



3 clinical trial failures caused by Host Cell Proteins

Host Cell Proteins in clinical trials

Host Cell Proteins are **process-related impurities** that can co-purify with therapeutic proteins in biopharmaceutical drugs and end up in the **final drug product** administered to clinical trial participants.

Some protein impurities can impact **patient safety, treatment efficacy, or drug product quality**.

In worst-case scenarios, residual Host Cell Proteins may cause **harmful immune reactions** in patients.

The cost of ignoring Host Cell Protein impurity risks

Adverse immune reactions can put clinical trial participants and future patients **at risk** – and jeopardize the development success of biopharmaceutical drugs.

Discovering severe adverse reactions during clinical studies usually results in **delays of many years** as the cause is investigated and the manufacturing process optimized.

It may even force the **withdrawal** of a promising compound from the pipeline.

Here are 3 examples of
clinical trial failures
due to Host Cell Proteins

Clinical trial 1

Drug

Recombinant human apolipoprotein

Expression system

E. coli



Trial suspension

A Phase II clinical trial was put on hold after a patient suffered a severe reaction during infusion.

Host Cell Protein

Flagellin

Consequence

The manufacturer required more than a decade to identify and eliminate the bacterial Host Cell Protein before the product could be successfully reintroduced.

Reijers JAA, Malone KE, Bajramovic JJ, Verbeek R, Burggraaf J, Moerland M. Adverse immunostimulation caused by impurities: The dark side of biopharmaceuticals. *Br J Clin Pharmacol*. 2019 Jul;85(7):1418-1426. doi: 10.1111/bcp.13938. Epub 2019 May 29. Erratum in: *Br J Clin Pharmacol*. 2019 Sep;85(9):2182. doi: 10.1111/bcp.14059.

Clinical trial 2

Drug

CTLA4-Ig fusion protein

Expression system

Chinese Hamster Ovary (CHO)

Trial suspension

Adverse events related to histamine release in patients resulted in a clinical hold.

Host Cell Protein

Monocyte Chemoattractant Protein (MCP-1)

Consequence

Further trials were delayed as the manufacturer launched an investigation to identify the impurity and improve immunoassays and orthogonal methods.



Vanderlaan M, Zhu-Shimoni J, Lin S, Gunawan F, Waerner T, Van Cott KE. Experience with host cell protein impurities in biopharmaceuticals. Biotechnol Prog. 2018 Jul;34(4):828-837. doi: 10.1002/btpr.2640.

Clinical trial 3

Drug

mAb blocking interleukin-13

Expression system

Chinese Hamster Ovary (CHO)

Trial suspension

The study was converted from Phase III to Phase IIb and discontinued early as a precautionary measure.

Host Cell Protein

PLBL2

Consequence

Nearly all treated patients showed an immune response. No direct clinical adverse effects were observed.

Hanania NA, Noonan M, Corren J, Korenblat P, Zheng Y, Fischer SK, Cheu M, Putnam WS, Murray E, Scheerens H, Holweg CT, Maciuca R, Gray S, Doyle R, McClintock D, Olsson J, Matthews JG, Yen K. Lebrikizumab in moderate-to-severe asthma: pooled data from two randomised placebo-controlled studies. *Thorax*. 2015 Aug;70(8):748-56. doi: 10.1136/thorax-jnl-2014-206719.



Early identification of Host Cell Proteins of concern

In the past, Host Cell Proteins causing adverse immune responses would often **not be discovered** until clinical trials.

At this stage, root cause analysis and process optimization are both **costly** and **time-consuming**.

Mass spectrometry (LC-MS)-based Host Cell Protein analysis can **identify** and **quantify** problematic impurities during development – enabling **data-driven risk assessment** to ensure the safety, efficacy, and quality of biologics.

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