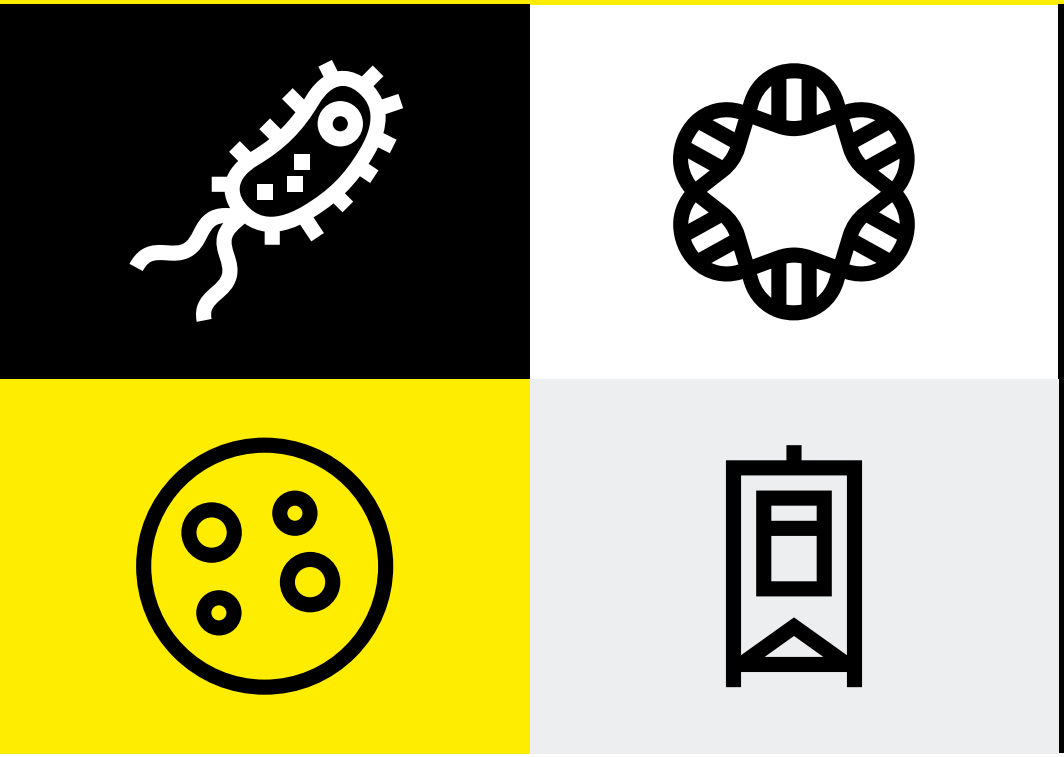
SARTORIUS

Animal-Derived Component-Free Policy

CellGenix® Preclinical and GMP Growth Factors and Cytokines



Technical Note

The quality, safety and efficacy of cell therapies are significantly influenced by the raw (ancillary) materials used in manufacturing. We prioritize safety and reliability to provide the highest quality products for clinical *ex vivo* cell processing.

Executive Summary

We follow a strict animal-derived component-free (ADCF) policy to ensure maximum safety of our preclinical and GMP growth factors and cytokines. As a result no animal or human-derived components are part of any of our growth factor and cytokine products.

The large majority of our growth factors and cytokines are produced in our dedicated animal-free facility (ADCF Level 2). These cytokines have never been exposed to animal components or byproducts. They can therefore be safely used without the need to perform time-consuming and expensive viral safety studies, thereby bringing a significant economic benefit.

Those very few growth factors and cytokines produced in our segregated animal-derived components (ADC) production area require either the use of ADC in the production process or a mammalian expression system to allow proper functional expression (ADCF Level 1).

Figure 1: *Our cytokine product portfolio is divided into two distinct ADCF levels:*

ADCF Level 2	ADCF Level 1
Animal-Free Facility: No ADC in product and production process ▪ Highest safety level: no exposure to animal or human components or byproducts ▪ Save time & money: no viral safety studies needed	ADC Production Area: No ADC in product, but ADC in production process ▪ Require animal or human expression system or ADC in production process ▪ Safety: documented evidence of viral/prion safety

ADCF Level 2

No ADC in product and production process

The final growth factor or cytokine product contains neither animal- nor human-derived materials. ADCF Level 2 cytokines are produced in our dedicated animal-free facility. No animal-derived components are used throughout the complete production process. All ADCF Level 2 cytokines are produced in *E. coli*.

By using only animal-free raw materials, equipment and lab supplies ADCF Level 2 cytokines have never been exposed to contamination by animal components or byproducts.

ADCF Level 2 cytokines

- CellGenix® rh OSM
- CellGenix® rh IFN-γ
- CellGenix® rh Activin A
- CellGenix® rh EGF
- CellGenix® rh Flt-3L
- CellGenix® rh GM-CSF
- CellGenix® rh IL-1β
- CellGenix® rh IL-2
- CellGenix® rh IL-3
- CellGenix® rh IL-4
- CellGenix® rh IL-6
- CellGenix® rh IL-7
- CellGenix® rh IL-10
- CellGenix® rh IL-15
- CellGenix® rh IL-18
- CellGenix® rh IL-21
- CellGenix® rh PDGF-BB
- CellGenix® rh SCF
- CellGenix® rh TNF-α
- CellGenix® rh TPO

ADCF Level 1

No ADC in product, but ADC in production process

The final growth factor and cytokine product contains neither animal- nor human-derived materials. They are derived from a mammalian cell bank or an ADC is used during the production process. These growth factors and cytokines are therefore produced in a segregated production area.

An ADC is only accepted for use in the production process if it presents no apparent health hazard and is compliant with the currently valid note for guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMEA/410/01) as well as the relevant parts of ICH Q5A. When available and applicable, pharmaceutical grade materials are used. The relevant safety aspects as defined in USP <1043> and Ph Eur 5.2.12 have been considered for our products.

No animal-derived material is used in the manufacturing process of IL-12. However, IL-12 is produced in Serum Independent CHO cells (CHOSI). Although derived from animal-originated cell line CHO (Chinese Hamster Ovary) cells are well characterized and widely used in the biotechnological industry. A possible threat caused by viral contimation is considered minimal.

The cell line used for production of TGF-β1 was derived from a well characterized human amniocyte cell line (CAP® [1]) which has been tested for human viral pathogens. A Biologics Master File (BB-MF) for the CAP® cell line was submitted to the U.S. Food and Drug Administration (FDA).

FGF-2 is produced in *E. coli*. With the exception of Heparin of porcine origin immobilized to Sepharose used for the initial purification step, the product is not in contact with animal- or human derived materials during its manufacturing.

ADCF Level 1 cytokines

- CellGenix® rh FGF-2
- CellGenix® rh IL-12
- CellGenix® rh TGF-β1

Raw Material Control

All materials used in the production process are formally approved by our quality management (QM). As part of our raw material control they are procured from reliable manufacturers and suppliers and their origin and impurity profile are assessed before use. The safety of the raw material is demonstrated by certificates of origin and validation reports. In addition, TSE certificates are provided for all our ADCF Level 1 and ADCF Level 2 growth factors and cytokines.

[1] CAP® is a registered trademark of CEVEC Pharmaceuticals GmbH, Germany

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Status: 02 | 2025