REALISING THE POTENTIAL OF CMC ACCELERATION IN TRANSFORMING PATIENT ACCESS TO NEW, INNOVATIVE THERAPIES

– AN AMGEN PERSPECTIVE
AMGEN IS A FULLY INTEGRATED BIOTECHNOLOGY COMPANY COMMITTED TO SERVING PATIENTS AND DELIVERING INNOVATIVE DRUGS TO TREAT UNMET MEDICAL NEED, AS FAST AND AS EFFICIENTLY AS POSSIBLE
INNOVATIVE SOLUTIONS ARE SHAPING AMGEN’S PRODUCT DEVELOPMENT AND REGULATORY LANDSCAPE

Accelerating CMC development based on appropriate risk-based approaches to minimise overall product development timeline critical
THE REGULATORY FRAMEWORK AND CMC

- Regulatory pathways exist for accelerating clinical development and/or MA review timelines for products of unmet medical need (and orphan products), e.g:
  - US FDA - Breakthrough Therapy Designation (BTD)
  - EU EMA – PRIME
  - JP PMDA - Sakigake

- Challenges occur when products are accepted for acceleration in one jurisdiction (e.g. BTD) and not others (e.g. PRIME or Sakigake)?

- Products following the accelerated pathway may have CMC challenges to meet clinical timelines
BALANCING CONVENTIONAL VS ACCELERATED CMC CONTENT AT INITIAL SUBMISSION

No reduction in quality but flexibility on type of information and timing to provide confirming data

Supported by ICH Q8 – Q11 enhanced understanding and quality risk management

Agency dialogue will be essential for success of accelerated CMC proposals
AMGEN ACCELERATED CMC REQUIRES FRONT-LOADED DEVELOPMENT

Ph1 dose escalation
Ph1b
Pivotal Ph2 Study (n=80)
Filing
Launch/Post-Launch

Commercial Process Development
Process/Product Characterization
Continued Process Verification
Confirmatory CMC data
Confirmatory Phase 3 (n = 200)

Prior Knowledge
Process Understanding
Product Understanding

Product selection,
Process design,
Analytical methods,
initial control strategy

Process improvements,
Site transfers
Comparability
Analytical development,
Updated control strategy

SKU selection,
Pivotal commercial process,
Process controls prior to
PV, PV strategy.

Final commercial control strategy
AMGEN CHALLENGES TO CMC ACCELERATION

- Stock Keeping Unit (SKU) selection
- Site selection and transfers for global supply
- Process changes (comparability)
- PPQ strategy timelines
- Reduced batch history to develop control strategy
- Representative clinical and development lots (batch history, stability)
- Stability data available at submission for viable shelf-life

Timelines that do not tolerate unplanned programme changes

2020 – 2022: Multiple MA submissions planned globally

Uncertainty of regulatory procedure creating all manner of CMC strategy

20 products in Phase 1/2; many with potential for accelerated procedures

IgG
BITE, HLE-BITE
Fusion proteins, bispecific mAb
siRNA
Synthetic molecules
CAR-T

Oncology,
Cardiovascular,
Inflammation
In clinical acceleration, Pivotal studies may be phase 2
- Incurs a relatively small patient population and short duration
  - e.g. progression-free survival, PK/PD biomarkers
- Often requires few batches (include representative development lots)
  - Exemplified with high activity biologics (BiTE program)

Significant challenges for criteria with ‘clinical qualification’ expectation
- Commit to report specification trend plots from Quality Management System
  - After confirmatory clinical trials (phase 3)
  - Confirmed stability profile
  - 15 lots drug substance (final specification)
## SPECIFICATIONS – OVERCOMING CHALLENGES OF LIMITED LOTS

<table>
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<tr>
<th>Options</th>
<th>Potential Challenge</th>
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| Manufacture lots to increase dataset                                   | • Cost  
|                                                                        | • Timing/resources                                                                                      |
| Use controlled variation of acceptable process parameter ranges, to expand attribute range | • Product specific process knowledge may not be fully available at time  
|                                                                        | • Process/product prior knowledge may not be available for new/novel modalities                          |
| Use prior knowledge of attribute to justify broader range              | • May require extensive product specific information  
|                                                                        | **Uncertain regulatory acceptance**  
|                                                                        | • Process/product prior knowledge may not be available for new/novel modalities                         |

**Process understanding will be dynamic through development**
STABILITY REMAINS ON CRITICAL PATH IN CMC ACCELERATION

• Released drug product needs a minimum shelf-life – 24 months
  – packaging, shipping, pharmacy requirements etc

• When Prior Knowledge insufficient or not BTD / PRIME designated:
  – Maximise use of data from representative lots
    • Understanding of ICH representative ‘primary’ lots
  – Post-approval commitments
    – (Added timepoints, more analytical testing as options)

• When Prior Knowledge available in BTD/PRIME:
  – Data modelling of DS and DP stability by modality
  – Supported by accelerated stability
  – ICH requires reinterpretation such that the expectations apply to the model
    • Model from at least 3 prior knowledge examples with data to proposed shelf-life
    • 3 product-specific lots with minimum 6 months data
Limited drug product stability package to be included at initial filing:

- 3 production lots at 3 months,
  - Launch site & scale, process, strength, container closure
- 3 primary lots at up to 12 months
  - Clinical site & scale, launch process, strength, container closure – used in clinic
- 2 supporting development lots at 30 months.
  - Clinical site & scale, launch process, strength, container closure – not used in clinic

- 6 months data for the production lots available for Day 120 RTQ.
- Drug product shelf-life for global launch of 24 months
- Supporting lots are representative of primary and production lots
  - Justify supportive lots as also ‘primary’
STABILITY MODELLING BASED ON PRIOR KNOWLEDGE – CASE STUDY (HMW SPECIES)

IgG mAbs stored -30°C (DS) or 5°C (DP) in similar container, strength and formulation.

Frozen drug substance does not change on storage to 36 months.

Drug product rates of change are comparable to 36 months within a statistical derived limit (e.g. 95% TI) – not shown

Accelerated stability data confirms OOT products for exclusion from the model
• mAb3

Stability data support that product shelf-life can be extrapolated against the model
ACCELERATED DATA TO IDENTIFY NON-FIT MOLECULES

Accelerated stability data confirms OOT products that can be excluded from the model

- mAb3

NB plot colours for mAb do not always correspond to those used in other plots
Drug product potency rates of change are comparable, within assay variability and no change within 36 months.

IgG mAbs stored -30°C (DS) or 5°C (DP) in similar container, strength and formulation.

Stability data support that product shelf-life can be extrapolated against the model.
SUMMARY OF CMC ACCELERATION AT AMGEN

- Amgen is exploring ways to accelerate CMC across its pipeline while maintaining a positive risk : benefit profile.
  - Both accelerated and standard agency review timelines
  - Modalities with significant prior knowledge
  - Newer modalities with little prior knowledge
  - Making full use of current regulatory tools

- Which approaches described at the EMA/FDA workshop on CMC acceleration in PRIME/BTD/Sakigake would justifiably be applicable for products under standard review procedures?
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