facility. Regardless of who performs your operations, or the agreements in place, you are required to ensure your products were made in accordance with section 501(a)(2)(B) of the Act so as to provide for their identity, strength, quality, purity, and safety, and are suitable for marketing.”

‘Two-fers:’ WL to Both

- Contracted Facility: “As a contract laboratory that tests drugs, your firm is responsible for complying with CGMP. In addition, it is also essential that your firm provide test results for evaluation and consideration by the owner of the product to consider in its final disposition decision.”
- Owner: Failure to properly evaluate contract laboratory to ensure CGMP compliance of operations occurring at the contract site. Did not audit the CTL; after FDA inspected, Owner audited and found critical and major deficiencies. – “Although you have agreements with other firms that may delineate specific responsibilities for each party, you are ultimately responsible for the quality of your products and the reliability of test results. Regardless of who tests your products or the agreements in place, you are required to manufacture these products in accordance with the Act to assure their identity, strength, quality, purity, and safety.”

Thank you