Faster than fast - Technology transfer to meet demand for a repurposed biologic

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Outline

Evaluation of existing medicines for COVID-19 treatment

Dynamic adaptation of the tocilizumab (Actemra) supply chain

Challenges and successes of an accelerated drug product technical transfer

Interactions with Health Authorities

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

5 Genentech and Roche sponsored trials

- **Actemra® (tocilizumab)**
  - COVACTA, MARIPOSA, EMPACTA: Phase II/III trials to evaluate the medicine in hospitalized patients
  - REMDACTA; Phase III combination study with remdesivir

- **Anti-ST2 & IL-22Fc**
  - COVASTIL: Phase II trial in patients hospitalized with severe COVID-19 pneumonia

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Mechanism of Action

- 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.

\(^1\)IL-6 in Inflammation, Immunity, and Disease; Tanaka T, Narazaki M, Kishimoto T, Cold Spring Harb Perspect Biol. 2014 Oct; 6(10): a016295. doi: 10.1101/cshperspect.a016295
EMPACTA study
Evaluating Minority COVID-19 Patients with Actemra*

**Groundbreaking in advancing inclusive research!**

Study enrolled patients who have been disproportionately affected by the COVID-19 pandemic: approximately 85% of the 389 patients were from minority racial and ethnic groups.

In the EMPACTA study, patients with COVID-19 associate pneumonia who received tocilizumab plus SoC were less likely to progress to mechanical ventilation compared to patients who received placebo plus SoC.

*Note: tocilizumab has not been shown to reduce mortality in the EMPACTA study.*

*While Actemra is being evaluated for the potential treatment of patients with severe COVID-19 associated symptoms, it is currently not approved for this use.*
Problem statement – What happened in March 2020

- Anecdotal evidence for use of Actemra in Italy and France.
- Actemra demand forecasts were projected to be >500% above 2019 baseline.
- Actemra stock-outs were projected to occur within a month.
Dynamically adapting the Actemra i.v. supply chain to increase supply

Status beginning of March 2020

- **Drug substance** was transferred to **Vacaville, CA** from Utsunomiya, Japan in combination with a process upgrade (improved yield).
- Vacaville submissions were under review at FDA and EMA.
- **Drug product** vials were manufactured in **Japan**.

Activities started with the onset of the pandemic (mid-March 2020):

- Expedited transfer of **drug product** manufacturing to **Hillsboro, OR**.
- **Accelerate** the submission of Vacaville **drug substance** site globally.
Challenges during technical transfer

1. Drug product primary container components sourced from Japan
   Use components of an approved product at Hillsboro, with caps of a different color; 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.
## Health Authority interactions – Approach

*Proactive dialogue facilitated pathways*

### FDA
- Engaged with Drug Shortage Staff
  - *Demand signals, supply outlook, and timing of potential shortage*
- Proposed a DP technical transfer and batch specific release for interim supply
  - *Protocol for CMC information 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 use of the ECMP guideline:
  - Technical transfer to Hillsboro is covered
  - Container-closure system (CCS) change had to be submitted separately as a Type 2 Variation
Health Authority interactions - Approach

*Protocol approach enabled expedited batch release*

- FDA protocol scope to
  - support a **risk-based approach** leveraging historical data.
  - support **expedited batch** release (incl. 7 day sterility testing).
  - support use of a **different vial and stopper** with a **different cap and seal color** and a **different secondary packaging** configuration.
  - provide approved **internal protocols** for generation of batch release, process verification, and stability data concurrent with manufacture, as well as a batch release checklist.

- Included descriptions of the manufacturing and testing sites, manufacturing process, in-process controls, release and stability testing requirements, and acceptance criteria.

- Proposed to submit **batch specific BLA amendments** for release that included in-process and release testing data and batch-specific environmental monitoring data.
Health Authority interactions – Outcome

Proactive dialogue facilitated pathways

**FDA**

- **accepted** proposals and provided regulatory discretion for release of 3 batches on a batch by batch basis.
- strongly recommended filing a **supplement** to the BLA for DP transfer as long-term supply strategy.

→ *Filed Comparability Protocol/PAS (June 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**.
- **Local importation licensure** to Mannheim, Germany was authorized to allow for secondary packaging.
- Within **6 months** from first batch distributed, the Type II Variation was submitted to EMA (October 2020).
Rest of the World Supply Strategy
Prioritized based upon demand signals

The Top 50 Actemra i.v. 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.
Key Take-Aways

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

- Active engagement with HAs to provide consultation and input into the strategy.
- Granting regulatory discretion for release is not sustainable.
Future Outlook – Topics of discussion

• General acceptability of visually different primary packaging materials in one market (e.g. different dimensions and cap colors)?

• Enablers for reliance pathways in ROW: Approval letters and/or assessment reports. What is possible without this information?

• EU/ROW: Use of common make-up (labelling) for emergency use in hospital setting possibly in combination with e-leaflet?
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