CELL CULTURE MEDIA AND REGULATORY

Media, GMP and ISO:13485.
A brief guideline for users

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Executive Summary

Although "GMP - certified" cell culture media do not exist on the market, the cooperation with the right media manufacturer guarantees sufficient and GMP - compliant documentation of the raw material "cell culture medium" to those customers who themselves are subject to high regulatory requirements.

Cell culture media and regulatory – an introduction

Cell culture media - customers who are not only involved in research but who are e.g. planning to go into clinical trials or who come from biopharmacy often face the same questions:

- *How can I, as a user, assess the quality and safety of my cell culture media?*
- *How can I document this?*
- *What should I pay attention to when choosing my media manufacturer?*

Today, cell culture-based techniques are used in a variety of fields: from established methods in vaccine production through toxicological investigations to novel cell-based therapies (ATMPs) - cell culture is becoming increasingly important.

Cell culture media play a not insignificant role in the manufacturing process of these products and applications.

The manufacturers of such products are often subject to strict legal regulations and (GMP) regulations. They must therefore ensure the safety of all materials introduced into the processes and also document this.

Often, in the supply chain, this demand for quality and safety can be passed down and be proven e.g. by the existence of a "GMP certificate" for the material in question.

In the case of cell culture media, it is not as easy as that. Why - and how it still can be done - is explained below.

GMP for cell culture media ?

Many ambiguities regarding the quality of cell culture media can be broken down to the question

"Are there GMP-certified cell culture media?" The answer is **"No".**

The explanation for this fact is rather simple: In order for a product to receive a regulatory "GMP certificate"[1], it must first of all be covered by corresponding legislation[2].

This is the case, e.g. for pharmaceuticals or active pharmaceutical ingredients (APIs). But not for cell culture media. These are classified only as "raw material" (EU - GMP Guidelines[3]) or as "ancillary material" (US - FDA) - and therefore do not fall into the category of a GMP - certifiable product. Since voluntary certification is not possible, there are simply no "GMP-certified" cell culture media.

It remains to be noted:

"GMP certified" media are not required by law / regulators - and therefore do not exist.

Alternative Certificates

What other options does the customer have to recognize if a media manufacturer can offer certified high product quality and product safety?

"Are there any other certificates?" Here the answer is **"Yes. The ISO 13485: 2016 for medical devices ".**

The certification of a media manufacturer according to ISO 13485 guarantees something very essential to the customer:

The fact that an extremely comprehensive quality management system is implemented and adhered to. This system covers the entire process chain, from supplier selection to the proper storage of the end product.

The still relatively new ISO 13485: 2016 has replaced the older version (2003) and takes even more account of the special requirements placed on QM systems in the medical device sector.

cGMP goes ISO : 13485

The new edition turned out so well that even the US regulatory agency FDA will adopt it. **The FDA is** already in the process of **replacing the cGMP regulations of the 21 CRFR 820 with ISO 13485: 2016.**[4]

Not only does this contribute to a desirable harmonization of international standards, it also highlights the high standard given to the new ISO 13485.

Additional Documentation

A comprehensive, regulatory-compliant documentation is essential for cell culture media customers who produce substances requiring registration.

Emphasis should be placed on **documented, extended tests** (sterility according to Pharm.Eu, endotoxin level, possibly function test on cell culture) which are **recorded in the CoA**[5].

Other documents such as MSDS[5], CoO[5] or, if necessary, certificates stating freedom from animal components should be available on request.

Above all, however, the media manufacturer should be able to prove and document compliance with important process parameters throughout the entire media production:

This is best done in the form of an extensive **master batch record (MBR)**, which you as a customer receive with the product.
This document should include amongst others things like batch numbers of the starting materials, weighing protocols and results of in-process-control tests.

Ask your media manufacturer for a MBR sample.
It should look familiar to customers who come from a regulated environment themselves – certainly many topics are to be found pretty similar in their own protocols.
A good media manufacturer will also be able to respond to customer-specific requirements at this point.

The aforementioned documents (CoAs etc.) and the MBR can be designed in such detail that all regulatory relevant parameters are covered.

This provides you, the customer, with a GMP-compliant complete documentation of the raw material "cell culture medium".

Practical requirements

In addition, there are of course also "practical" requirements a media manufacturer needs to meet :

The entire production process should take place in a clean room system designed for the production of cell culture media. The customer should pay particular attention to the actually critical process step in media production, namely the aseptic filling:

In order to avoid contamination, **aseptic filling** of cell culture media should always be carried out **in accordance with EU GMP regulations for sterile medicinal products in the room classification "GMP A in B" [6].**

Another point that may be of importance to producers of regulated substances :

Does your media manufacturer offer production in **single-use and / or dedicated equipment**, which is used exclusively for the production of **your media**?

This can be a very effective measure to eliminate cross – contamination risks from the outset - without much validation effort.

Get to know your media manufacturer

Above all it certainly makes sense to get to know your media manufacturer better. Discuss your requirements and how they can be implemented.
If possible, audit your manufacturer. Even if this is initially associated with effort: it is certainly worthwhile in the "long run".

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Appendix

[1] - The colloquial term "GMP certificate" is actually the "confirmation of a manufacturer's compliance with GMP" - and only applies to the certified product, not to the manufacturer or the production site itself

[2] - for the pharmaceutical sector: Directive 2003/94 / EC for medicinal products for human use and Directive 91/412 / EEC for veterinary medicinal products.

[3] - see GMP Guide Annex 2, p. 9, point 18; Guidelines on Good Manufacturing Practice for Advanced Therapy Medicinal Products, p.11, point 2.30

[4] - see for example here: https://www.fda.gov/media/123488/download

[5] - CoA = Certificate of Analysis ; MSDS = Material Safety Data Sheet ; CoO = Certificate of Origin

[6] - See Annex 1 to the EC Guide to Good Manufacturing Practice (Manufacture of Sterile Medicinal Products), S.4