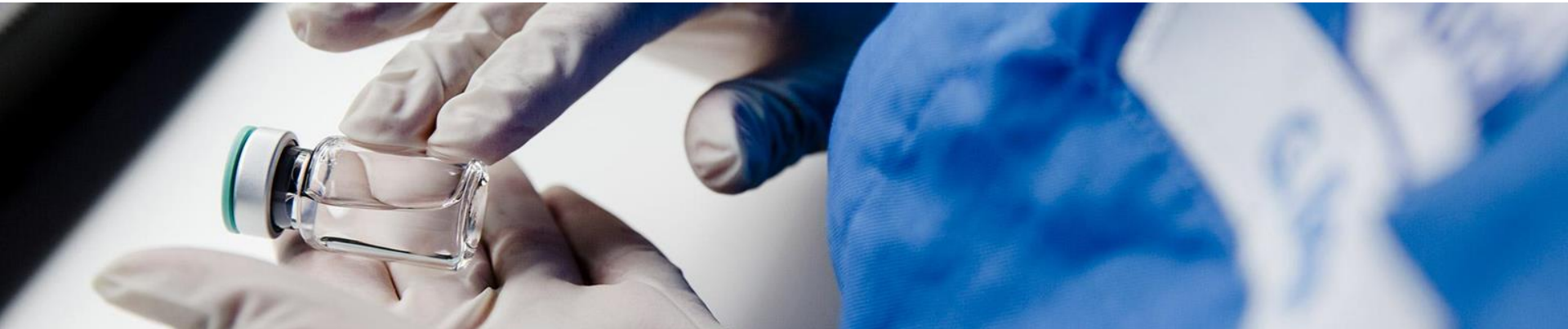

Accelerated Technology Transfer to Meet Demand for a Repurposed Biologic: Challenges, Successes and Lessons Learned

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Content



1. **Evaluation of existing medicines for COVID-19 treatment**
2. **Dynamic adaption of the tocilizumab (Actemra) supply chain - two case studies**
3. **Acceleration of drug product technical transfers: challenges and successes**
4. **Learnings and future outlook**

Genentech / Roche COVID-19 Response: By The Numbers

5
sponsored
clinical trials of
our medicines in
COVID-19



20+



investigator-initiated,
company-supported studies
for 6 of our FDA-approved
medicines*

\$42M



funding for emergency
response and longer-term
community recovery
efforts

1000+



patient support
service calls per day

5



Roche diagnostic
tools

*These medicines are being evaluated for the potential treatment of patients with severe COVID-19 associated symptoms, such as pneumonia. None of these medicines are FDA-approved to treat COVID-19 or associated symptoms.

Roche's Investigational Medicines for COVID-19

20+ investigator-initiated,
company-supported studies
for 6 of our FDA-approved
medicines[^]

ACTIVASE®
ALTEPLASE
A RECOMBINANT TISSUE PLASMINOGEN ACTIVATOR

 **ACTEMRA®**
tocilizumab

TNKase®
I-SINGLE-BOLUS
Tenecteplase

 **AVASTIN®**
bevacizumab
100 MG/4 ML INJECTION FOR IV USE

Esbriet®
(pirfenidone) tablets 267mg
801mg

 **Pulmozyme®**
dornase alfa INHALATION
SOLUTION

4 Genentech and Roche
sponsored ACTEMRA trials

Actemra[□] (tocilizumab)

COVACTA
MARIPOSA
EMPACKTA

Phase II/III trials to evaluate the medicine in
hospitalized patients

REMDACTA

Phase III combination study with remdesivir in
hospitalised patients

[^]These medicines are being evaluated for the potential treatment of patients with severe COVID-19 associated symptoms, such as pneumonia. None of these medicines are FDA-approved to treat COVID-19 or associated symptoms.

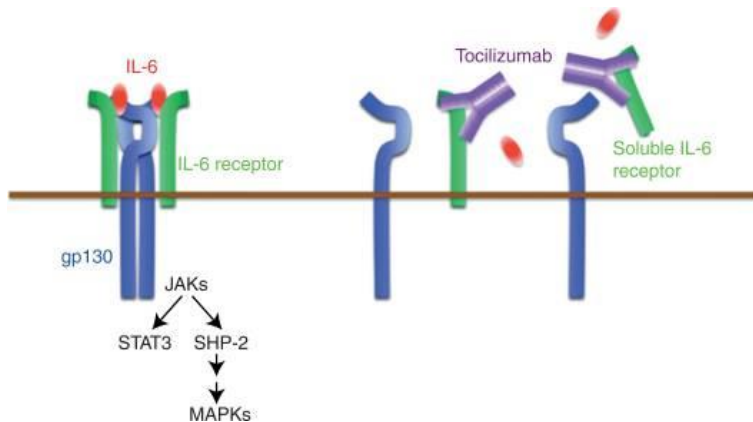
ACTEMRA - Mechanism of Action

 **ACTEMRA**[®]
tocilizumab



ACTEMRA (tocilizumab) is an **anti interleukin-6** (IL-6) therapy

- IL-6 is a common protein found in all joints in the body and is a natural substance that can raise inflammation.
- During the so-called “cytokine storm,” a potentially fatal immune reaction induced by hyperactivation of T cells, a major boost in IL-6 production is observed.¹



IL-6 binds to soluble and transmembrane IL-6R and the complex, then induces homodimerization of gp130, leading to activation of the signaling system.

Tocilizumab, blocks IL-6-mediated signaling pathway by its inhibition of IL-6 binding to both receptors.

¹IL-6 in Inflammation, Immunity, and Disease; Tanaka T, Narazaki M, Kishimoto T, [Cold Spring Harb Perspect Biol](https://doi.org/10.1101/cshperspect.a016295). 2014 Oct; 6(10): a016295. doi: [10.1101/cshperspect.a016295](https://doi.org/10.1101/cshperspect.a016295)

ACTEMRA – Health Authority Submissions



FDA

- **FDA** approved an Emergency Use Authorisation on 24 June 2021 for patients aged 2-years and older who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).

EMA/RoW

- Marketing Authorisation variation submissions are commencing for Actemra use in the treatment of COVID-19 in hospitalized adults.

Health Authority applications include:

- UK's **RECOVERY**¹ investigator initiated, open label, platform study, which demonstrated a statistically significant reduction in 28-day mortality with Actemra + usual care vs usual care.

supported by

- Data from the Roche-sponsored **COVACTA**, **EMPACTA** and **REMDACTA** studies which provide additional safety and efficacy data in the COVID-19 clinical trial setting.

1. RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet. 2021 May 1;397(10285):1637-1645.

ACTEMRA – Case Studies




Two case studies for the **expansion of manufacturing capacities:**

1. Addition of a drug product site from the Roche network
2. Addition of a drug substance CMO site

ACTEMRA – Capacity Expansion Case Studies


Part I: Drug Product

Problem Statement:

A photograph showing several people in white lab coats sitting around a table, looking at documents and writing, suggesting a meeting or collaborative work environment.


As Covid-19 pandemic surged in early March, demand forecasts were projected to be >500% above 2019 baseline. Since then, demand numbers have been changing as the pandemic progressed but remained consistently and significantly over the 2019 baseline demand.

Background:

A photograph of a pharmacist wearing a blue lab coat, a hairnet, and orange gloves, holding a clear plastic vial in a laboratory setting.

The drug substance process was transferred to a new internal site as part of product specific global supply plan. Submissions for this drug substance transfer were under review at FDA and EMA as of March 2020. The drug product (vials) was sourced from a single manufacturing site in Japan.

Opportunity:

A photograph of a male technician wearing safety glasses and a white shirt, looking through a handheld device in an industrial or manufacturing setting.

Quickly transfer the drug product process to an additional site in the United States along with the analytical release testing methods.

Challenges During the Drug Product Technical Transfer

1 Drug product primary container components sourced from Japan

Use components of an approved product at the acceptor site, with caps of a **different color**; start leachables and extractables studies.

2 Compounding step to formulate for filling

Use compounding procedure for another approved product at Hillsboro.

3 Labeling and packaging configuration different based upon equipment at Hillsboro

Use Hillsboro site packaging configuration and DHCP letter to inform users of change.

4 No data to support approved shelf-life

Set shelf-life to 6 months in accordance with ICH guidelines.



Drug Product Capacity Expansion: Health Authority Interactions

Proactive dialogue facilitated pathways - Approach



FDA

- **Engaged with Drug Shortage Staff**
 - Demand signals, supply outlook and timing of potential shortage and manufacturing challenges
- Proposed a DP tech transfer and **batch specific release** for interim supply:
 - Protocol for CMC information and outline of the process and concurrent data generation for submission
- Meetings with CDER OBP reviewers and OC staff on specific approaches and data expectations

EMA

- **Engaged with Quality Defects and Rapporteur**
- EMA issued guidance for COVID-19 transfers called “**Exceptional Change Management Process (ECMP)**” in April 2020
- Discussion with EMA on application of the ECMP guideline:
 - Technical transfer to new DP is covered
 - Container-closure system (CCS) change has to be submitted separately as a Type 2 Variation

Drug Product Capacity Expansion: Health Authority Interactions

Proactive dialogue facilitated pathways - Outcomes



FDA

- **FDA** accepted proposals and provided **regulatory discretion** for release of 3 batches on a **batch by batch basis**.
- FDA strongly recommended filing a supplement to the BLA for DP transfer as long-term supply strategy
 - Filed Comparability Protocol/PAS (Jun 2020) and subsequent CBE-30 (Nov 2020) following data availability

EMA

- **Review and approval** of the **CCS variation** was **expedited** and achieved in 14 days
- Accelerated import licensure process to import material for packaging in EU.
- Within 6 months from first batch distributed, the Type II Variation was submitted to EMA (Oct 2020) and approved in Feb 2021.

Drug Product Capacity Expansion: Health Authority Interactions

Global Approach – Priorities Based Upon Demand Signals



The top 50 Actemra IV markets were actively approached:

- **Common label make-up** (in lieu of country specific) was readily accepted.
- Acceptability of drug product from Hillsboro for rest of the world was primarily based on
 - **Reliance pathways** from US and EU acceptability of Hillsboro filled material
 - **Temporary or special licenses** on a lot by lot basis or for a pre-defined emergency use duration.
- Only a few countries requested a full review of the Hillsboro DP site prior to accepting material

ACTEMRA – Capacity Expansion Case Studies

Part II: Drug Substance



Problem Statement:

The introduction of another Covid-19 treatment at the approved/submitted Actemra drug substance manufacturing site in Q4 2020 significantly impacts the Actemra production capacities.



Background:

The Actemra drug substance supply was planned to come out of one source based in the US (approved by FDA and EMA in Q2 2020). Global submission of this site is ongoing. With the increased Actemra demands since the onset of the pandemic, an alternative drug substance supply point had to be identified.



Opportunity:

Accelerate the drug substance technical transfer to a CMO building on the expertise from recent transfers. Use regulatory tools like Comparability Protocols where possible (e.g. US). Keep regulators engaged in conversations via our affiliate network.

Challenges During the Drug Substance Technical Transfer

1 Aggressive timelines

Build on prior knowledge and agile decision making processes

2 General availability of raw materials

Use internal allocation processes to supply CMO with sufficient amounts for raw materials

3 Available stability data vs. timelines

Engage with our affiliates / Health Authorities early on to evaluate options

4 Need for inspections
(new facility at the acceptor site)

Collaborate with EMA to trigger an inspection; liaise with our affiliates to evaluate inspection requirements

Key Take-Aways - ACTEMRA transfers

 **ACTEMRA**[®]
tocilizumab



Tech Transfer:

- **Small, empowered, focused cross-functional teams** from donor and recipient sites.
 - Identified decision makers and limited governance of the work.
- Reliance on **prior knowledge, risk management** and understanding gaps and differences to support product quality assessments.



Health Authorities Engagement:

- Available and **active engagement** with **HAs** to provide consultation and input into the strategy
- Granting regulatory discretion for release is not sustainable

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Doing now what patients need next