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Management of Outsourced Activities & QP Responsibilities

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GMP Inspector

HPRA GMP Information Day

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Contents

- Background,
- Assessment of contract acceptors prior to outsourcing,
- Contracts/ Quality agreements,
- Ongoing monitoring and review of outsourced activities,
- QP responsibilities with respect to outsourced activities,

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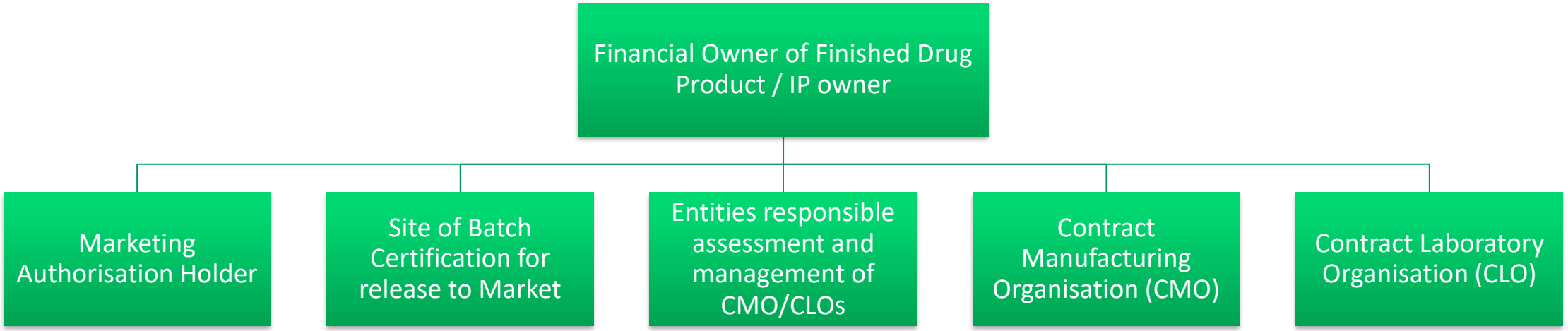
Background

- EU GMP Guide; Chapter 7 and sections of Annex 16,
- What is an Outsourced Activity ?
- Examples of Outsourced Activities:
  - Manufacturing or testing activities outsourced by batch certification site to a third party,
  - Services provided by a third party,
    - Calibration services, Pest Control services, PDE assessments,
  - Third party assessment and oversite of contract manufacturers/ laboratories,
- Can batch certification for release to market be outsourced by an MIA holder?

Background


Financial Owner of Finished Drug Product / IP owner
Marketing Authorisation Holder
Site of Batch Certification for release to Market
Entities responsible assessment and management of CMO/CLOs
Contract Manufacturing Organisation (CMO)
Contract Laboratory Organisation (CLO)

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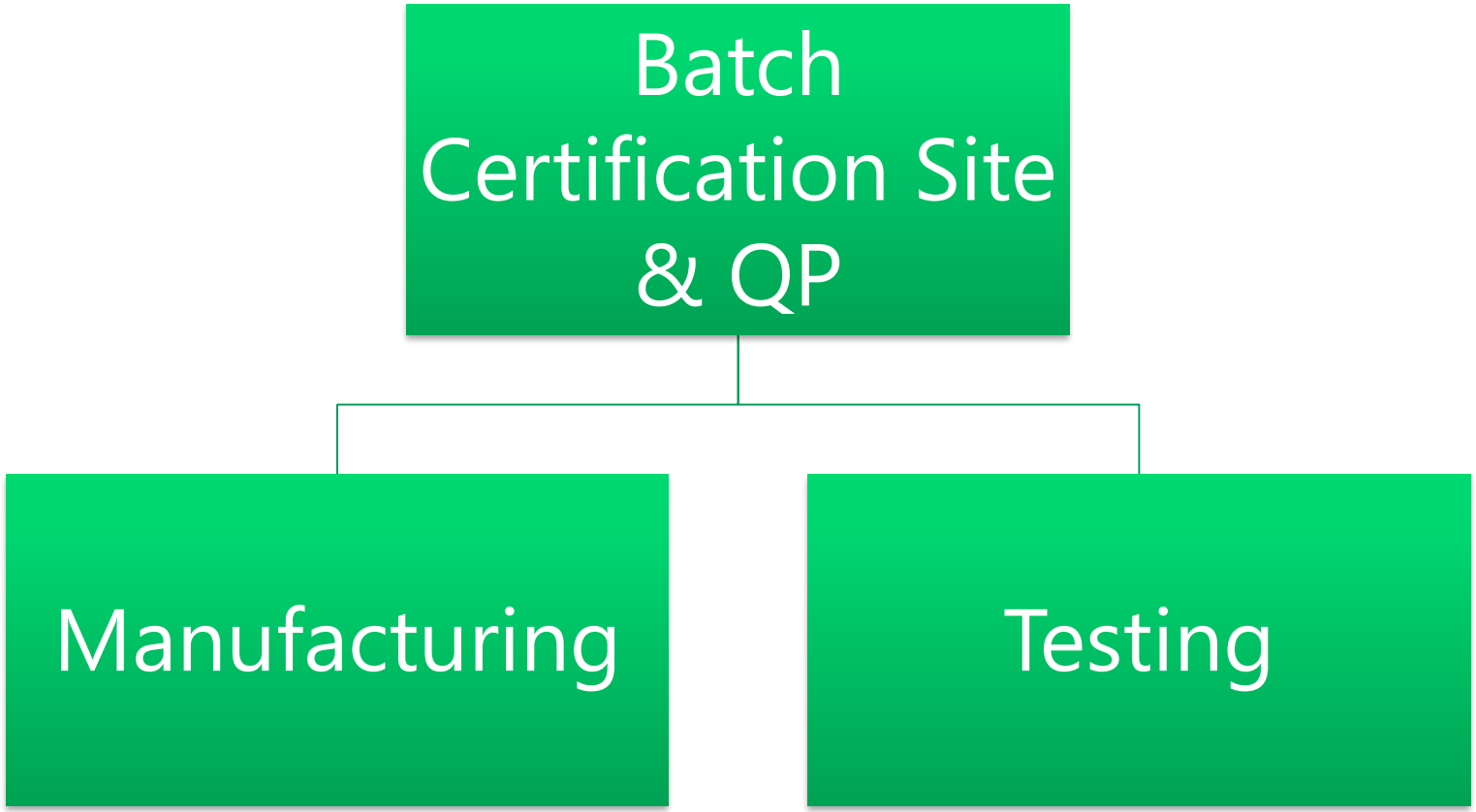

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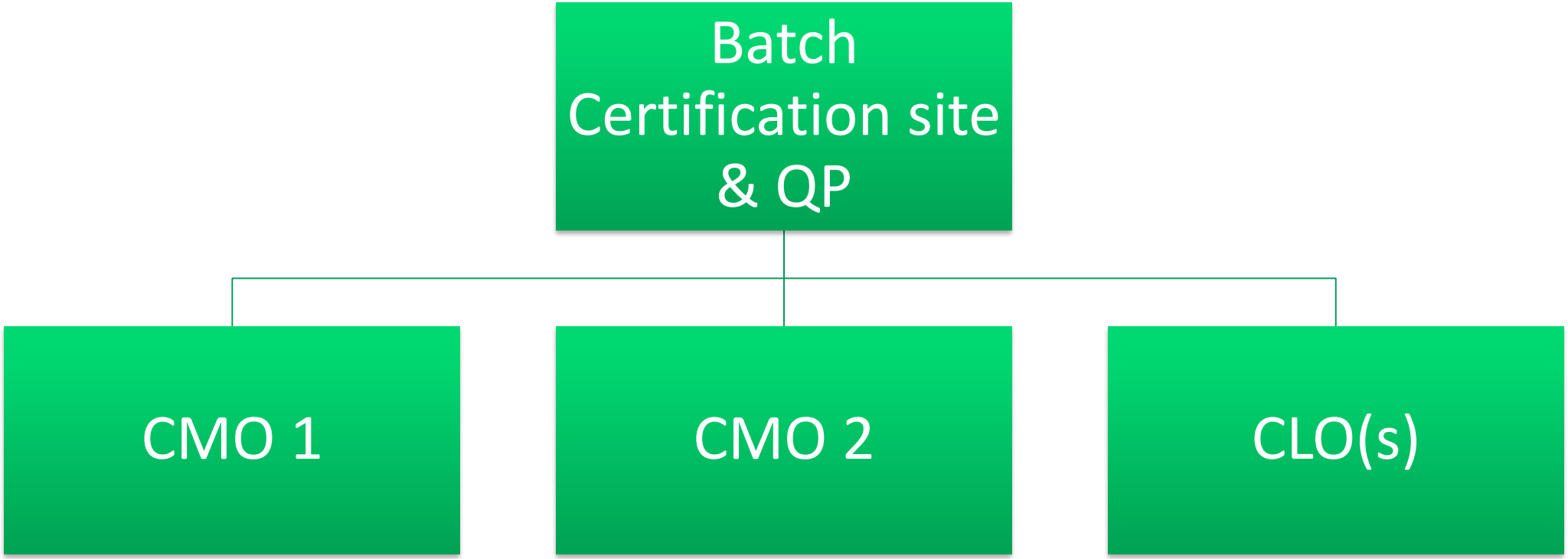
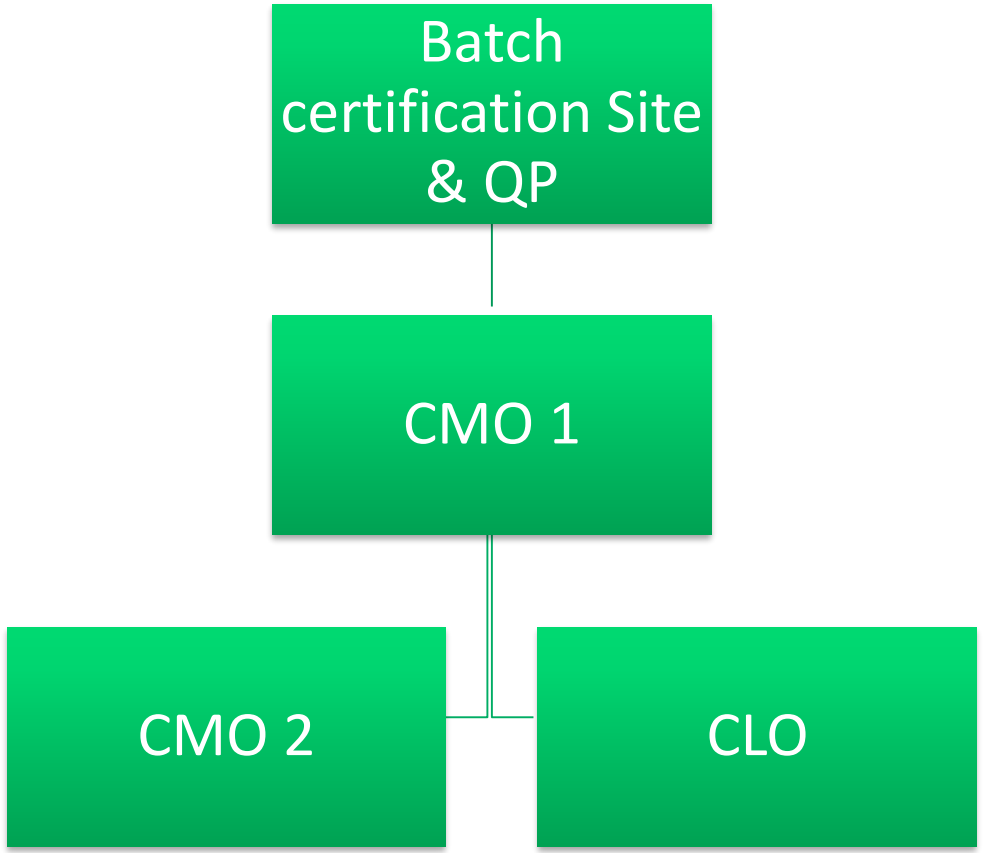
Background

- *EU GMP Guide Annex 16- 'General Principles':*
  - *…QP is responsible for ensuring that each individual batch has been manufactured and checked in compliance with laws in force in the Member State where certification takes place, in accordance with the requirements of the marketing authorisation (MA) and with Good Manufacturing Practice (GMP).*

Background



Background



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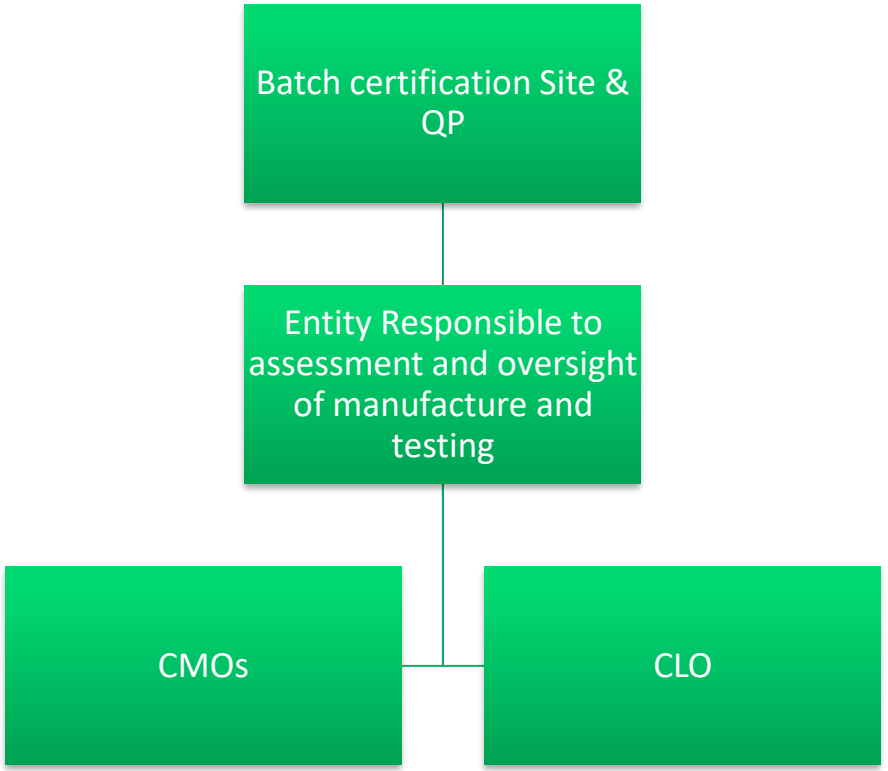
Background

- *Chapter 7, 7.11: The Contract Acceptor* ***should not subcontract to a third party any of the work*** *entrusted to him under the Contract* ***without the Contract Giver's prior evaluation and approval of the arrangements***. ***Arrangements made between the Contract Acceptor and any third party should ensure that information and knowledge****, including those from assessments of the suitability of the third party,* ***are made available in the same way as between the original Contract Giver and Contract Acceptor***.

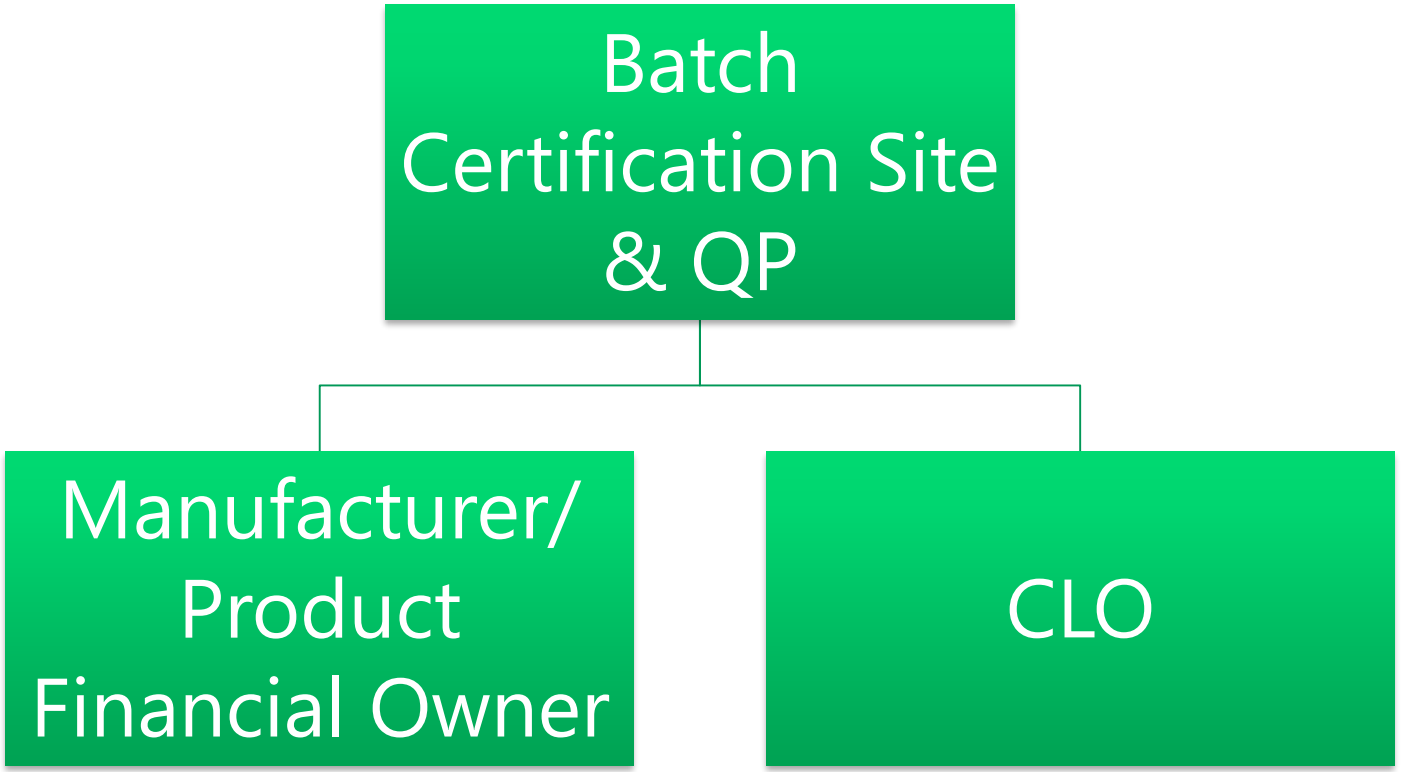
Background


Batch certification Site & QP
Entity Responsible to assessment and oversight of manufacture and testing
CMOs
CLO

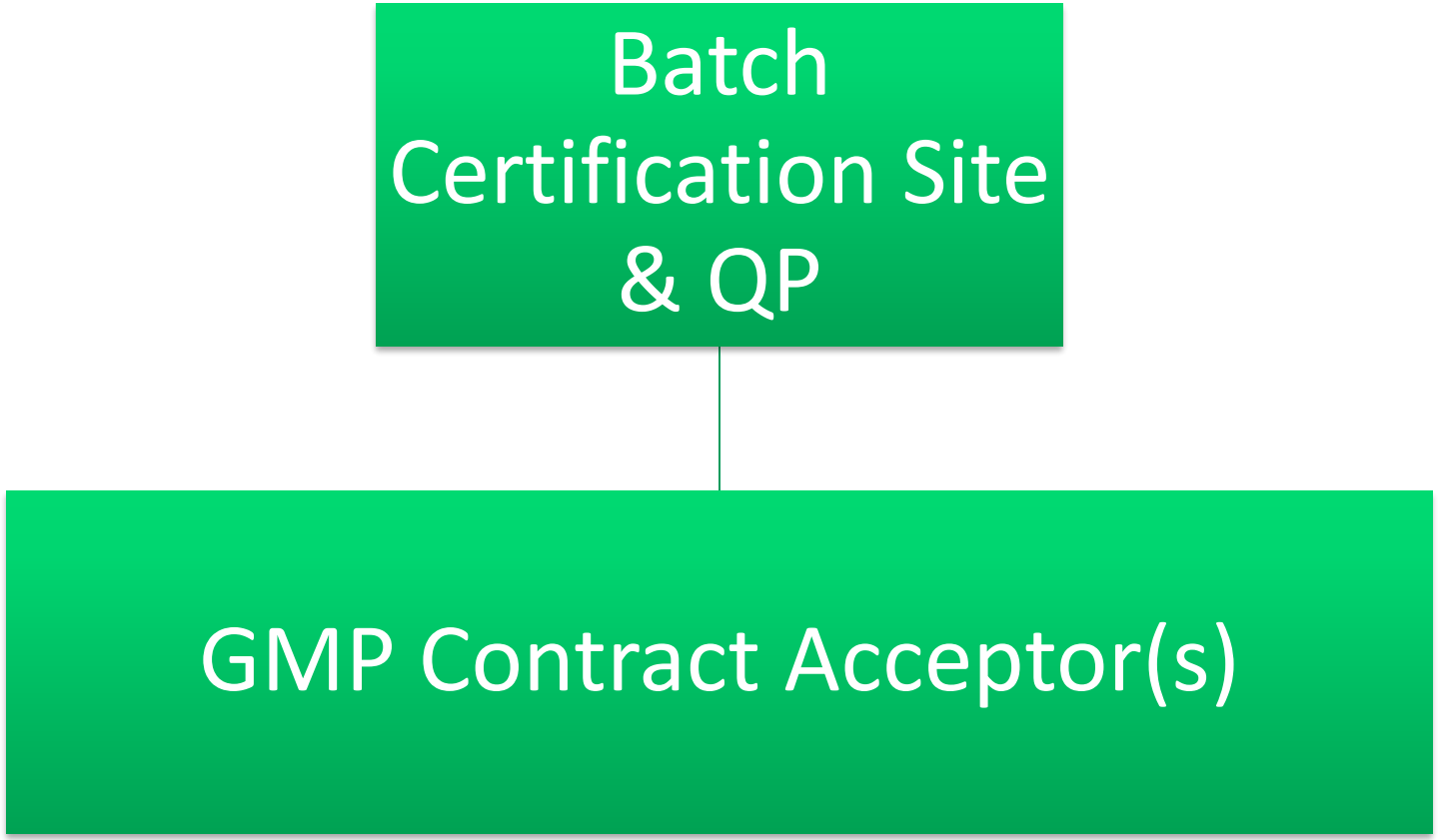
Background

- *EU GMP Guide Annex 16 paragraph 2.1:*
  - ***Relying on assessment by third parties**, e.g. audits, **should be in accordance with Chapter 7 of the GMP Guide** in order to appropriately define, agree and control any outsourced activity.*

Background


Batch Certification Site & QP
Manufacturer/ Product Financial Owner
CLO

Background



Background

- 1. Assessment of the contract acceptor prior to outsourcing activities,
- 2. The Contract/ Quality Agreement,
- 3. Ongoing oversight and performance review of contract acceptor,

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Assessment of contract acceptor prior to outsourcing activities

- Prior to outsourcing, the contract giver is responsible for assessing the legality, suitability and the competence of the Contract Acceptor to carry out successfully the outsourced activities.
- The contract giver's prior assessment should ensure that the contract acceptors has adequate premises, equipment, knowledge, experience, and competent personnel.
- The level of prior assessment will differ depending on the criticality & complexity of the GMP activity being outsourced.

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Prior Assessment of Contract Manufacturers and Laboratories

- A Quality Risk Management (QRM) process should be used to determine the level of prior assessment required:
  - Supply chain complexity,
  - Other products manufactured at the site,
  - Does the contract acceptor support any other industries?
- EU GMP certification
  - Does the company have an EU GMP certificate or confirmation of GMP compliance from local competent authority for MRA region?
- Legal registration as a company.

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Prior Assessment of Contract Manufacturers and Laboratories

- Audit of the facility should be performed:
  - By Batch certification site or by a third party contracted by the batch certification site,
  - Audit scope should be suitable and clearly reflect the activities being outsourced,
  - The audit contents should reflect that the contract acceptor's systems have been assessed in line with the QRM process.
  - Audit report should clearly demonstrate review of the Pharmaceutical Quality System.
- Transport validation study maybe required.

Prior assessment of service provider

- Contract giver should ensure that a contract acceptor has adequate knowledge, equipment, experience and competent personnel to perform the GMP activities outsourced.
  - Is accreditation available and is it relevant?
  - Does the service provider personnel have experience working in a GMP environment?
  - Is the service provider appropriately qualified?
  - Equipment used by service provider.
  - Is the contract acceptor legally registered as a company?

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Contracts/ Quality Agreements

- *EU GMP Guide Ch. 7 Paragraph 7.7:*
  - *There should be a written Contract/Agreement covering:*
    - *The outsourced activities,*
    - *The products or operations to which they are related,*
    - *Any technical arrangements made in connection with it.*

Contract/ Quality Agreements

The contract/agreement

- Should be compliant with EU GMP Guide, Marketing authorisation of relevant products and any specific regulations in force relating to the contract acceptor and contract giver.
- Should clearly identify which party undertakes each step of the outsourced activity and responsibilities in this regard.
- Should clearly indicate that all records relating to the outsourced activities should be made available to the contract giver.
- Should permit contract giver or their representative to audit the outsourced activities performed by contract acceptor and mutually agreed subcontractors.
- Contract should clearly detail responsibilities and timelines for the contract acceptor for notifying the contract giver of any quality events i.e. deviations, complaints, quality defects, change controls that may have the potential to impact product quality.

Contract/ Quality Agreements

The format of the Contract/ quality agreement, should be defined in the contract giver's QMS.

If the contract is not in the contract giver format/template, then a review should be performed to ensure the contract/agreement fulfils the contract giver's QMS requirements for a contract/ agreement.

Contracts/ Agreements should be regularly reviewed and kept up-to-date.

The contract should state clearly that the contract acceptor should not subcontract any work to a third party without contract giver prior evaluation and approval of the arrangements.

Agreements should also clearly detail that the contract acceptor is responsible for informing the contract giver of any changes in their GMP or legal status.

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Ongoing oversight of Outsourced Activities

- The Contract giver should monitor and review the performance of the contract acceptor.
- The level of oversight/direct supervision of outsourced activities should be determined using QRM principles.
- The Batch certification site & QP is responsible for ensuring that a review of records and results related to the outsourced manufacturing and testing of batches, is performed.
  - This may include a review of manufacturing and testing records by the batch certification site personnel, or rely on a confirmation provided by a QP listed on the contract acceptor's MIA.
- In addition to the ongoing review of records relating to outsourced activities there should also be regular review of the contract acceptor:
  - Periodic review of the contract acceptor, GMP performance,
  - Repeat audit of a CMO/CLO at a frequency determined using QRM principles,

Periodic review of Contract Acceptors performance

- Periodic review contract acceptor performance should utilise QRM principles and should consider:
  - Number and criticality of vendor complaints and deviations raised for the contract acceptor,
  - Number and criticality of customer complaints, quality defect reports received attributed to contract acceptor activities,
  - Product recalls initiated due to contract acceptor activities,
  - Review of the number, complexity and criticality of any changes notified by the contract acceptor,
  - Re-verification of legal and GMP status,
- The QMS of the contract giver should clearly document the status of different contract acceptors and guidance should clearly detail how the outcome of the periodic review process will impact this status.
- In addition to periodic review of performance, there should also be a process to take immediate action when warranted, for example, when a contract acceptor receives a statement of non-compliance or warning letter from competent authorities.

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Annex 16 and Outsourced Activities

- *General Principles…..* ***QP is responsible for ensuring that each*** *individual* ***batch has been manufactured and checked in compliance*** *with laws in force in the Member State where certification takes place,* ***in accordance with the requirements of the marketing authorisation (MA) and with Good Manufacturing Practice (GMP).***

Annex 16 and Outsourced Activities

- ***1.7.1 All activities associated with manufacture and testing*** *of the medicinal product* ***have been conducted in accordance with the principles and guidelines of GMP.***
- ***1.7.2 The entire supply chain of the active substance and medicinal product up to the stage of certification is documented and available for the QP.*** *This should include the manufacturing sites of the starting materials and packaging materials for the medicinal product and any other materials deemed critical through a risk assessment of the manufacturing process. The document should preferably be in the format of a comprehensive diagram, where each party, including subcontractors of critical steps such as the sterilisation of components and equipment for aseptic processing, are included.*
- ***1.7.3 All audits of sites involved in the manufacture and the testing*** *of the medicinal products and in the manufacture of the active substance* ***have been carried out and*** *that the audit reports* ***are available to the QP performing the certification.***
- ***1.7.4 All sites of manufacture, analysis and certification are compliant with the terms of the MA*** *for the intended territory.*
- ***1.7.18 The required technical agreements are in place.***

What does this mean for QP certifying for release?

- Based on Annex 16 the QP certifying for release:
  - Has the responsibility to ensure that suitable GMP has been applied throughout the entire supply chain,
  - Should be able to demonstrate oversight of outsourced activities either by direct involvement or by adequate systems,
  - Should have access to any audit reports for the entire supply chain of the products they are certifying for release to market,
  - Should have access to any quality/GMP agreements in place for the entire supply chain of products they are certifying,
    - If subcontracting is being permitted, it should be ensured that the requirements of Annex 16 paragraph 1.7.18 and Chapter 7 paragraph 7.11 are met.

What does this mean for QP certifying for release

- Annex 16 Paragraph 1.7.18:
  - *The required technical agreements are in place.*

- Chapter 7 Paragraph 7.11:
  - *The Contract Acceptor should not subcontract to a third party any of the work entrusted to him under the Contract without the **Contract Giver's prior evaluation** and approval of the arrangements. **Arrangements** made between the Contract Acceptor and any third party **should ensure that information and knowledge**, including those from assessments of the suitability of the third party, **are made available in the same way as between the original Contract Giver and Contract Acceptor.***

Oversight of QP certifying for release

- QP and batch certification site may be asked to demonstrate that arrangements are defined and adequate systems are in place that allow oversight of the following:
  - Process Validation activities,
  - Cleaning Validation activities,
  - Analytical methods validation,
  - Changes that may have impact on the product being certified,
  - Deviations that may have an impact on the product being certified,
  - Quality Defect Reports/ Product recalls that may represent an impact to the product being certified,

Annex 16 and Outsourced Activities

- Annex 16 paragraph 1.7 does allow for the QP to delegate tasks to members in the same Pharmaceutical quality system or third parties. Provided this delegation is **well founded**.
  - Q.1 What's considered well founded for delegation in the same organisation?
  - Q.2 What's considered well founded for delegation to a third party?

Annex 16 - Sharing of responsibilities between QPs

- Products manufactured in the EU/EEA
  - *1.4.2* ***The QP who performs certification of the finished product batch may assume full responsibility for all stages of manufacture*** *of the batch* ***or this responsibility may be shared with other QPs who have provided confirmation for specified steps*** *in the manufacture and control of a batch. These could be other QPs who are operating under the same manufacturing authorisation (MIA) holder or QPs operating under different MIA holders.*
  - *1.4.3* ***Any sharing of responsibilities amongst QPs*** *in relation to compliance of a batch* ***must be defined in a document formally agreed by all parties. This document should detail responsibility for assessment of the impact any deviation(s)*** *has/have on compliance of the batch with GMP and the MA.*

Annex 16- Sharing of responsibilities between QPs

- Products imported from third countries:
  - *1.5.2 ……the* ***QP certifying the finished medicinal product batch may take account of the confirmation by, and share defined responsibilities with, other QPs in relation to any manufacturing or importation operations taking place at other sites in the EU and other manufacturing authorisation holders defined in the relevant MA.***

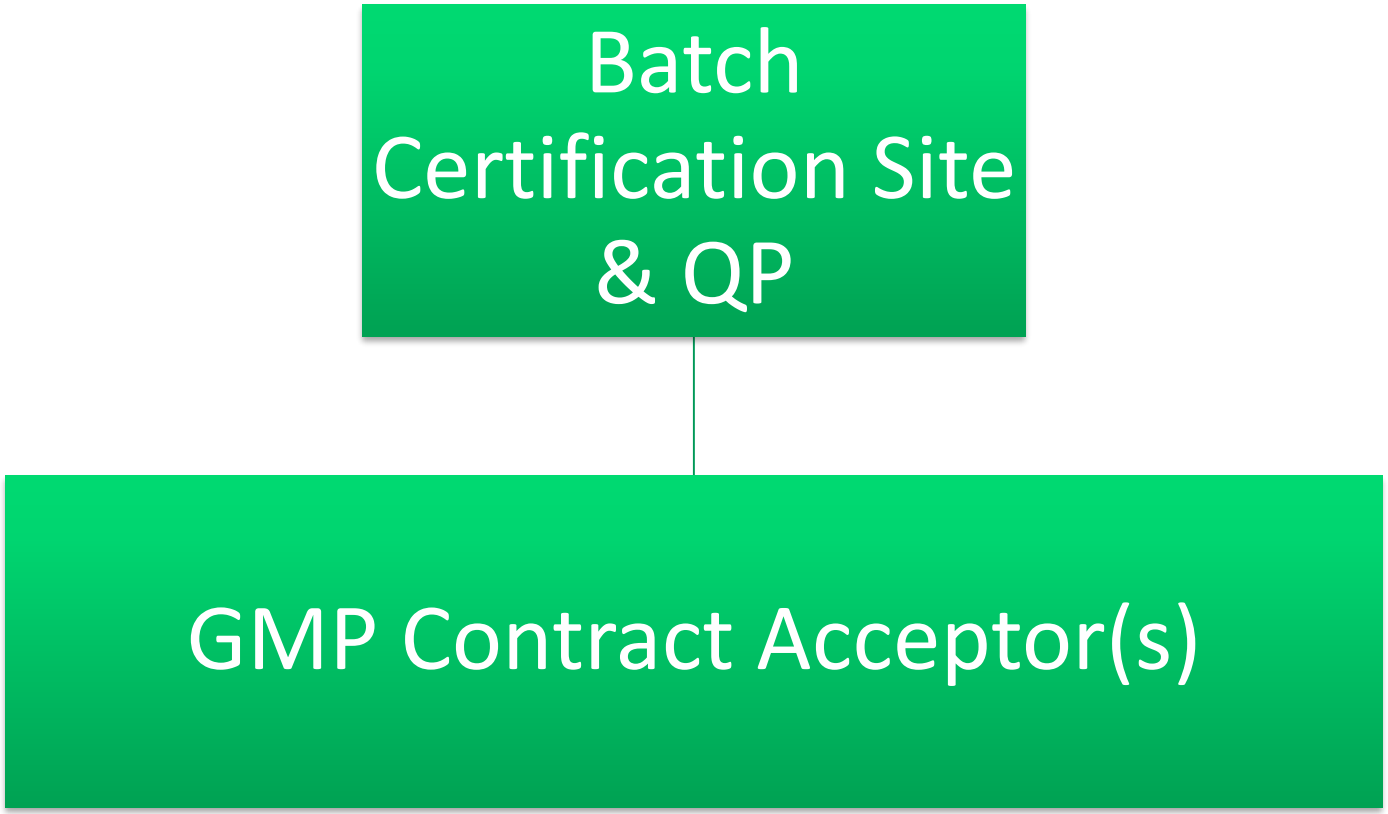
Sharing of responsibilities between QPs

- What does this mean:
  - QP certifying for release can rely on QP confirmation by QP at EU CMO site for activities performed at that site. If clearly defined in contract/agreement. In this regard the releasing QP may not have responsibility to ensure review batch records and quality records for each batch is performed, for activities at the EU CMO which are being confirmed by a QP at that site.
  - QP certifying for release can rely on QP confirmation by QP at EU CMO for manufacturing activities performed in third country. However, the QP providing confirmation must be named as a QP on the MIA of a site that is performing further manufacturing in the EU or acting as the site of physical importation for the relevant batch(s).
  - It is the releasing QP that is choosing to share responsibility and as such the sharing of the responsibility should be **'well founded'** by the releasing QP .
    - In this regard, the arrangements should be managed as per Chapter 7 of the EU GMP Guide.

Annex 16- Sharing of responsibilities between QPs

- ***1.3…Regardless of how many sites are involved, the QP performing certification of the finished product must ensure that all necessary steps have been completed*** *under accepted pharmaceutical quality systems* ***to assure compliance of the batch with GMP, the MA and any other legal obligations*** *in the Member State where certification is taking place.*
- EU GMP Guide Supplementary requirements-Annex 16:
  - *Q2:Can there be more than one QP involved in the certification of a given batch?*
  - *A2: In such cases,* ***the overall responsibility for correct manufacture of the batch lies with the QP performing final certification*** *of the batch before release for sale.*

Responsibilities with respect to outsourced activities



Resources

- Directive 2001/83/EC on the Community code relating to medicinal products for human use

EUR-Lex - 32001L0083 - EN - EUR-Lex (europa.eu)

- Eudralex Vol 4, GMP Guide Chapter 7: Outsourced Activities

https://ec.europa.eu/health/system/files/2016-11/chapter4_01-2011_en_0.pdf

- Eudralex Vol 4, GMP Guide Annex 16: Certification by a Qualified Person and Batch Release

https://ec.europa.eu/health/system/files/2016-11/v4_an16_201510_en_0.pdf

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Thank you