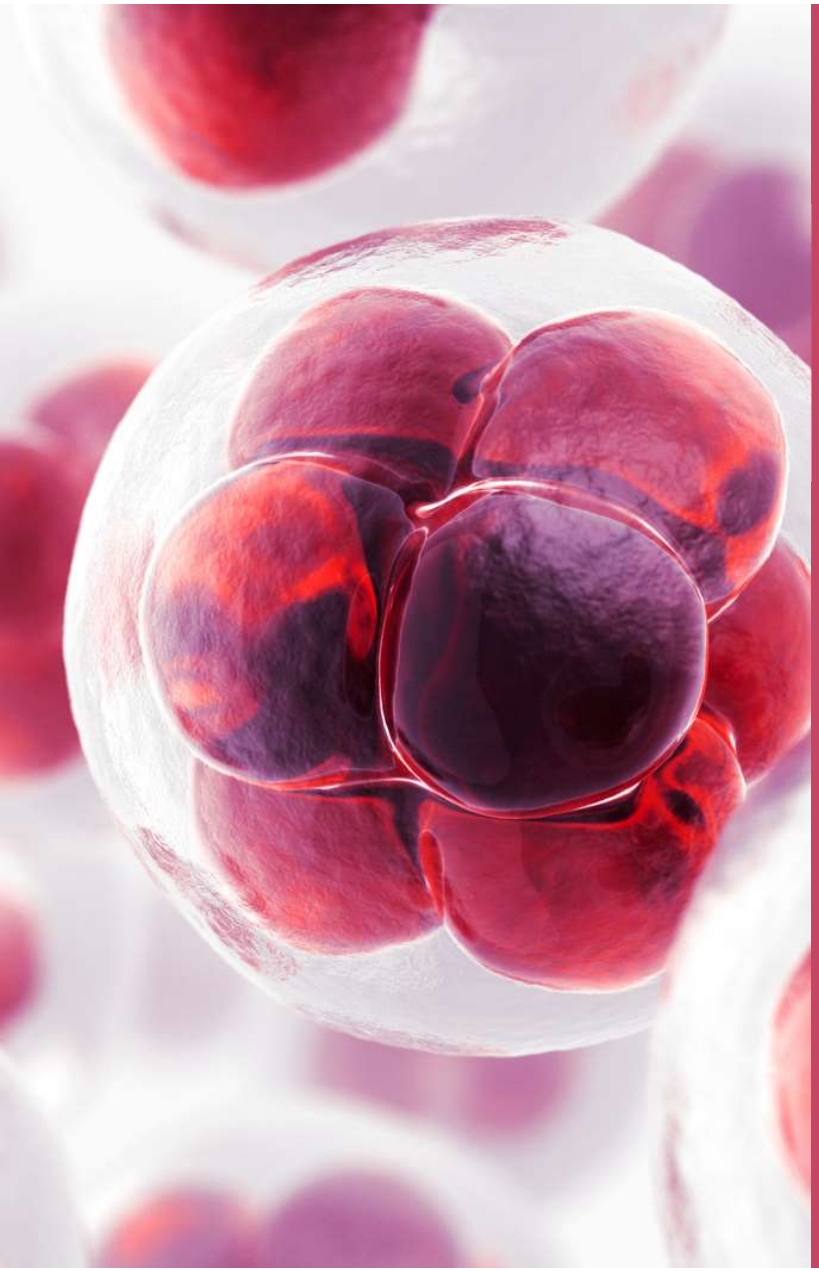

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Leveraging Affordable Solutions for Advanced Therapies

Your
ATMP
community

Leveraging Affordable Solutions for Advanced Therapies.

Mission

at.las is a translational organisation, focused on early development and accelerating the ‘go-to-patient’ process for advanced therapies by bridging the innovation gap

Approach

Matchmaking

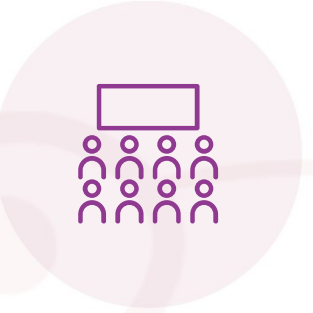
Facilitate contact between ATMP stakeholders

Learning

Stimulate the exchange of expertise

Innovating

Initiate collaborative projects to solve sector challenges



Training

Set up / promote ATMP specific training programs

at.las - learning

Webinars / seminars

- Data Integrity: Manage your Data end to end.
- Clinical Development of ATMPs: narrowing the gap between clinical trial and go-to market.
- ATMP development/insights into the Belgian Framework around CTR/CTIS

Joris De Wolf (eyetec) will set the scene and cover the guidelines and directives.
Sam Vanleene (anicells) and Louise De la Mane (UZ Ghent) will talk about their own experience as QP in the translation of the guidelines into a capable process.
Bram Keymolen will moderate the Panel Discussion where David Craeye (Fishway) and Marlin Frechette (FUJIFILM Irvine Scientific) will join and share their experiences and insights from the viewpoint of user and manufacturer of raw materials.

Do not hesitate adding your comments and questions in the chat!

Supplier qualification

Applied to Pharmaceutical Industry

Joris De Wolf
eyetec
ATMP and Sterile manufacturing QA lead

eyetec
compliant pharma solutions

Intro

What is supplier qualification?

- Vital part of the general quality system
- Process to choose the correct supplier for components, raw materials and critical services
- Process to thoroughly evaluate candidates
- Identifying and mitigating associated risks
- More than just performing an Audit!

Intro

Why perform supplier qualification?

- Responsibility of the manufacturer to ensure product quality end to end
- Ensure product quality is up to your own standards
- Provide confidence in supplier to deliver consistent quality
- Regulatory requirement

How to perform supplier qualification

- List potential suppliers
- Assess potential suppliers
- Mitigate associated risks
- Approve the supplier
- Monitoring

Rules and Regulations

- Expectations from GMP regulating authorities
- Found throughout and built into the general GMP guidelines:
  - FDA: USA government
    - https://www.fda.gov/regulatory-information
  - EMA: European Government → Eudralex
    - https://ec.europa.eu/health/medicinal-products/eudralex_nl
  - PIC/S: global CO-OP from 54 participating authorities
    - https://picscheme.org/en/publications

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Rules and Regulations

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

- EU directive 2001/83/EC: Medicinal product for human use

Article 8 of EU-Directive 2001/83/EC
"*The application [of a marketing authorization] shall be accompanied […] by […] a written confirmation that the manufacturer of the medicinal product has verified compliance of the manufacturer of active substance with principles and guidelines of good manufacturing practice by conducting audits.*"

Article 46 of EU-Directive 2001/83/EC
"*The holder of a manufacturing and/or import authorisation shall at least be obliged […] to use only active substances, which have been manufactured in accordance with GMP for active substances and distributed in accordance with GDP for active substances and … to ensure that the excipients are suitable for use in medicinal products by ascertaining what the appropriate GMP is.*"

Article 46b of EU-Directive 2001/83/EC
"*Active substances shall only be imported if they have been manufactured in accordance with standards of good manufacturing practice at least equivalent to those laid down by the European Union*". This can be shown by a written confirmation or the exporting country is included in the so called white list or a waiver has been granted.

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Rules and Regulations

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

- EU Guidelines: Eudralex part I chapter 5 (starting materials 5.27 – 5.39)

5.27 The selection, qualification, approval and maintenance of suppliers of starting materials, together with their purchase and acceptance, should be documented as part of the pharmaceutical quality system. The level of supervision should be proportionate to the risks posed by the individual materials, taking account of their source, manufacturing process, supply chain complexity and the final use to which the material is put in the medicinal product. The supporting evidence for each supplier / material approval should be maintained. Staff involved in these activities should have a current knowledge of the suppliers, the supply chain and the associated risks involved. Where possible, starting materials should be purchased directly from the manufacturer of the starting material.

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Rules and Regulations

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- EU Guidelines: Eudralex part I chapter 5 (starting materials 5.27 – 5.39)
  - Destinction made: Active substance vs Excipients

Active substances[1]

Supply chain traceability should be established and the associated risks, from active substance starting materials to the finished medicinal product, should be formally assessed and periodically verified. Appropriate measures should be put in place to reduce risks to the quality of the active substance.

Audits should be carried out at the manufacturers and distributors of active substances to confirm that they comply with the relevant good manufacturing practice and good distribution practice requirements. The holder of the manufacturing authorisation shall verify such compliance either by himself or through an entity acting on his behalf under a contract. For veterinary medicinal products, audits should be conducted based on risk.

Excipients

Excipients and excipient suppliers should be controlled appropriately based on the results of a formalised quality risk assessment in accordance with the European Commission 'Guidelines on the formalised risk assessment for ascertaining the appropriate Good Manufacturing Practice for excipients of medicinal products for human use'.

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Rules and Regulations

EUROPEAN MEDICINES AGENCY
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- EU Guidelines: Eudralex part II chapter 7 (outsourced activities)
  - Responsibilities of contract giver

7.4 The pharmaceutical quality system of the Contract Giver should include the control and review of any outsourced activities. The Contract Giver is ultimately responsible to ensure processes are in place to assure the control of outsourced activities. These processes should incorporate quality risk management principles and notably include:

7.5 Prior to outsourcing activities, 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 is also responsible for ensuring by means of the Contract that the principles and guidelines of GMP as interpreted in this Guide are followed.

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Rules and Regulations

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- EU Guidelines: Eudralex part II Annex 16 (QP certification)
  - Roles and responsibilities

QP : Qualified person of the MAA holder is responsible for supplier qualification

In addition, the QP has responsibility for ensuring points 1.7.1 to 1.7.21 are secured. These tasks may be delegated to appropriately trained personnel or third parties. It is recognised that the QP will need to rely on the pharmaceutical quality system and the QP should have on-going assurance that this reliance is well founded.

1.7.6 The source and specifications of starting materials and packaging materials used in the batch are compliant with the MA. Supplier quality management systems are in place that ensure only materials of the required quality have been supplied.

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- EU Guidelines: Eudralex part II Chapter 2 (personnel)
  - Roles and responsibilities

In the end: It is a joint effort

2.9 The heads of Production, Quality Control and where relevant, Head of Quality Assurance or Head of Quality Unit, generally have some shared, or jointly exercised, responsibilities relating to quality including in particular the design, effective implementation, monitoring and maintenance of the quality management system. These may include, subject to any national regulations:

vi. The approval and monitoring of suppliers of materials;
vii. The approval and monitoring of contract manufacturers and providers of other GMP related outsourced activities;

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- EU Guidelines: Eudralex part IV: ATMP specific
  - More focus on Risk based approach (general for everything in part 4)
  - No specific mentioning of mandatory supplier qualification
    - Is suggested as a tool for risk mitigation as part of the control strategy
    - All elements of supplier qualification (e.g. Quality agreements, auditing, questionnaire,…) are mentioned

7.15. The ATMP manufacturer should verify compliance of the supplier's materials with the agreed specifications. The level of supervision and further testing by the ATMP manufacturer should be proportionate to the risks posed by the individual materials. Reliance on the certificate of analysis of the supplier is acceptable if all the risks are duly understood and measures are put in place to eliminate the risks or mitigate them to an acceptable level (*e.g.* qualification of suppliers). For raw materials that are authorised as medicinal products in the EU (*e.g.* cytokines, human serum albumin, recombinant proteins) the certificate of analysis of the supplier is not required. Where available, the use of authorised medicinal products is encouraged.

9.16. All incoming materials should be checked to ensure that the consignment corresponds to the order. The specific requirements for raw and starting materials are described in Section 7. For other materials, reliance on the documentation provided by third parties (*e.g.* supplier) is acceptable provided that all risks are duly understood and that appropriate measures are put in place to eliminate the risks or mitigate them to an acceptable level (*e.g.* qualification of suppliers). Where necessary, identity verification and/or testing should be considered.

Rules and Regulations

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- EU Guidelines: Eudralex part IV: ATMP specific
  - More focus on Risk based approach (general for everything in part 4)
  - No specific mentioning of mandatory supplier qualification
    - Except for primary packaging materials

> 9.75. The level of documentation regarding the demonstration of suitability of the primary packaging material should be adapted to the phase of development. For production of authorised ATMPs, selection, qualification, approval and maintenance of suppliers of primary packaging materials should be documented.

- General conclusion for ATMP: a process for supplier qualification is expected and should be applied based on the risk of the material or service

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Rules and Regulations

- Other guidelines:
  - PIC/S Guide to GMP – Part I: Chapter 5 – Production (Starting materials and packaging materials), Chapter 7 – Outsourced Activities
  - PICS/ Guide to GMP – Part II: Chapter 7 – Materials Management
  - ISO 13485 – Clause 7.4.1 Purchasing process, 7.4.2 Purchasing information, 7.4.3 Verification of purchased products
  - FDA Quality System Regulation 21 CFR Part 820.50 – Purchasing controls


Thank you for your attention

Supplier Qualification: Best Practices

Louise De la Mane - Qualified Person Clinical Trials Cell- and Gene Therapy UZ Gent

Sam Vanleene - QA/QC Manager anicells

anicells

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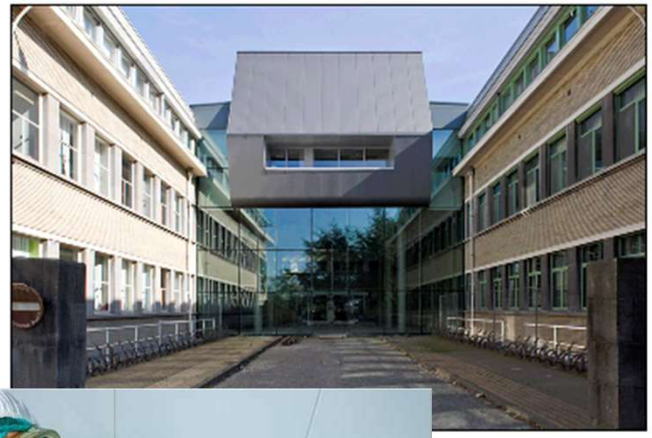
GMP unit Cell Therapy

UZ GENT

- GMP Production of iATMPs
- Our goal is to facilitate **moving research "from bench to bedside"** at the U(Z) Gent by providing expertise, equipment and a licensed facility for the production of cell and gene therapeutics to investigators.
- Focus on production for phase I/II clinical trials



- **Dendritic Cell Vaccines:**
  - Midrix-4-lung: Phase 1 completed
  - Midrix-Neo: Phase 1 completed
- **Production Virus Specific T-cells with CliniMACS Prodigy (TRACE, phase III)**
- **Production mRNA encapsulated Lipid Nanoparticle (LNP) vaccines**

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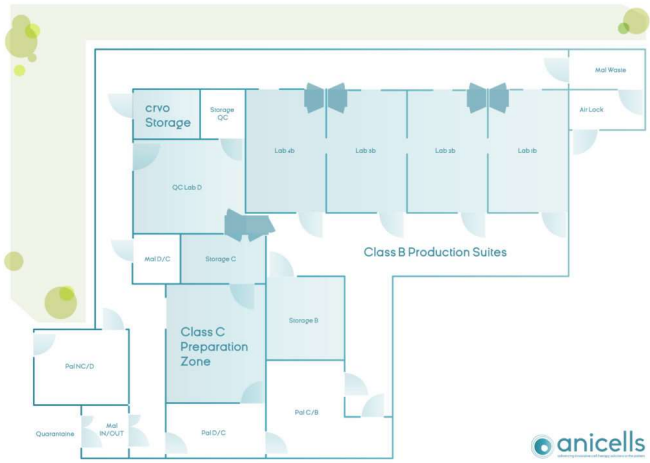
advancing innovative cell therapy solutions to the patient

- GMP compliant manufacturing of cell- and gene therapy
- Support services for clinical cell therapy development

- Main focus on Ph I/II clinical trials
- Aim to facilitate the go-to-patient process

- **Dendritic Cell vaccines**
- **CAR T-cells**
- **Mesenchymal Stem Cell-derived EVs**
- **…**



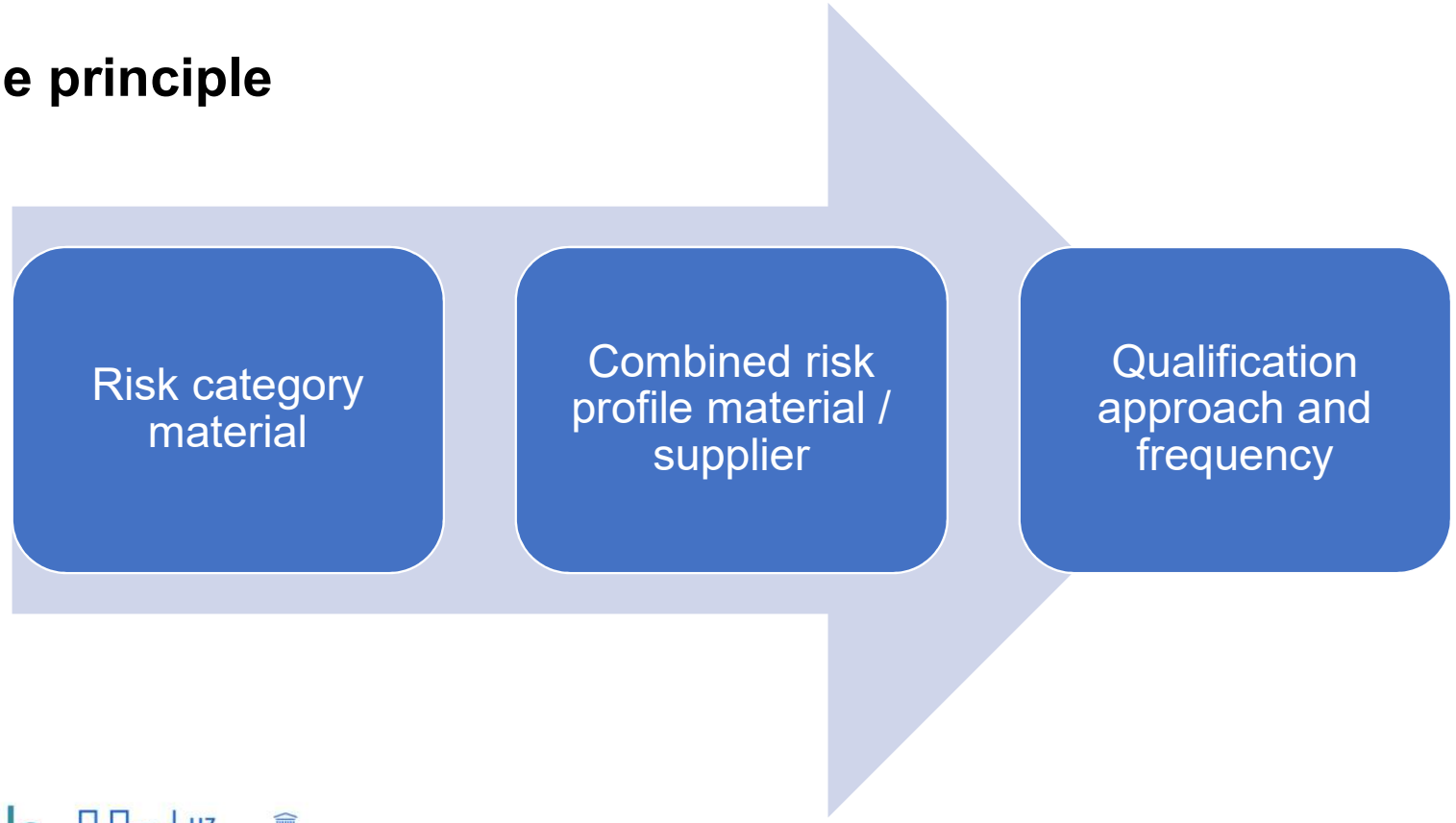
What is Supplier Qualification and why do it?

- Provides confidence that supplier can supply materials and components with a consistent quality in compliance with regulatory and clients' requirements
- More than auditing, it can be used as a risk assessment tool to identify and mitigate the associated risk of materials and components
- Includes initial qualification and requalification

➢Requires an adequate change management system - changes at the supplier´s site (for example manufacturing process etc.) should be assessed to determine impact on pre-established requirements

Comparison processes **UZ Gent** and **anicells**

- **Same principle**



Side note

Registered drugs, medical devices and in vitro diagnostics with an approved MA require no supplier qualification or incoming QC testing.

Comparison processes **UZ Gent** and **anicells**

- **Different emphasis**

- Focus and approach of risk analysis is different:

  BUT important aspects in both processes

  1) Biological origin per EP 5.2.12

  2) Certification of quality system of supplier

  3) Intended use of material

- 1-step supplier qualification process vs. 2-step supplier approval and qualification process

- Reduction of incoming QC after qualification of supplier

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Biological origin

- In accordance with **EP 5.2.12**
  - Origin (human, animal, free of human or animal material)
  - Viral safety
  - TSE / BSE risk
  - Overview of control measures to minimize / remove contamination and impurities during the production process
  - CoA with identity, purity and biological activity
- Products from human blood or tissue must comply with the applicable law on human body material, including serological test results.

Example: “GMP grade” culture medium

- **CellGenix GMP DC Medium (Sartorius)**

➢ Category of use: production reagent

➢ Quality parameters:

- ISO 9001 certification
- Biological origin
- Commercial off-the-shelf

Example: “GMP grade” culture medium

- **CellGenix GMP DC Medium (Sartorius)**

➢ Category of use: production reagent ➔ High risk

➢ Quality parameters: ➔ (++)

- ISO 9001 certification (+)
- Biological origin
- Commercial off-the-shelf (+)

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Example: “GMP grade” culture medium

- **CellGenix GMP DC Medium (Sartorius)**

➢ Category of use: production reagent ➔ High risk

➢ Quality parameters: ➔ (++)

- ISO 9001 certification (+)
- Biological origin
- Commercial off-the-shelf (+)

➔ Medium risk profile

➢ Paper audit via questionnaire, QTA optional

➢ Incoming QC ➔ functionality test

➢ Qualification requires analysis of 3 batches ➔ based on past results: no reduction of incoming QC

➢ Periodic review: yearly review of deviations and complaints, 3-yearly questionnaire

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Example: “research grade” reagent

- **Growth factor PRE-GMP rHu GM-CSF (Gentaur)**

➢ Category of use: production reagent

➢ Quality parameters:

- No certification for quality standard
- Biological origin
- Limited information available

Example: “research grade” reagent

- **Growth factor PRE-GMP rHu GM-CSF (Gentaur)**

➢ Category of use: production reagent ➔ High risk

➢ Quality parameters: ➔ -

  - No certification for quality standard
  - Biological origin
  - Limited information available

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Example: “research grade” reagent

- **Growth factor PRE-GMP rHu GM-CSF (Gentaur)**

➢ Category of use: production reagent ➔ High risk

➢ Quality parameters: ➔ -

- No certification for quality standard
- Biological origin
- Limited information available

➔ High risk profile

➢ On-site audit and QTA

➢ Incoming QC

➢ Qualification requires analysis of 10 batches

➢ Periodic review: yearly review of deviations and complaints, 3-yearly audit

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Example: “GMP grade” reagent

- **Peptide for in vitro stimulation of EBV-specific CD4+ and CD8+ T-cells**

➢ *Risk Category of the product*

- Based on risk assessment (FMEA) considering standard risks in accordance with EP 5.2.12 , each risk is scored based on probability of occurrence, detectability and severity of the risk
- The probability of occurrence takes into account the manufacturing process of the incoming good and quality system of the production unit (GMP, ISO,…)
- The severity is based on the impact on the patient and compliance. Score is lower when material is not part of final drug product (e.g., washing steps in production process)
- Risk Category of product: **Low**
    - ISO13485 certificate
    - Not part of final drug product

Risicocategorie goed	Leverancier uit ICH-land	Leverancier uit niet-ICH-land
Hoog	Cat II	Cat III
Midden	Cat II	Cat II
Laag	Cat I	Cat II

➢ *Combined risk product/supplier*: **Cat I**

➢ **Immediate qualification**

➢ **No requalification (unless changes or problems with supplier)**

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Conclusion

- **Risk based** qualification approach per material
- Early evaluation of materials to be used in development is recommended
- Preferred use of raw materials free from human or animal substances
- Significant difference between “GMP grade” vs. “research grade” **=** availability of information
  - ➔ GMP grade ≠ GMP certification

Challenges

- Time consuming
- Long response time of suppliers
- Often no readily available information at suppliers – no “GMP grade” alternative
- Large number and fast-changing materials (early development)
- Requires a reliable change notification system from the supplier
- Developers underestimate the impact of material and/or supplier changes

Thank you for your attention!

Questions? Remarks? Ideas for next topics?
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