VENDOR QUALIFICATION

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VENDOR QUALIFICATION

FDASIA Title VII Drug Supply Chain Provisions, July 2012

- SEC. 711. ENHANCING THE SAFETY AND QUALITY OF THE DRUG SUPPLY.

  Section 501 (21 U.S.C. 351) is amended by adding at the end the following flush text:

  ‘‘For purposes of paragraph (a)(2)(B), the term ‘current good manufacturing practice’ includes the implementation of **oversight and controls over the manufacture of drugs** to ensure quality, including managing the risk of and establishing the safety of raw materials, materials used in the manufacturing of drugs, and finished drug products.’’.

21 CFR Part 4, Combination Products

- 4.4(b)(1) Combination Product with a Device ► 21 CFR 820.50
  - 21 CFR 820.50 Purchasing Controls
  - **Evaluation of suppliers, contractors, and consultants**

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VENDOR QUALIFICATION
Q10 PHARMACEUTICAL QUALITY SYSTEM

- **G. Management of Outsourced Activities and Purchased Materials (2.7)**

- **The pharmaceutical company is ultimately responsible** to ensure processes are in place to assure the control of outsourced activities and quality of purchased materials. These processes should **incorporate quality risk management** and include:

- (a) **Assessing prior to outsourcing operations or selecting material suppliers**, the suitability and competence of the other party to carry out the activity or provide the material using a defined supply chain (**e.g., audits, material evaluations, qualification**).

- (b) **Defining the responsibilities and communication processes … in a written agreement** between the contract giver and contract acceptor.

- (c) **Monitoring and review of the performance of the contract acceptor** or the quality of the material from the provider, and the identification and implementation of any essential improvements.

- (d) **Monitoring incoming ingredients and materials** to ensure they are from approved sources using the agreed supply chain.

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VENDOR QUALIFICATION – WARNING LETTER REFERENCE

- **30Apr14**

- In addition to the issues discussed above, you should note that CGMP requires the implementation of quality oversight and controls over the manufacture of drugs, including the safety of raw materials, materials used in drug manufacturing, and finished drug products. *See* FDCA, as amended by the Food and Drug Administration Safety and Innovation Act (Pub.L. 112-144, Title VII, section 711). We note that **you have chosen to hire a contract testing laboratory** to perform some of the required testing of your finished drug products. **FDA inspected this laboratory (b)(4) and observed deficiencies in its practices**. If you choose to contract with a laboratory to perform some functions required by CGMP, it is **essential that you select a qualified contractor** and that **you maintain sufficient oversight of the contractor's operations to ensure that it is fully CGMP compliant.** Regardless of whether you rely on a contract facility, you are responsible for assuring that drugs you introduce into interstate commerce are neither adulterated nor misbranded. *See* 21 CFR 210.1(b), 21 CFR 200.10(b).

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VENDOR QUALIFICATION PROGRAM

Vendor Qualification SOP

- Screen ► Audit ► Evaluate ► Approve ► Monitor
  - Processing complexity
  - Potential product/patient risk from product failure, etc.
- Finished Product
- API
- Key Excipient
- Critical Analytical Services
- Container/Closures
- Secondary Packaging Materials
- Contracted Service Provider

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VENDOR QUALIFICATION PROGRAM

CONTRACTED SERVICE PROVIDER ACTIVITIES

- Access numerous areas of your facility and provide a wide variety of services including some that may be critical in maintaining regulatory compliance and achieving business goals.
- Vendor Management SOPs: Train vendors and company personnel interacting with them to prevent mismanagement of vendors & the deviations that can result.
    - o Initial Training. Criteria for retraining – vendors & company personnel? Time, Vendor history, FDA findings?
    - o Who do they report to on arrival and departure?
    - o Document activities performed. Review & Confirm via exit interview.
    - o What kind of findings require notification at time of discovery?
    - o What kind of findings require prior QA authorization before proceeding further. Internally assess what was impacted - Products/Materials/Systems Risk assessment?
    - o What activities could not be performed, why and when this will be completed. Internally assess the risk of this delay. Mitigation strategy?

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VENDOR QUALIFICATION

CONTRACTED SERVICE PROVIDERS

- o Plan for the temporary/unexpected replacement of your vendor technician. What kind of training and supervision will be required based on type of task to be performed.
- o Deviations involving vendor actions and/or inadequacy of company oversight or supervision → **Investigate globally**. Identify any systemic issue that could impact other vendors. Vendor SOP inadequacy?

- Recognize & mitigate the potential for miscommunication, misinterpretation and/or non-compliance with vendor SOPs by the vendor & the company. Do the following apply?
  - o Large number of vendors/contractors working in multiple departments (Warehouse, Laboratory, Production, Stability, Preventive Maintenance, etc.) in numerous buildings on your campuses - and
  - o Large number of company personnel in multiple departments, at multiple levels of responsibility and authority and, at times, multiple countries, interacting with them.
  - o Whether all these diverse activities governed by one or multiple SOPs, what do your deviation investigations tell you about its/their adequacy?

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SOP Misinterpretation/Miscommunication – Why?

- SOP approved with inadequate, vague or incorrect sections
- Those responsible, at different levels of responsibility, for implementing the SOP requirements are not always involved in the review to identify the vague, incomplete and, at times, incorrect, sections of the SOP.
- Infrequency of interacting with vendor issues
- Time since initial training
- Include this topic for review in the internal audit program

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VENDOR QUALIFICATION

CMO VENDOR QUALIFICATION PROCESS

Vendor Qualification SOP

- Screen ► Audit ► Evaluate ► Approve ► Monitor
  - Processing complexity
  - Potential product/patient risk from product failure, etc.
- Team Expertise for the Initial Audit ► Tailored to evaluate applicable GxP requirements *at the specific vendor* (Production/Analytical/QA?)
  - Equipment train: Condition; Degree of automation; Closed/Open Systems; Cal/PM
  - Laboratory operations: Instruments; Methods; Documentation; Cal/PM
  - Dedicated/Non-dedicated Equipment: Cross contamination controls
    - » Cleaning – Manual, CIP, COP – Verification/Validation
  - Sterility – Aseptic fill (standard fill room/RABS/Isolator), Autoclaves, Ovens, Tunnels
  - Tech Transfer

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Quality System (OOS/Deviation/Stability Investigations, Reprocess/Rework, Change Control, Training), Facilities & Equipment Systems (Cal & PM), etc.

- **Harmonize any Dissimilarities with your Systems**
  - o Deviation Classifications (Critical/Major/Minor; High/Moderate/Low Risk, etc. and definitions of same)
  - o Root Cause Categories/Sub-categories/sub-sub categories
  - o Impact on meaningful trending during global assessment of all your vendors
  - o **Triggers** for a deviation, **timely** investigation, search for **recurrence** of same, similar or related deviations and time period searched.
  - o Time frames for reporting issues relating to OOS, Deviations, Stability, Potential Field Alert issues, etc. should be clearly defined with **measurable terminology**.
    - "**Immediately**" notify … vs. Within x hours of discovery, notify…
    - "Day??? 24 hours or any time by the next day (47 hours and 59 minutes?????)
    - Time zones???

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VENDOR QUALIFICATION

- Documentation Clarity and Adequacy: Batch records, Analytical work sheets, Validation documents, OOS, Deviation Reports, etc.
  - Good Documentation Practices
  - Justification for changes
  - **Vendor "in house" terminology, unusual acronyms and use of terminology out of context**. (USP water; non-GMP; Not calibrated – for Info only; Laminar to describe HEPA filtered air; Sterilize ≠ Sanitize; Validation Protocol ≠ Report; Open a CAPA to investigate an issue, etc., etc.,∞)
  - **Self-explanatory to the vendor ≠ Self-explanatory to the company**
  - Evaluate their suitability to remotely evaluate quality issues
    - Detectability of subtle issues to identify of a trend before it results in risk
    - **Can quality issues be "masked" by this type of documentation?**

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VENDOR QUALIFICATION

- Training – will your product require specialized training for the vendor
- Vendor's suppliers? Vendor qualified suppliers or company's qualified suppliers?
- Overall Quality Culture
- CMO strengths & weakness may impact your monitoring process

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VENDOR QUALIFICATION – THE AUDITING PROCESS

- **Planned Audits After Initial Qualification/Classification/Approval Status**
  - Qualified, Certified, Approved, Conditional Approved, etc.
- **Communication, Planning, Window for the Audit**
  - Auditor/Auditor Team expertise
  - Processing equipment and systems operational and not static
  - What if all your batches have already been produced for the year?
  - If operational for non-dedicated equipment, but with another client's material/product, how much accessibility will be provided?
  - Will the vendors other clients be on site and how will this further limit access to equipment, processes, documents and SMEs.

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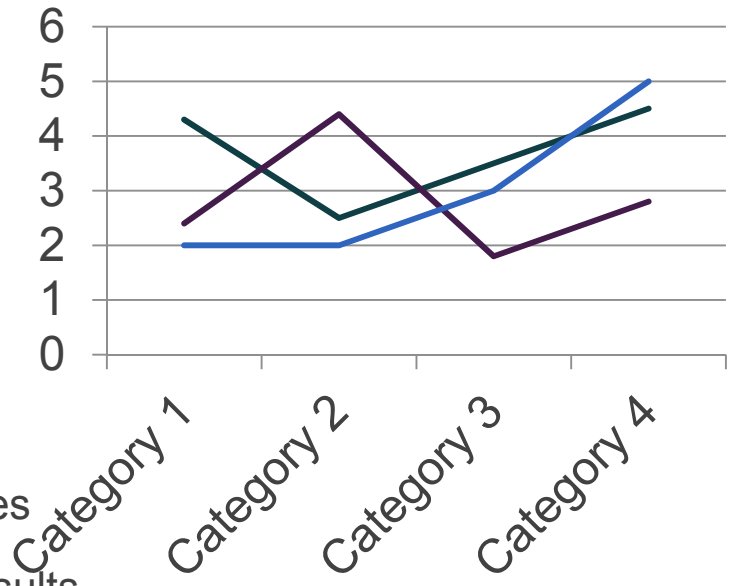
VENDOR QUALIFICATION – PERFORMANCE MONITORING

- **Performance Monitoring – What will be reviewed?**
  - OOT but stable or drifting OOS
  - OOS
  - Failures/Rejects
  - Reprocess/Rework
  - All or representative number of batch records
    - o Batches with deviations
    - o Batches with uninvestigated abnormal losses
  - Independent confirmation of analytical test results
  - Stability late pulls
  - Environmental monitoring excursions – viable non-viable, pressure, humidity, temperature, etc.



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VENDOR QUALIFICATION – PERFORMANCE MONITORING

- Complaints
- Applicable facility deviations/alarms (Environmental controls, stability chambers, water system, etc.).
- Regularly communicate findings/concerns with vendors and the action plans designed to achieve continuous improvement.

FACTOR TO KEEP IN MIND

- If manufactured on your own production floor, you would have access to review all of these issues and more. What should be reviewed from this vendor to give you the same comfort level?
- Based on product and vendor history, which are the right metrics to measure quality from this vendor and at what frequency?

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VENDOR QUALIFICATION – PERFORMANCE MONITORING

- Develop a company system to **feed relevant vendor "performance" issues** to the **Vendor Qualification Group.**
- The performance history of your various vendors can be collected in different departments, systems, databases, etc.
- Develop a means that allows the Vendor Qualification Group to query each of these systems for performance related issues.

  Identify areas of particular focus for next scheduled or for cause audit

  What do your audits tell you that performance monitoring does not?

  - Enhance monitoring to detect these potential risks
  - Enhance Partnership and Communications with your Vendors

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VENDOR QUALIFICATION - COMMUNICATION PROCESS

Q10 - Define and document **responsibilities** and **communication processes** for quality-related activities **in a written agreement** between the Owner and Contracted Facility.

SOPs should provide the necessary step by step instructions that may not be included in the high level written agreements, understandable to **all** users to prevent misunderstanding and/or miscommunication. For example:

- Email, Fax, Memo, Phone call
- Clarify which is preferred or required for a specific issue, e.g., OOS, FAR, etc.
- Phone Call: Method of documentation. What key elements must always be included in the Memo of the phone call, e.g., Person & title; Subject; Date of call; Date of discovery of issue; etc.
- Timeliness for reporting (Field Alerts, OOS, Deviation, Stability Failures, Complaints)

Unclear, vague or incorrect documentation of these communications can significantly weaken the justifications and conclusions of vendor investigations. Interviews months later may not accurately clarify these vague communications.

Documented evidence v.s. Oral history.

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VENDOR QUALIFICATION - COMMUNICATION PROCESS

- Vendor SOP Training – Were ALL those responsible for communicating key information between the company and the vendor effectively trained in the Vendor SOP(s)?

  o QA, Laboratory, Production, Warehouse (at various levels of responsibility/authority)

- If yes, when and how? Was it based on SOP self read and understand – years ago?
- The SOP should **avoid using subjective qualifiers** requiring the readers to interpret the intent. This can lead to inconsistent implementation and/or miscommunication. For example:

  » "**Immediately**" notify … vs. Within x hours of discovery, notify…

  » Report "**significant**" … Define "significant" with some examples

  » "**Day**" – How long is it? 24 hours? 47 hours 59 minutes? Work shift?

  » "**Isolated event"** vs. …once in the last twelve months.

  » Use measurable terminology. SOP compliance cannot otherwise be established.

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VENDOR QUALIFICATION - COMMUNICATION SYSTEMS

Issues to keep in mind

- Not all involved at your site or at the vendor, that are frequently engaged in these activities, may have been trained or fully understood these requirements
- In the stress, urgency and time constraints of completing a significant deviation investigation report involving the vendor, sometimes vague, incomplete and, at times, incorrect communications can be accepted, reviewed and approved.
- The familiarity with the facts of the event by the principals involved at the company and vendor, including the respective QAs, may contribute to this and impact the objectivity and thoroughness of the final review.
- This may only become apparent later when the investigation is reviewed during a company audit or FDA inspection.
- What is the likelihood that a long, complex investigation report involving potential risk to product/patient will be reviewed during an inspection?
- What is your mitigation strategy in dealing with this prospect?

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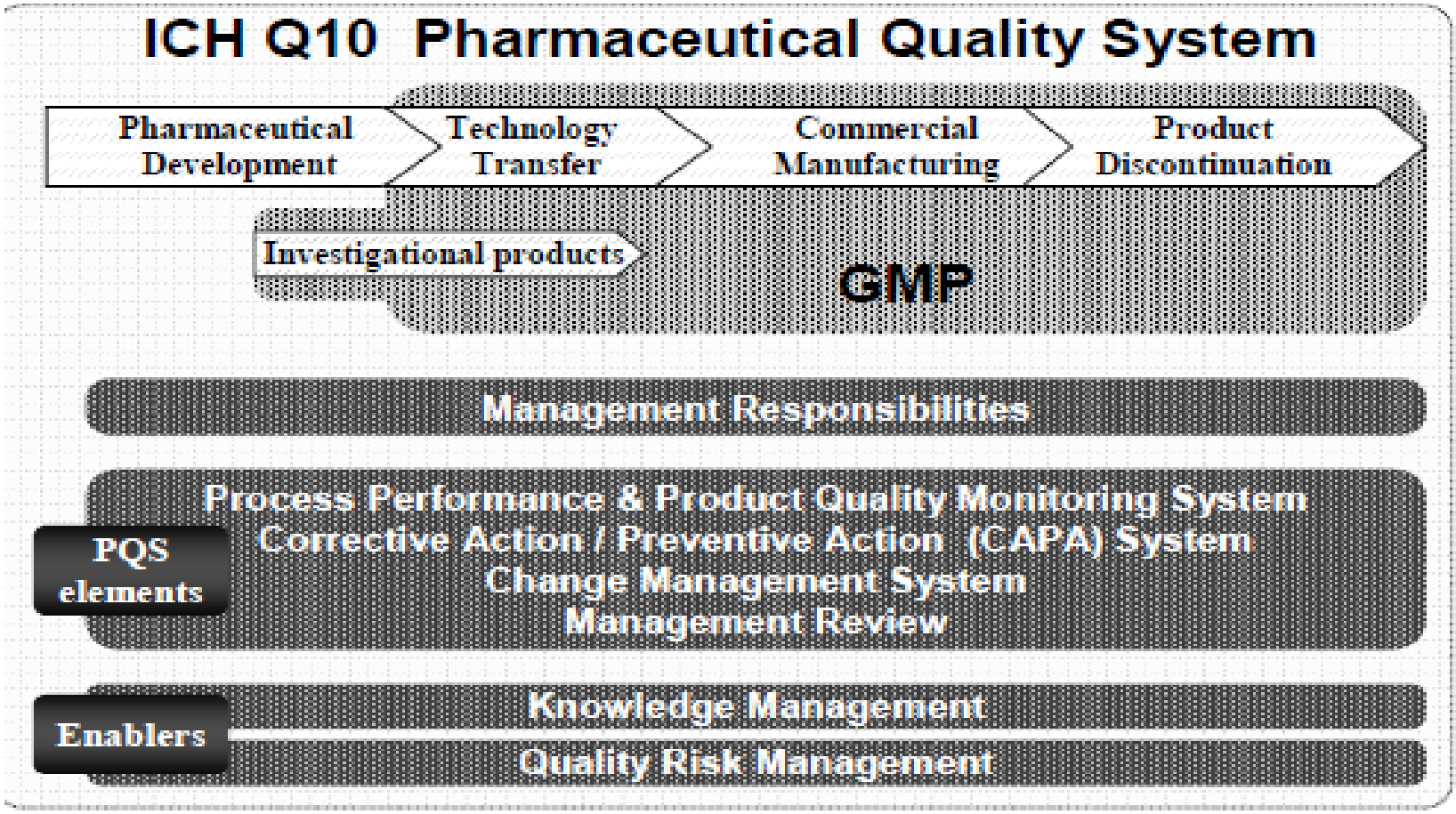
VENDOR QUALIFICATION
Q10 KNOWLEDGE MANAGEMENT

- Product and process knowledge should be managed from development through the commercial life of the product up to and including product discontinuation.



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VENDOR QUALIFICATION – KNOWLEDGE MANAGEMENT

- Once contracted out, retain or acquire the expertize necessary to understand the product and process knowledge of your product and the systems necessary to accurately and consistently produce it.

- This type of expertise is critical in detecting any drift from the norm, that is, to "read between the lines" of the documents provided by the vendor (e.g. deviation investigation reports, batch records, CoAs, validation reports, etc.) and detecting potential risk and addressing it before it impacts your product.

- Over time after a history of good deliverables, the process of reviewing the same type of documents can become routine and it may become more challenging to maintain the same level of rigorous and through review.

- Oversight can be further challenged by change of personnel both at the vendor and pharma company that can result in a loss of familiarity and/or complete understanding with some of the requirements and a loss of the experience of knowing what can go wrong.

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- Then there are always the inevitable circumstances that seem to further burden oversight, for example:
  - The designated person communicating, reviewing, receiving or sending materials to or from the vendor is out because of: Mandatory training; Supporting the inspection from FDA, MHRA, TGA, etc.; Out due to *[fill in the blank*]
  - It was unusually busy; We were understaffed; Recent reorganization scrambled people around
  - Circumstances which, at times, are only accepted and not mitigated.
- While time of occurrence of these circumstances may not always be predictable, we should accept these interruptions will happen and the SOP should have a general plan to deal with them.

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Have an umbrella, it might rain.

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Include vendor performance monitoring as an element to cover during in internal audit program

VENDOR RESPONSES TO AUDIT FINDINGS

- Were all findings satisfactorily addressed?
- If not, assess risk and a follow up action plan.
- Monitor and track vendor follow up responses to ensure significant issues are not overlooked and/or unnecessarily delayed?

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VENDOR QUALIFICATION PERFORMANCE MONITORING

Make sure your Audits and Performance Monitoring & Trending provide you a clear view your vendor's operations and controls

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VENDOR QUALIFICATION
VISIBILITY OF VENDOR CONTROLS

YOUR PERFORMANCE MONITORING & TRENDING EYE

HOW MUCH DOES IT SEE IN BETWEEN YOUR AUDITS?

DOES IT PROVIDE THE NECESSARY QUALITY OVERSIGHT?

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FDA WARNING LETTER CITATIONS

- **April 11, 2014**

- b) Your firm has **failed to validate the (b)(4) used to produce sterile drug products since 2011.** The inspection documented that **you relied solely on the vendor's qualification.**

- In your response, you indicate that **you have commissioned the vendor to perform process and product-specific (b)(4) validation**. We remind you that **it is your responsibility to review the validation data** on the efficacy of the (b)(4) in producing a sterile effluent. Your response is inadequate in that it fails to address the impact on product produced since 2011.

-

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FDA WARNING LETTER CITATIONS

- **October 23, 2012**

- **1. Your firm has not established the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals [21 C.F.R. § 211. 84(d)].**

- a. **Your firm accepts and relies upon the suppliers' Certificates of Analysis (CoAs) for drug components without conducting adequate vendor qualification.**

- **Without establishing the reliability of vendors, there is no assurance that drug product components, containers or closures are appropriate for their intended use**.

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FDA WARNING LETTER CITATIONS

November 18, 2011

- For example, your firm accepts and relies upon **the Certificate of Analysis (CoA) from your stopper suppliers without conducting adequate vendor qualification**

- b) Your firm does not sample incoming components/raw materials in a manner that represents the batch for the determination of acceptance or rejection of the material. Your firm fails to have a scientific justification for the sampling approach used for incoming materials. For example, you only sampled 3 (b)(4) of drums of a batch of (b)(4) received in February 2007 (less than (b)(4) samples). Your firm also lacks a written procedure describing the material sampling process.

- **20Jul10**

- 4. There **is no assurance that your firm establishes the reliability of the supplier's analyses through appropriate validation of the supplier's test results** at appropriate intervals [21 C.F.R. § 211.84(d)(2)].

- For example, your vendor qualification has not provided adequate evidence that the manufacturer can consistently supply raw materials that meet appropriate quality attributes. **Suppliers are not monitored and regularly scrutinized to ensure ongoing reliability.** Specifically, your firm has not adequately qualified the supplier of methyl salicylate API. There is no assurance that the API suppliers are in compliance with CGMPs, without supplier qualification by your firm and knowing how APIs have been manufactured, tested, and if quality is consistently assured. There is also no assurance that your firm has established the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals.

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FDA WARNING LETTER CITATIONS

- **September 29, 2010**

- In addition, **your site personnel do not conduct sampling on incoming material**. Your Quality Assurance (QA) Manager indicated that **your vendors sample the materials prior to shipping to your site**, and that the supplied samples are then tested by your facility. These **samples are also composited by your vendors**. Your sampling **practices are unacceptable for the following reasons:**

- • **Your approach provides limited or no information regarding the material's variability**
  • In the case that the material fails to meet the established specification, the root cause determination may be limited by the sampling approach
  • You have no information on **how your vendor conducts the sampling** with no assurance that the samples were properly collected by your vendor
  • There is **no assurance that the samples were collected from the batch** of incoming material received
  • The sample is **composited, without justification**
  • The actual **effect of transportation on the batch within its container is not assessed**, such as segregation or contamination that may occur during transportation.

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FDA WARNING LETTER CITATIONS

- 21 Apr 08

- Your vendor qualification program should provide adequate evidence that the manufacturer can consistently provide reliable and safe materials. Suppliers should be monitored and regularly scrutinized to assure ongoing reliability. It is your responsibility to ensure that raw materials received are suitable and approved by the quality unit prior to use.

- 30Jul12

- 5. Your firm has not conducted at least one specific identity test and has not established the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals [21 C.F.R. § 211.84(d)(2)].

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THANK YOU

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