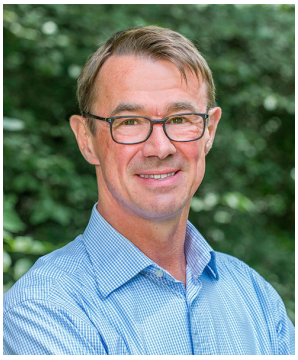
CELL & GENE THERAPY INSIGHTS

SUPPLY CHAIN FOCUS: CRITICAL RAW & ANCILLARY MATERIALS

CHANNEL CONTENT

EDITORIAL

How to standardize quality requirements of raw materials



"Audits allow cell and gene therapy manufacturers to ensure that the raw material supplier has a clearly defined system for quality monitoring in place. This will help to determine if they are compliant with local and global quality requirements."

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The manufacture of cell and gene therapies (CGT) is particularly sensitive and requires a comprehensive understanding of the materials used in the manufacturing process to ensure a safe, efficacious, and high-quality product. Successful CGT manufacturing is therefore dependent on the use of high-quality raw materials (ancillary materials according to the USP). The manufacturing of raw materials for CGT manufacturing is however not well regulated and is not supervised by any health authority. Despite arising guidance in this area existing guidelines are, essentially, recommendations rather than guidelines. Geographical discrepancies make regulatory considerations even more complex. Each

region has its own regulatory agencies that view CGT manufacturing in a different way. Getting a clear understanding of regulatory requirements around the quality of raw materials can therefore be challenging. Consequently, we advise to choose raw materials that comply to all global regulatory guidelines. Current existing guidelines are:

- USA: USP Chapter <1043> [1], USP Chapter <92> [2]
- Europe: Ph. Eur. General Chapter 5.2.12 [3]
- Global: ISO Technical Standard-20399 [4]

An additional challenge arises from the fact that all current regulations and guidance documents are not aimed at the manufacturers of the raw materials. Instead, they assign ultimate responsibility for quality and suitability of the raw materials to the user, the CGT manufacturer. Raw material suppliers and the quality of their products is not certified by regulatory bodies, the user himself is responsible to verify compliance to quality standards. As one result, most CGT manufacturers decide to perform identity and purity testing as raw material control tests. Potency testing for raw materials is however difficult, especially since there is a large variability and poor comparability of available biological assays.

Standardization of quality requirements of raw materials would bring much needed regulatory harmonization. Until such quality standards are set, CGT manufacturers need to work in close cooperation with their supplier to get the necessary support. Raw material suppliers should offer full transparency to mitigate the risk to an acceptable level. They can do this by providing:

1) DETAILED BATCH SPECIFIC TEST RESULTS ON THE CERTIFICATE OF ANALYSIS (COA)

Detailed batch specific test results make it easier for both the CGT manufacturer and the regulatory agencies to assess the raw material product quality as well as regulatory compliance. It in addition makes it easier to compare raw materials from different batches or suppliers. Batch specific test results including their validated test methods should cover identity, quantity, purity and impurities, and safety.

2) THE POSSIBILITY TO AUDIT THE MANUFACTURING SITE

Audits allow CGT manufacturers to ensure that the raw material supplier has a clearly defined system for quality monitoring in place. This will help to determine if they are compliant with local and global quality requirements.

3) COMPREHENSIVE PRODUCT-SPECIFIC DOCUMENTATION (E.G. DRUG MASTER FILES (DMF), REGULATORY SUPPORT FILES, TSE CERTIFICATES, & CUSTOMIZED DOCUMENTATION FOR REGIONAL AUTHORITIES)

Being able to provide product-specific documentation for critical raw materials to authorities speeds up the regulatory approval process. Since regional authorities can ask for varying documentation, we recommend choosing a raw material supplier that is able to offer customized documentation on request.

4) DOCUMENTATION ON PRODUCT STABILITY & CONSISTENCY STUDIES PERFORMED BY QUALITY CONTROL

Extensive stability studies should be conducted by the raw material supplier to determine the maximum shelf life for all raw materials and recommended storage conditions. These studies ensure that the raw materials remain consistent throughout the

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recommended storage times under appropriate storage conditions. To ensure the quality and consistency of raw materials, consistency studies should in addition be performed by the raw material supplier. The importance of batch-to-batch consistency of critical raw materials is also emphasized in Ph. Eur. General Chapter 5.2.12 [3] and ISO Technical Standard-20399 [4].

5) WELL DEFINED ANIMAL-DERIVED COMPONENT-FREE (ADCF) POLICY

Materials of biological origin, particularly of human or animal origin, can present risks, including transmission of adventitious agents or introduction of biological impurities. This does not necessarily limit the use of animal-derived components for manufacturing raw materials. The main purpose of defining ADCF is to provide necessary information for a user's risk assessment of raw materials. ISO Technical Standard-20399 [4] defines two ADCF levels:

- Level 1 (product level): the raw material does not contain any materials from animal or human source as its ingredients.
- Level 2 (production level): in addition to ADCF level 1, raw material is produced without the use of any materials from an animal or human source. This includes excipients, equipment or containers that come into contact with the raw material during production.

6) CHANGE NOTIFICATIONS PRIOR TO RELEVANT PRODUCT CHANGES

Changes related to product specifications, labels, formulation, packaging, expiry dates or the production process should be communicated well in advance. This ensures that the CGT manufacturer can put the necessary preparations in place without causing delays in their production process.

To help improve existing regulatory guidance we are actively involved in many regulatory initiatives and discussions. Together with the USP we have written the first version of USP chapter <92> [2]. We were also actively involved in the discussions for the setup of Ph. Eur. General Chapter 5.2.12 [3] and contributed to the ISO Technical Committee TC276. This committee issued the first global guidance for raw materials suppliers and users – ISO Technical Standard 20399 [4] – which is currently being processed into an ISO standard to improve global reach and acceptance. The guidance provides general requirements and guidance to ensure the quality and consistency of raw materials used in CGT manufacturing.

An initiative in which we are currently involved is one from the Alliance for Regenerative Medicine (ARM). They approached the European Directorate for the Quality of Medicines (EDQM) about the possibility of setting up a certification scheme for raw materials according to European Pharmacopoeia (Ph. Eur. General Chapter 5.2.12 [3]). This initiative is of critical importance because compliance to this general chapter is already demanded by regulators. Hence, a certification scheme would ease the regulatory burden for CGT manufacturers.

Another initiative that we are involved in is from the European Medicines Agency (EMA), who is evaluating the possibility of introducing a master file system in Europe. Drug Master Files (DMF) for raw materials are currently only available in the USA and Japan. A DMF is a regulatory instrument that provides confidential detailed information about the manufacturing conditions of a raw material (product's chemistry, manufacture, raw materials used, stability, purity, impurity profile and packaging). It enables the raw material manufacturer to protect its intellectual property by allowing the FDA (or PMDA in Japan) to review the information in support of a third party's submission. Using the detailed information provided in a DMF, the FDA can make a thorough assessment of the raw

material's quality and lot-to-lot consistency. Because of its great value to CGT manufacturers we have submitted eCTD DMFs to the FDA for our serum-free media and the large majority of our GMP cytokines. We currently offer the largest collection of eCTD DMFs for cytokines and growth factors.

Although these initiatives are promising, we propose that special workgroups should be set up that work on setting global quality standards for raw materials for CGT manufacturing. This would help reaching more global alignment between regulatory agencies.

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3. Ph. Eur. General Chapter 5.2.12 Raw materials of biological origin for the production of cell-based and genet therapy medicinal products
4. ISO/TS 20399-1:2018 Biotechnology – Ancillary materials present during the production of cellular therapeutic products – Part 1: general requirements. ISO/TS 20399-2:2018 Biotechnology – Ancillary materials present during the production of cellular therapeutic products – Part 2: Best practice guidance for ancillary material suppliers. ISO/TS 20399-3:2018 Biotechnology – Ancillary materials present during the production of cellular therapeutic products – Part 3: Best practice guidance for ancillary material users

BIO

Bernd Leistler

Bernd Leistler has a long track record as protein specialist. He joined CellGenix in 2003 and is currently responsible for all GMP and preclinical cytokine products for further manufacturing use, as well as process development for protein production which includes new packaging formats. Following his degree in chemistry he completed his dissertation on the structure, function, folding and assembly of oligomeric proteins. His professional career started at a leading manufacturer of diagnostic autoantibody immunoassays, where he managed the Biotechnology Department and developed it as a corporate service unit for recombinant and conventional human autoantigens and allergens.

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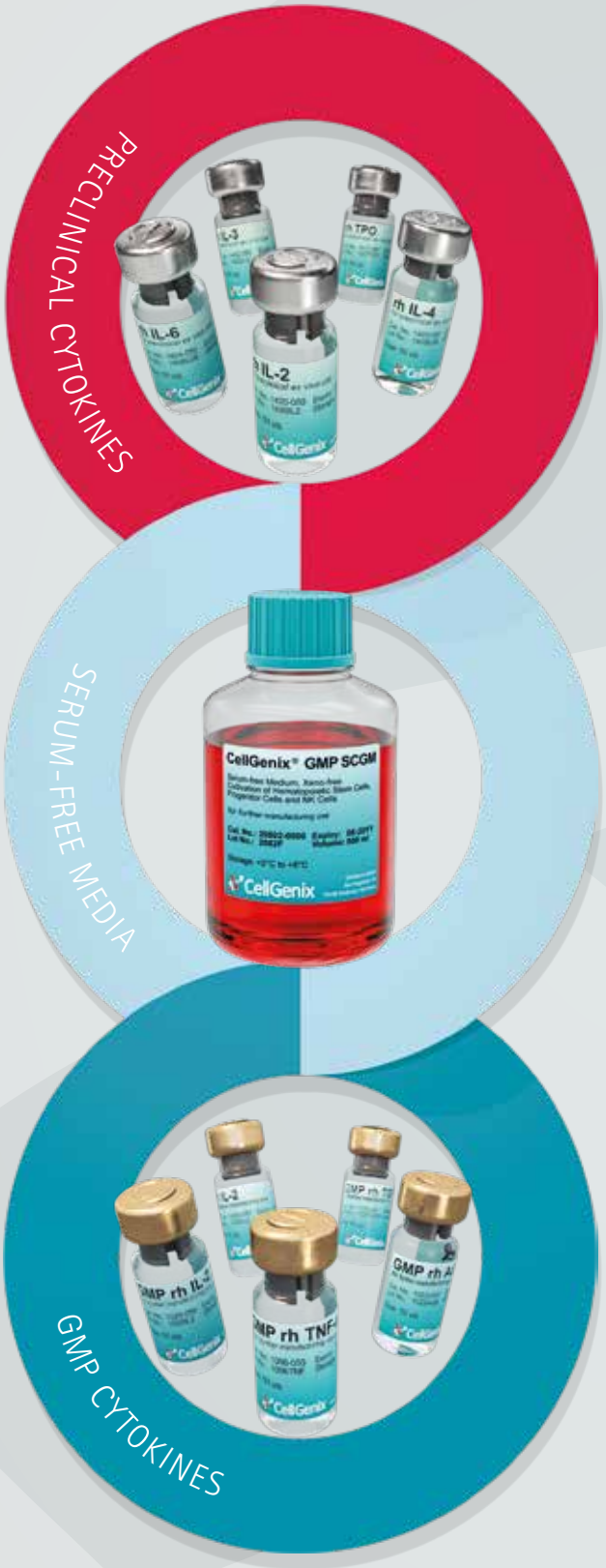

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