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From Benchtop to Approval in Record Time A Case Study of Ronapreve

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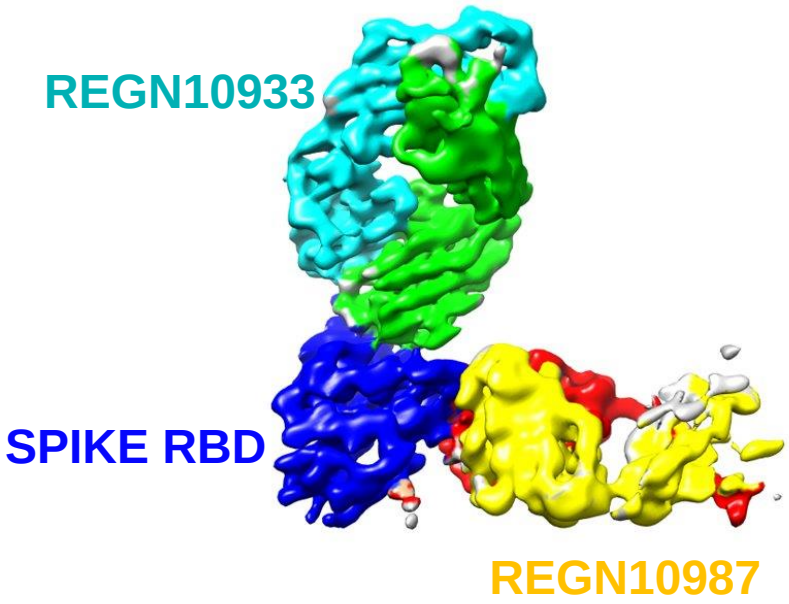
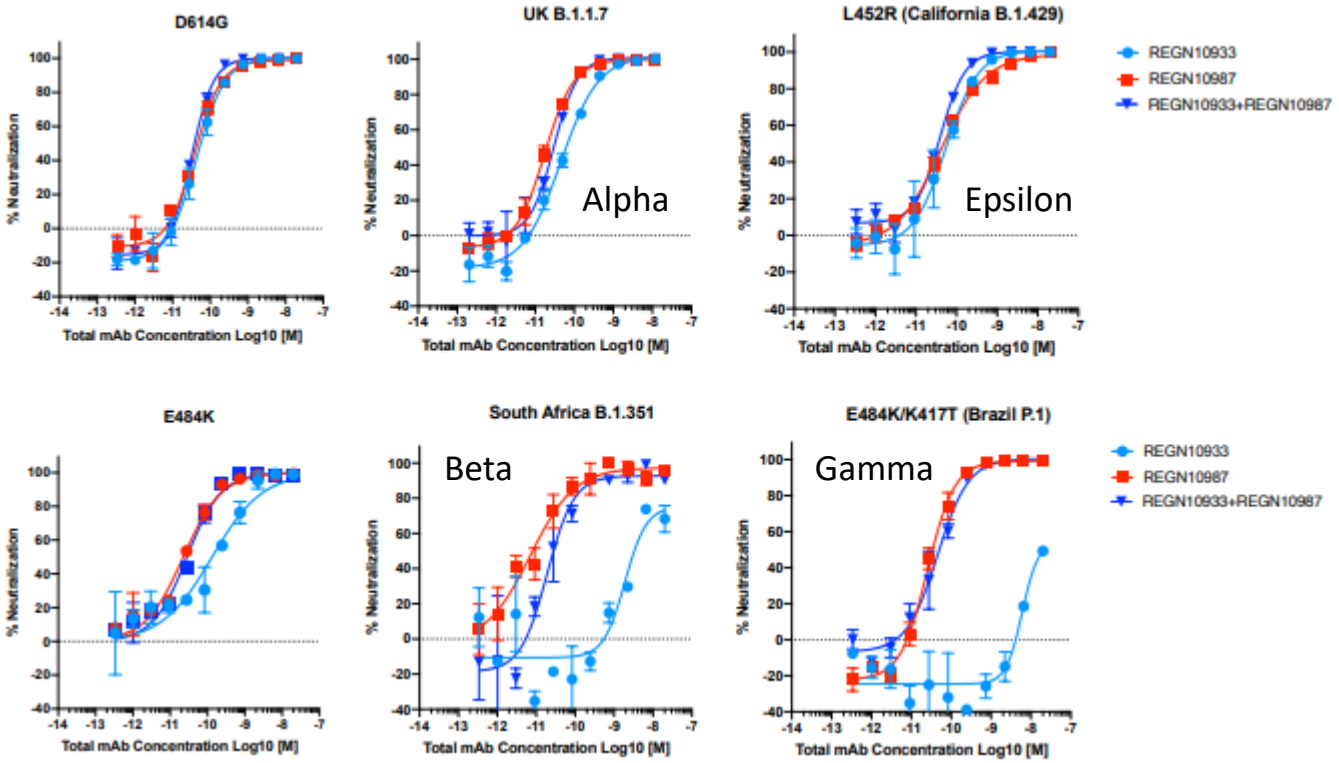
PART 1

REGENERON®

Ronapreve, an antibody cocktail, was designed to safeguard against viral resistance by targeting two non-overlapping epitopes on the viral spike protein



Cryo-EM map at 3.9 Å

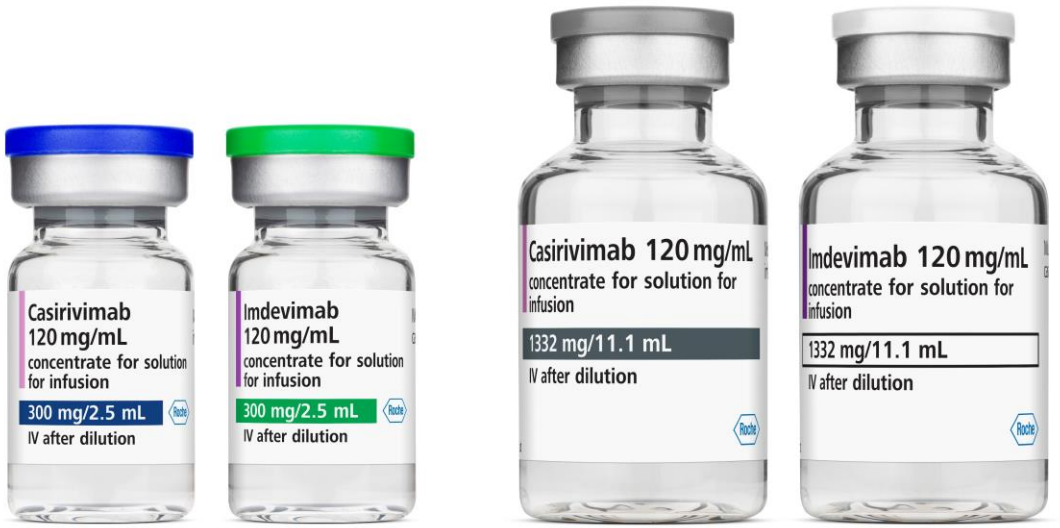


REGN10933 (casirivimab) and REGN10987 (imdevimab) bind specifically to distinct, non-overlapping epitopes on the receptor binding domain of the spike protein. Both antibodies neutralize virus infectivity by blocking binding to ACE2 receptors on human cells

A key element of having two epitopes (mAb cocktail) is to reduce the likelihood of viral resistance

2 publications in SCIENCE (Vol 369, Issue 6506, Yr 2020) for details

Ronapreve® (REGEN-COV) Drug Product



Product Highlights

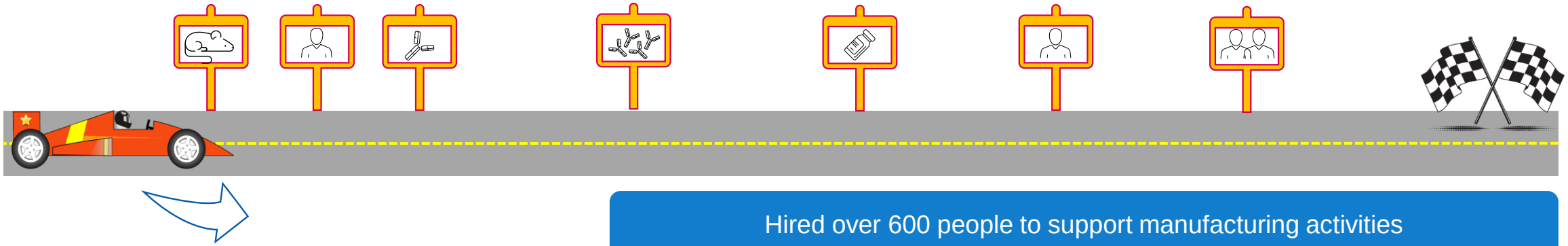
- Two antibody (casirivimab and imdevimab) product for both IV and SC administration
- A single platform formulation at 120mg/ml for individual antibodies
- A co-formulation is EUA approved in the USA
- Emergency Use Authorization (EUA) granted by the FDA (21 Nov 2020)
- **First full approval in Japan (20 July 2021)**
- MAA fully approved by the EMA (12 Nov 2021)
- BLA accepted by the FDA for priority review (Oct 2021)

Antibody cocktail development and production at pandemic speed

70 Days from Immunization to Lead Selection

45 Days from Lead Selection to Drug product development, tox studies and GMP Drug Product manufacturing

< 12 Months from IND to CMC BLA readiness



Hired over 600 people to support manufacturing activities

92 cell lines expressing 92 anti-SARS-COV2 mAbs were made within 18 days of receiving DNA constructs in March/April 2020

Simultaneous production at 3 manufacturing scales in April 2020

6 Formulated Drug Substance process transfers across 4 sites and 4 production scales

50 Process Performance Qualification lots at 6 manufacturing sites (27 FDS and 23 DP)

End-to End Discovery to Production

Enabled by integrated application of core technologies developed over 30 years, effective, tried and tested business processes, and culture - ***Nothing new was created for covid***

VelociSuite® Technologies

VELOCIGENE®
High-throughput generation of any desired genetic alteration in mouse embryonic stem cells

VELOCIMOUSE®
High-throughput generation of mouse models directly from embryonic stem cells

VELOCIMMUNE®
Mice mount robust immune response expressing human antibodies

VELOCIMAB®
Rapid discovery of mAbs and construction of high titer, ultra-stable CHO cell lines

Process Knowledge

Speed-to-clinic standard approach using platform knowledge from > 40 VelociSuite molecules -

- Combine with robust and predictable platform manufacturing process
- **No cell line-specific process development required**
- **ZERO** experimentation or optimization occurs for speed to clinic production
- Platform formulation
- Platform analytical methods

Culture

- “Make it Happen”: No tolerance for bureaucracy
- “Be Great Together”: Shared sense of success and excellence; familiarity and respect at all levels
- “Do What’s Right”: No shortcuts in the application of GMP or the focus on patient safety

Ways of Working

- Facilities maximally leverage platform
  - Functional equivalency
  - Shared SOPs across facilities / sites
- Standard procedures in place to compare new molecules to platform to leverage data

Overcoming obstacles

Alternative routes able to be taken because of technology, platform, experience and culture

TIME!

- We relied on our platform
  - >40 VelociSuite ® Molecules
- Platform manufacturing process, formulation and analytical methods
  - Leverage platform data for long lead items: stability, virus clearance
  - ***Ask the right questions***
- Wealth of experience with transfers and scale ups across Regeneron network

Bulk Production Capacity-Process Transfers to Ireland Facility

- History of Success - Over 70 successful process transfers
- Plants designed with transfers in mind; identical equipment across process areas and sites
- Shared SOPs and training across facilities; ↓risk of operational differences
- **Culture-** Strong inspection history; Zero observation Regeneron culture.

Workforce Challenges

- Employee experience with platform
- Onboarding and Training: FTEs able to work across multiple suites
- Workplace protocols to prevent transmission of essential employees

Filling Capacity Challenges

- Rapid pivot to transfer to multiple CMOs
- History of successful transfers and use of multiple CMOs
- Unprecedented collaboration and cooperation with FDA

Lack of Product/Process Specific Data

- Leverage **Platform and Prior Knowledge** using risk-based approaches
- Execute at risk with confidence in platform and processes

Global Raw Material Shortages

- Materials in inventory
- Platform processes improve inventory management
- Culture - Prediction of pandemic impact and pre-emptive ordering

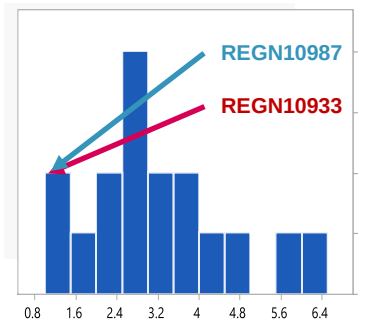
Product Stability for Rapid Response

Built upon foundation established by platform technologies and business processes

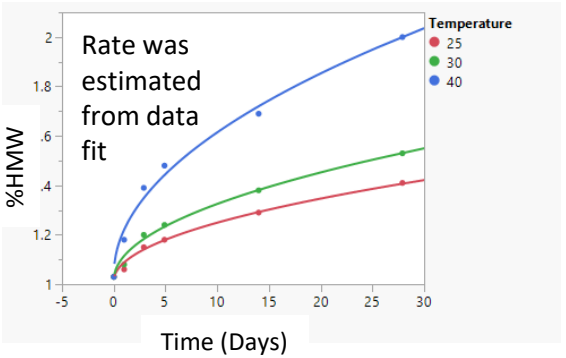
EUA Justification of Shelf Life

- Regeneron platform manufacturing process: platform formulation used to deliver stable formulations for more than 20 clinical programs
- **Predictive modelling** applied for predicting and justifying shelf-life stability at 2 – 8 ºC
- 24 months of shelf life was approved for the EUA of vial drug products
- Comparison of stress stability data with stress and long-term stability data from similar Regeneron monoclonal antibodies in similar platform formulation

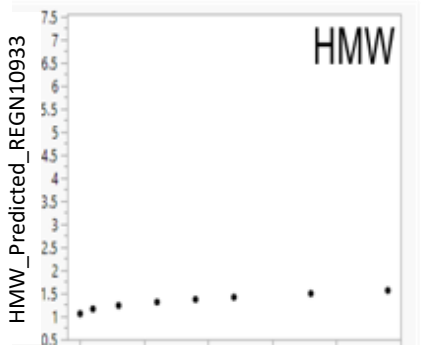
%HMW formation rates;
Similar to other high concentration formulations

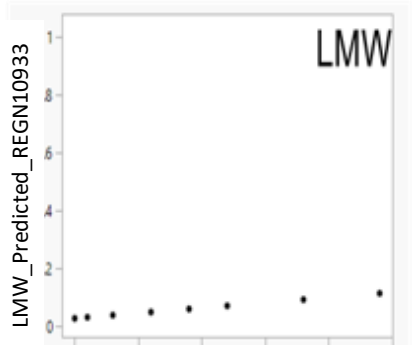


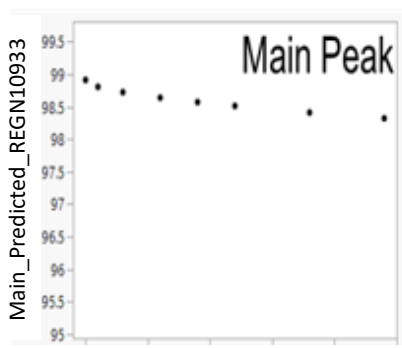
HMW Content at 25, 30, and 40°C



Predicted change at 2-8 °C (Arrhenius fits)







Commercial Readiness

Built upon foundation established by platform technologies and business processes

History and PV Approach:

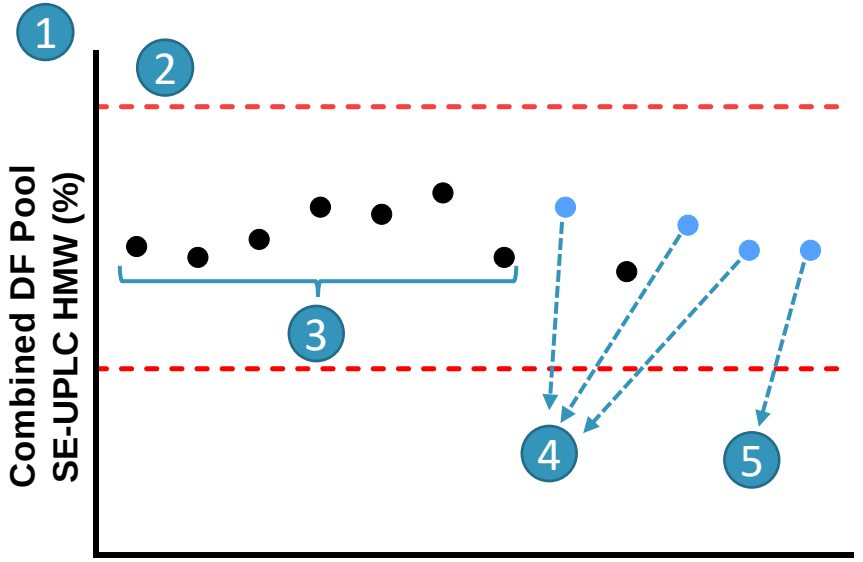
History of successful transfers and commercialization across manufacturing areas. Scientifically driven PPQ strategy. Leveraging of a ***strong CPV process post PPQ***.

Facility Operation and LCM:

Common SOPs where possible. Cell cultures, purification and aseptic organization of operators. Coordination of changes across suites

Facility Design:

Facilities designed to be identical, and if not identical, ***functionally equivalent***



1. Evaluation of relevant inputs and outputs for all unit operations including statistical evaluation of non-routine, enhanced testing. (*enhanced PPQ level sampling built into tech transfer process for pre-PPQ lots*)
2. Statistically generated meaningful, validation criteria to demonstrate process consistency
3. Presentation of data for PPQ lots in context of manufacturing history (blue), including non-PPQ lots produced post protocol (Black).
4. Process area 1 PPQ Lots
5. Process area 2 PPQ Lot

Closing Remarks

- Proprietary platform technologies developed over decades have enabled rapid response to SAR-COV-2
- Business processes built on platform knowledge and standard procedures facilitate leveraging historical data for application to new molecules
- Unprecedented collaboration among industry and with FDA
- Progression from IND → EUA → BLA readiness with no shortcuts in the application of GMP