



# Evaluating Contract Manufacturing for Biotech and Cell/Gene Therapy

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# The Supplier



- An external organization that may be supplying the following:
  - *Raw Materials*
  - *Intermediates*
  - *DNA/RNA constructs and viral vectors*
  - *Cultured/Modified Cells*
  - *Drug Substance/API*
  - *Excipients*
  - *Reference Standards*
  - *Laboratory and analytical services*
  - *Aseptic Filling services*
  - *Final Dosage Formulation and Manufacturing*
  - *Warehousing services*
  - *Shipping and distribution services*
  - *QA, QP, QPPV Services*

# Key Points to Cover

- *Implement a structured process to define objectives and identify candidates following Risk Management Guidelines*
- *Assess the proficiency and structure of the supplier through an integrated approach to Supplier qualification through physical, operational and performance assessments of leading indicators of quality status and performance*
- *Align your network with the quality standards, management and liabilities of the Supplier by partnering and influencing*
- *Evaluate the financial impact on your organization by performing a business risk assessment for potential quality, compliance and regulatory risks*

# Principles of Risk Assessment – ICH Q9

- Risk assessment consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards...
- For risk assessment purposes, three fundamental questions are often helpful:
  - 1. What might go wrong?
  - 2. What is the likelihood (probability) it will go wrong?
  - 3. What are the consequences (severity)?

# Risk Identification, Analysis and Evaluation – ICH Q9

- ***Risk identification*** is a systematic use of information to identify hazards referring to the risk question or problem description...Risk identification addresses the “What might go wrong?” question, including identifying the possible consequences...
- ***Risk analysis*** is the estimation of the risk associated with the identified hazards. It is the qualitative or quantitative process of linking the likelihood of occurrence and severity of harms...
- ***Risk evaluation*** compares the identified and analyzed risk against given risk criteria...

# Example of a Risk Assessment Tool

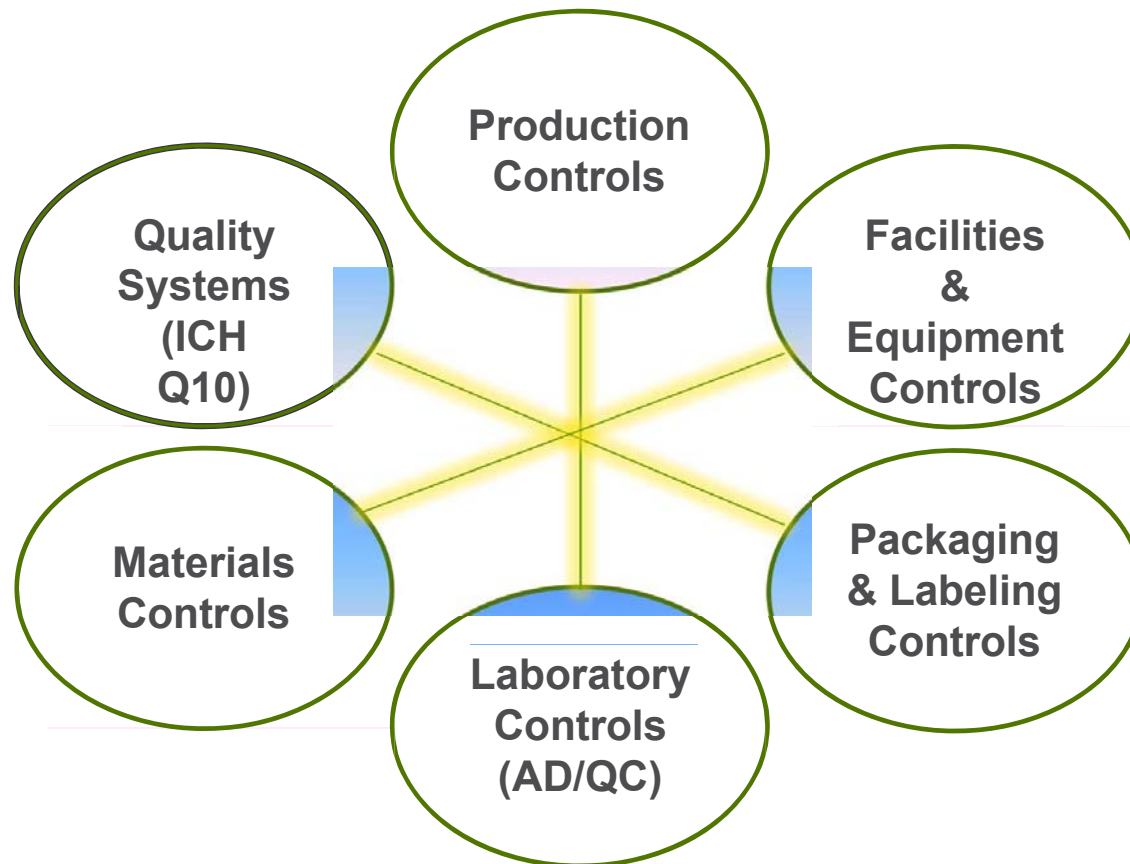
## Risk Ranking Matrix:

		Severity		
		Minor	Moderate	Critical
Frequency/Likelihood	Frequent/Likely	Medium	High	High
	Intermittent/ Average	Low	Medium	High
	Remote/Rare	Low	Low	Medium

# Pharmaceutical Quality System - ICH Q10

- Key Areas:
  - Process performance and product quality monitoring system
  - Corrective action and preventive action (CAPA) system
  - Change management system
  - Management review of process performance and product quality

# Critical to assess the Supplier's competency across the "Expanded" Pharmaceutical Quality System





# ICH Q10 and Assessment of Suppliers

- ***2.7. Management of outsourced activities and purchased materials***
  - ...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)**

# Leading Indicators for Supplier Selection - I

Assessment of these indicators in likely chronological order:

## 1. Review of literature published by or about the Supplier

- Look for content that details their quality Policy, Vision and Mission
- Review articles published in Professional Journals by the Supplier (If any) for technical, scientific and GMP content
- Assess these articles for alignment with your organization's needs, goals and Quality Strategy

## 2. Researching technical capabilities of the Supplier

- Beyond literature searches, interviews (remote and in person) with the Supplier's technical leaders and hands-on technical staff are a good way to assess their competence as well as the number of staff they have with the appropriate knowledge and skills

## 3. Researching Supplier's Regulatory history

- Search for any 483 documents on [www.FDA.gov](http://www.FDA.gov) to review the Supplier's regulatory inspection observations (if any)
- Search for any notifications, recalls, warning letters, etc. on [www.FDA.gov](http://www.FDA.gov), as well as in other countries (if the Supplier is located in or exports to those countries)

# Risk Indicators for Supplier Selection - II

4. Researching financial stability (challenging with private Companies)
  - Annual Reports
  - Company documents
5. Client References (to be received with a “grain of salt”)
  - Try to get references from three prior clients, or at least two references that have had recent experience with projects similar to your company’s
  - \_ Suppliers will most likely refer you only to clients that had "good" experiences.
6. Performing “Due Diligence” Site Visit(s):
  - Manufacturing Site Visit (Led by your Development and Manufacturing Staff)
  - Quality System audit (Led by your QA Lead Auditors, and QA Staff, A Rep from Regulatory CMC may be useful too)
7. Performing risk assessments based on the findings
  - Use risk assessment tools (FMEA, ICH Tools, etc.) to determine a risk level for likelihood of failure (or success)

# Due Diligence – Key Risk Reduction Activity

- It is highly advisable to have a Due Diligence visit and assessment by the sponsor **PRIOR** to contracting with the Supplier
- Too often, this is done only by representatives from Development and/or Manufacturing; for critical operations, adding QA and Analytical Development representatives can help identify general quality issues with the facilities, quality systems, labs, documentation, etc.
- If these materials are to be exported to the EU, a QP visit is very helpful to enable release of the materials in the EU.
- For Clinical Materials, QP assessments and Audit reports may suffice
- For commercial materials going to the EU a BLA, ELA, or GMP Certificate is essential

# The “Ideal” cross-functional Due Diligence team:

- **Should include representatives from:**
  - Technology SMEs, for novel/niche technologies, processes and analytics
  - Process Development / Scale Up Engineering
  - Manufacturing
  - GMP Quality (someone able to assess also QC labs and equipment)
  - Analytical Development
  - Regulatory CMC, if you expect to use the materials manufactured in a filing

# Risk Assessment Post Due-Diligence Visit

- After the visit, draft a joint assessment for key quality indicators:
  - Is the facility suitable for the type of work to be performed?
  - (GMP vs. non-GMP, Biotech vs. Small Molecules, Oral vs. Parenteral dosage form, etc.) from a containment, environmental, process and safety perspective
  - Are their staff capable and qualified to execute your technology?
  - Review Company organization (MFR, QA/QC, Analytical Labs, Engineering, Regulatory Affairs, etc.)
  - Review document lists (SOPs, Non-Proprietary Analytical Methods, Validation reports for Facility/Equipment, Environmental Monitoring, Site Master File, etc.)

# Quality Management System Audits

- The Supplier should be formally qualified prior to beginning of GMP work
  - If GMP work is begun prior to qualification, there is a real risk of losing materials and funds - if site qualification is not achieved, after the fact
- Some low-risk suppliers may require only a “Paper” audit by questionnaire
  - Low risk Raw Materials (Some may only require a CoA: NaCl, Ethanol, etc.)
  - Common Components (If compatibility and leachables/extractables information is available from the fabricator/supplier)
  - Standard Packaging supplies
- If determined necessary, a formal qualification audit is required to be performed by the sponsor’s auditor (Staff or Contract, as long as they are qualified and have the relevant experience for the type of supplier)
- A QMS audit goes in depth beyond the Due Diligence audit and focuses on cGMP Quality Management Systems and compliance to regulatory expectations (FDA, EMA, etc.)

# Qualification of your Auditors

- The auditor(s) performing the qualification audit must be documented as qualified to perform the audit based on a combination of their education, training and experience
- This applies to both in-house and contract auditors
- Qualification of in-house auditors can be based on their CVs, work experience and documented training
  - Some companies require “Auditor Qualification” courses that include training, audit participation and generation of audit reports before qualification is achieved
- Both in-house and external staff need to certify that they have not been debarred by a Regulatory Authority (FDA, etc.) from working in a GxP industry or institution



# Organizational Risks – The Quality Unit must be “independent of production” I

- ICH Q7 Good Manufacturing Practice Guide for API
  - Chapter 2. QUALITY MANAGEMENT
    - 2.13 There should be a quality unit(s) that is **independent of production** and that fulfills both quality assurance (QA) and quality control (QC) responsibilities. This can be in the form of separate QA and QC units or a single individual or group, depending upon the size and structure of the organization.

## Organizational Risks – The Quality Unit must be "independent of production" II

- **Eudralex - Volume 4 Good Manufacturing Practice Guidelines for Medicinal Products (the EU GMP)**

- Part 1 Chapter 2 (personnel)

- 2.3 Key Personnel include the head of Production, the head of Quality Control, and if at least one of these persons is not responsible for the duties described in Article 51 of Directive 2001/83/EC<sup>1</sup>, the Qualified Person(s) designated for the purpose. Normally key posts should be occupied by full-time personnel. **The heads of Production and Quality Control must be independent from each other.** In large organizations, it may be necessary to delegate some of the functions listed in 2.5, 2.6 and 2.7.

## Not Having an "Independent" Quality Unit is a Leading Indicator of High Compliance Risk

- Based on decades of experience, the regulatory agencies (and ICH) have identified the need for an "Independent" Quality Unit
- Their concerns are based on prior examples of:
  - Undue influence of Manufacturing or the Testing Labs on QC to approve poor test results and close Out of Spec investigations, as to not delay release of materials
  - Undue influence of Manufacturing on QA to approve batch records, test results and product disposition decisions, even with concerns about product safety and compliance

# Conflict of Interest



- When income, bonuses, promotions, etc. are not taken out of the QA approval process – there is a risk of the appearance of conflict of interest, or actual occurrences of conflict of interest
- A strongly supported and independent Quality Unit can identify compliance issues and report them to Senior Management, if required
- In some organizations, Quality reports directly into Regulatory Affairs. This in itself is not in violation of regulations, though QA should have the authority to independently and objectively audit RA processes, systems and training files for compliance to standards, guidelines and SOPs

# Conflict of Interest - Examples

- Not all Business Risks are Compliance Risks, but **ALL** compliance Risks are also Business Risks
  - Example: Data fabrication to cover-up test performance problems (not common, but it has happened in more than one company in the US, and is reported to be a major problem in some countries)
  - Example: Delay or refusal of internal or client Quality Audits by plant management to “hide” a problem in the plant that has GMP impact (seen with some OUS sites)
  - Example: Withholding paycheck from QA Manager until a batch of product is released (a true case in the USA!)

# Technical Competency I

- You have the right to request a “test” of performance, especially if the technology being used is not “standard” (if refused, be concerned):
  - Manufacture a test lot prior to committing to full production plan (yes, it’s quite costly, but if time is not of the essence and your can afford it, this can elucidate Supplier capabilities and identify technical/functional gaps)
  - Give contract testing labs analytical test cases (a reference standard of the drug or impurity, for example) to analyze. Then compare timeliness, performance and results across labs

# Technical Competency II

- If you are deploying a novel or “exotic” technology that is new for the Supplier, extra care must be taken to ensure that the Supplier is capable of adopting and executing new technologies for them
  - Review examples of prior success
  - Interview the process/analytical development management and staff
  - Small-scale deployment for proof of concept is highly recommended, if possible.
  - Robust technology transfer practices must be in place and managed appropriately (See PDA Technical Report 65 on Technology Transfer)

# Specific Competencies Critical for Cell Therapy I

- **Is the CMO already providing cell-based therapy manufacturing?**
- **Has the CMO shown prior examples of successful tech transfer?**
- **How well is Environmental Monitoring managed and reported?**
- **What methods and controls are in place to minimize contamination?**
  - ◆ **Biological Safety Cabinets**
  - ◆ **Isolators**
  - ◆ **Robotics**
- **How is disinfection and decontamination addressed?**
  - ◆ **Manual application of bactericides and sporicides**
  - ◆ **Chlorine Dioxide Gas**
  - ◆ **VHP**
  - ◆ **Other technologies**
- **Qualification and standardization of ancillary reagents/components**
  - ◆ **Separation reagents/activation reagents**
  - ◆ **Specialty buffers**
  - ◆ **Growth matrixes and scaffolding**
  - ◆ **3D printing**
  - ◆ **Custom Cell Culture vessels/bags/reactors**



# Specific Competencies Critical for Cell Therapy II

- **How are the capabilities and qualification of the manufacturing staff assessed and monitored?**
  - ◆ Are the staff trained on “mock” materials prior to being qualified to work on the donor/stem cells?
  - ◆ How is training delivered:
    - ◆ OJT
    - ◆ Video
    - ◆ Simulation
- **Are there enough qualified staff to cover in case of absence?**
- **Is the QC lab experienced with the specific methods required:**
  - ◆ Histology
  - ◆ Cytometry
  - ◆ EM
  - ◆ DNA methods
  - ◆ Biochemical methods

# Specific Competencies Critical for Gene Therapy

- In addition to the Cell Therapy skills and requirements, the following are critical for Gene Therapy:
  - ◆ Qualified/validated source of DNA or RNA and viral vectors
  - ◆ Incoming quality testing of the oligonucleotides and vectors
  - ◆ In-Vivo DNA/RNA expression measurement methods
- Qualification and standardization of ancillary reagents
  - ◆ activation reagents, viral vectors, media, cytokines, non-conventional buffers
- Customized analytical methods
  - ◆ In process controls
  - ◆ Release testing
  - ◆ Potency testing

# Ensuring appropriate staffing levels

- Special attention must be paid to the capabilities, equipment and staffing of the Supplier's functional areas: Facilities, Production, Analytical Labs, etc:
  - Are there enough people to get the job done, especially with the skill sets you require for your technology/process?
  - Ask to meet and chat with the staff in the plant and labs during your visit/audit
  - Are the QC labs empty, or occupied by analysts? (avoid “ghost labs”), is anyone working in the Manufacturing area?
  - New hires will take months to become fully competent in the local procedures and with your processes, this often causes errors or delays

# Assessing Supplier's Supply Chain

- **With regards to distribution, raw material and reagent supply channels, quality/regulatory requirements**
  - **Assess the Supplier's access to Raw Materials, reagents, components and equipment**
    - Do they have qualified secondary suppliers for key materials?
  - **Assess the Supplier's oversight of incoming materials (did they qualify critical suppliers of critical raw materials and solvents?)**
  - **Security and reliability of shipping to and from the Supplier**
    - are they capable of cold chain shipping and receiving, if required?
    - Customs issues for international shipping
    - Reliability and capabilities of the shipping firm used
  - **Does the Supplier have technical and scientific resources available at other sites (if they are part of a multi-site corporation)**
  - **Is the distribution network reliable, especially where temperature-controlled shipping and storage is required**

# Summary: Ranking Suppliers for assessment by Key "Leading Risk Indicators"

- **Technological capabilities**
- **Quality Management System**
- **Facility (Capabilities, Maintenance, Cleanliness)**
- **Environmental Monitoring (at levels required)**
- **Containment and product protection, plant safety**
- **Production Equipment calibration, validation, and maintenance**
- **Analytical test lab: Equipment calibration and maintenance, method qualification/validation**
- **SOPs and Work Instructions**
- **Staff: Enough qualified (with the right experience/training/education) staff to perform the work**
- **Validation of building management systems and computerized platforms**
- **Regulatory Inspection/compliance history**

## Preparing a Risk Assessment Table – Comparison across Suppliers

- Preparing a risk evaluation of potential sourced Suppliers to determine the significance and ranking of each risk
- Selecting valid and meaningful “Risk Categories” is key to generating a useful table
- Input should be based on a consensus discussion in a cross- functional setting (Face to Face is best)
- Lack of information for a specific category should be assigned a value based on the risk of failure (Low/Medium/High)
- The participants should be Subject Matter Experts in the relevant fields
- A “Neutral” facilitator can help negotiate the final risk levels

# Example: Risk-based comparison of three Suppliers for manufacturing GMP materials

1= Low 5=Medium 10=High (Risk Assessed)	Site A	Site B	Site C
Equipment Availability	10	10	5
Personnel Competency	10	10	10
Adequate SOPs/MBR	5	10	5
Technical Competence	10	10	5
Commercial Experience	10	5	5
Financial Stability	10	5	10
Enough Stability Data to support Site Change	5	5	10
Can show Process/Product Comparability/Val.	10	10	10
GMP Compliance Status	10	10	5
Gaps to close for QMS	10	10	1
Track Record with QA - Partnering	5	5	5
Likelihood of Regulatory Inspection Success	10	10	5
Equipment Availability	10	10	5
(Low Score=Lower Risk / High Score=Higher Risk)	<b>A</b>	<b>B</b>	<b>C</b>
<b>Relative Risk Scores:</b>	<b>1000</b>	<b>975</b>	<b>685</b>

# Example: Risk comparison for a Hosted Software Solution

Risk Categories	Vendor A	Vendor B
Already a Sponsor-Qualified Vendor	5	1
Likelihood of Delayed Integration	10	1
Likelihood of Integration Management Failures	5	5
Poor Management of Data Transfer Errors	10	1
Poor Alerting of Data Generation Errors	1	5
Application not ready by Due Date	1	1
Risk of poor functionality	1	1
IT-related concerns	5	1
Limited Flexibility of use	5	1
Poor Alerting of Errors	1	5
<b>Relative Risk Scores:</b>	<b>44</b>	<b>22</b>

Number Value	Risk Levels
1	Low
5	medium
10	High



# Once you have contracted with the Supplier...

- Next Steps for risk mitigation:
  - Relationship Management Team
  - Quality Agreement
  - Monitor Key Metrics:
    - Lost Lots
    - Deviation Rate, severity and on time resolution (look for recurring deviations)
    - Effectiveness of CAPA
    - Batch Review/Approval cycle time

- ***2.7. Management of outsourced activities and purchased materials***
  - (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 needed improvements

# Applying Q10 for Maintaining quality performance and risk reduction at the Supplier

- Institute ***ongoing measurements*** of Supplier performance against Key Performance Indicators (KPI):
  - ***Quality*** of work performed for MFR/QC/QA (error/Failure rate)
  - ***Timeliness*** of work for MFR/QC/QA (% on-time delivery)
  - ***Proper*** and ***timely*** resolution of Deviations, Out of Spec investigations, Process Failures
  - ***Timeliness and openness of communication*** to MFR/QC/QA
  - Willingness to ***accommodate Sponsor's documentation*** needs
  - Willingness to ***listen to Sponsor's process and Quality SMEs***
  - Appropriate management of ***budgets, change requests***, etc.
- Manage the relationship based on the performance metrics on a regular basis

## Using a "Relationship Management Team" to Monitor for Leading Risk Indicators

- Face to Face meetings before and at start up of activities is of great value in developing relationships across functional peers
- Regular meetings are a must (weekly, or Bi-weekly at least) – by teleconference if Supplier is not local (as often is the case)
- The right people must attend these meetings (cross-functional SMEs who understand the processes & can also make decisions)
- Even when there is a great distance, periodic F2F meetings are important to maintain the relationships across functional peers
  - Quarterly, if possible – location could be alternated between Sponsor and Supplier
- An executive level “Leadership Team” is important for solving disagreements not solvable by the working group
- This team should regularly assess any changes or “drift” in behavior, responsiveness, timeliness, number of deviations and lost lots

# The Importance of Quality Agreements

- **Examining the importance of quality technical agreements (QTA)**
  - The quality agreement is typically subservient to the contract, master services agreement, etc.
  - It is an expectation of ICH Q10 to have this in place and QP (Qualified person, in the EU) certification may not be obtained if a QTA (Quality Technical Agreement) is not in place between the Sponsor and the Supplier
- **Make sure that notification times are reasonable**
  - Number of days for the Supplier to notify the sponsor of: Regulatory Inspections; Deviations; Production Failures; OOS, OOT, delays; etc.
  - A robust Change control process must be in place to ensure that the Supplier does not make any changes that could affect product SISPQ\* or a regulatory filing by the Sponsor (IND, NDA, MAA, etc.)

# ICH Q10 and Quality Agreements

- ***2.7. Management of outsourced activities and purchased materials***
  - (b) Defining the responsibilities and communication processes for quality-related activities of the involved parties. For outsourced activities, this should be included in a written agreement between the contract giver and contract acceptor.

# The Global Supplier Outsourcing Unit

- **Developing a global Supplier outsourcing unit covering both strategic and operational activities accountable for sourcing and selecting potential Suppliers based on requirements**
  - **For companies working with multiple Suppliers over diverse projects, there is a benefit in establishing a Supplier outsourcing unit**
  - **This unit can manage the Due Diligence and Qualification activities**
  - **Coordinate the Risk Assessments**
  - **Work to maintain the cross-company relationship**
  - **Collect and present the ongoing performance metrics**

# QUESTIONS?



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