ACCELERATED CMC DEVELOPMENT AND STRATEGIES TO MEET FAST TO PATIENT ACCESS

2019-CASSS NORTHERN CALIFORNIA REGIONAL FORUM

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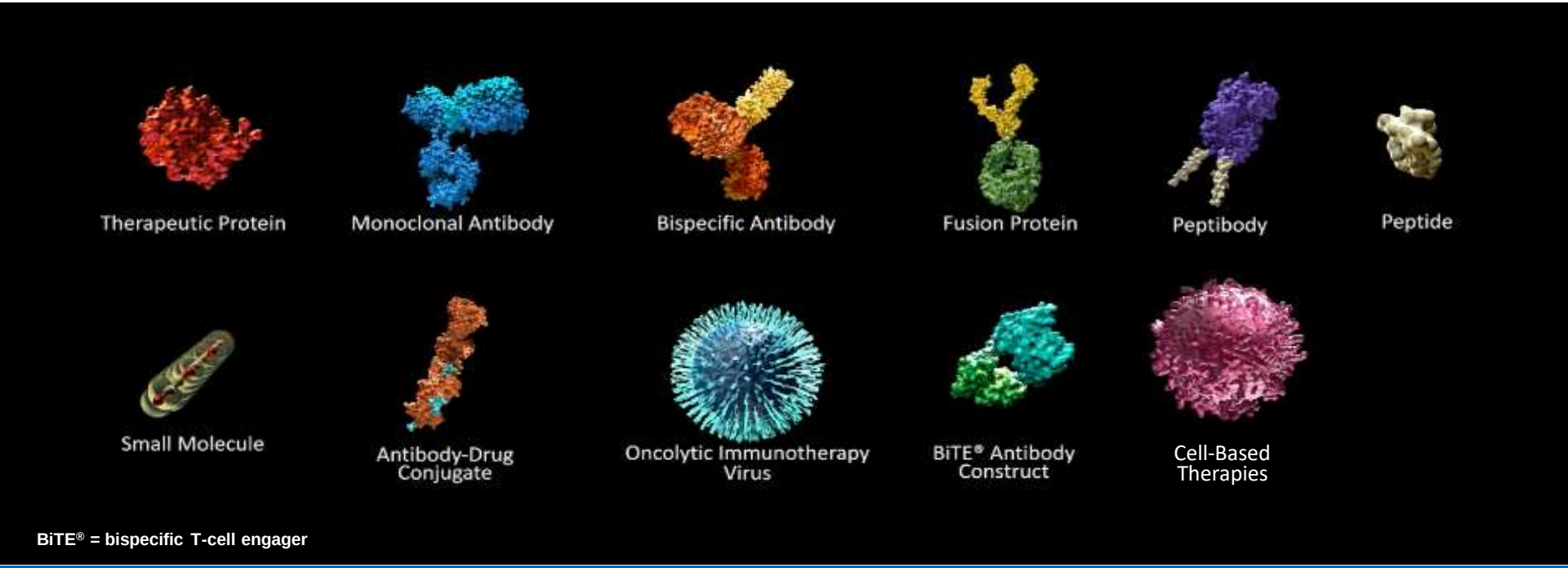
AMGEN

Pioneering science delivers vital medicines™

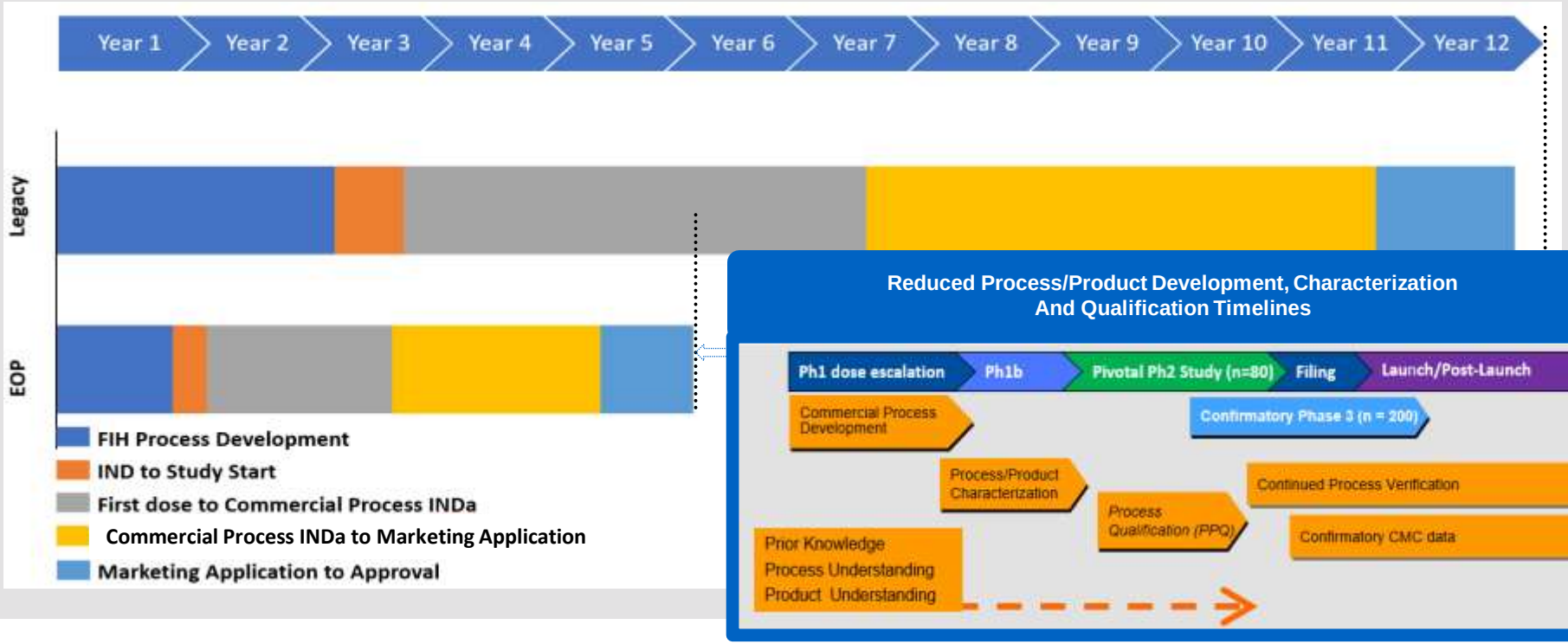
INNOVATIVE SOLUTIONS ARE SHAPING AMGEN'S PRODUCT DEVELOPMENT AND REGULATORY LANDSCAPE



BiTE® = bispecific T-cell engager

Accelerating CMC development based on appropriate risk-based approaches to minimize overall product development timeline critical

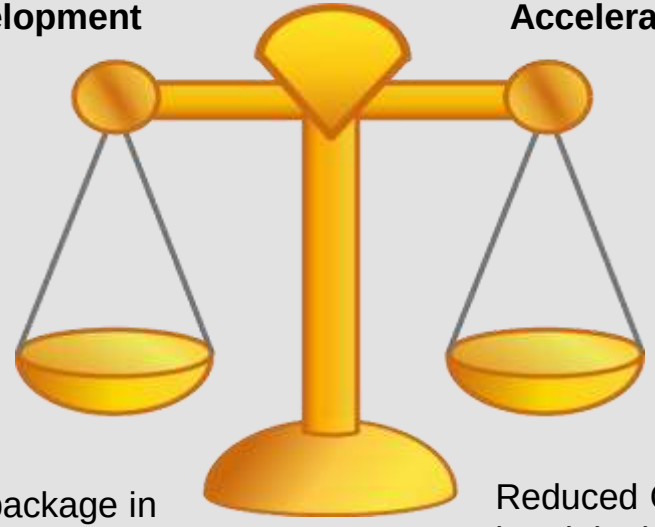
CMC DEVELOPMENT TIMELINES SIGNIFICANTLY REDUCED TO ENSURE FASTEST ACCESS FOR PATIENTS- FRONTLOADING CMC



BALANCING CONVENTIONAL VS ACCELERATED CMC CONTENT AT INITIAL SUBMISSION

Conventional CMC Development

CMC Acceleration



Full CMC package in original application

Reduced CMC package in original application + “tools” for deferred data

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

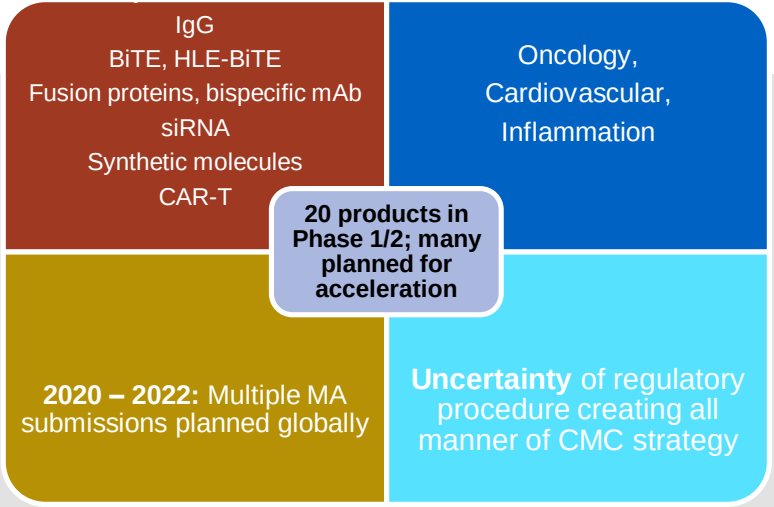
Agency dialogue will be essential for success of accelerated CMC proposals

CHALLENGES WITH REGULATORY FRAMEWORK AND CMC ACCELERATION

- **Regulations and guidance out of date and not suitable for 21st Century modalities and precision medicine (i.e. stability requirements)**
- **Current regulatory framework includes procedures aimed at accelerating development, for ONLY products of unmet medical need and Orphan Designated products**
- **Even products suitable for accelerated procedures may require clinical proof of concept, making changes in CMC timeline potentially too late.**
- **What can be done to accelerate other products or those accelerated in one jurisdiction (e.g. US BTD) and not others (e.g. EU PRIME or Sakigake)?**

AMGEN CHALLENGES TO CMC ACCELERATION

- **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**



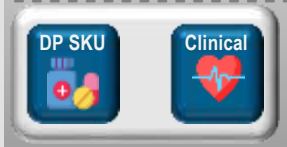
Timelines that do not tolerate error or unmitigated surprises

KEY ACCELERATION LEVERS

1. **FIH Resupply:** Define guardrails for using FIH resupply material to initiate registrational trials
2. **PPQ Strategy:** Prerequisite criteria for considering use of DS pivotal material for DP PPQ
3. **DP SKU Strategy:** Opportunity to coordinate with clinical dev on clinical/commercial SKU strategy
4. **Site Selection:** Early commercial site selection required prior to pivotal production

- ❑ Optimizes clinical exposure throughout development
- ❑ Provides early and relevant batch data and clinical experience
- ❑ Streamlines early production activities and planning

- **Compelling Clinical Data**
- DS pivotal process = DS commercial process
- DS pivotal mfg site =DS commercial mfg site
- DS material meets process and product evaluation criteria; attributes are representative



- ○ **Dose selection is critical path**
- ○ Adhere to platform SKUs in clinical trial design
- ○ Design adaptive clinical trial readouts to verify commercial SKU strategy
- ○ Leverage real-time clinical readouts

- ➢ Eliminates/reduces analytical comparability events
- ➢ Enables pivotal production at commercial facility

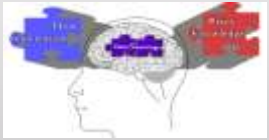
Incorporating these levers drives significant commercialization acceleration

KEY ACCELERATION LEVERS

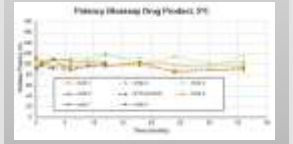
1. **Leveraging Prior and Platform Knowledge:** Applying information and data from prior experiences, programs, technologies, etc.

2. **Stability Modeling:** Opportunity to leverage modality data to model an acceptable stability profile

3. **Global Agency Engagement:** Novel acceleration strategies should be discussed and agreed to by Health Authorities as needed



- ❑ Applied to platformed modalities and associated attributes
- ❑ Leveraging process understanding and manufacturing technologies
- ❑ Advancements in Process Analytical Technologies



- **Significantly accelerates product advancement as stability data requirements are often rate limiting**
- Opportunities to leverage post-approval commitments in favor of earlier patient access
- Supported by accelerated data

- Informs on company strategies, positions and expectations around accelerated programs
- Mitigates or reduces anticipated risks
- **Creates a working partnership between industry and Health Authority regulators to deliver novel and life-saving therapies to patients efficiently**

Incorporating these levers drives significant commercialization acceleration

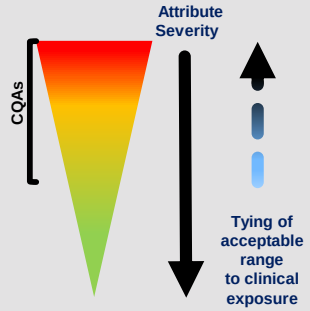
STABILITY REMAINS ON CRITICAL PATH

- **Released product needs a minimum ‘comfortable’ DP shelf-life of 24 months**
- **When Prior Knowledge insufficient or not BTD / PRIME designated:**
  - **Maximise use of data from representative lots**
    - Understanding of ICH representative ‘primary’ lots
  - **(Commitments** providing data post-approval, evaluation of trends**)**
  - **(Added timepoints, more testing options** to add confidence**)**
- **When Prior Knowledge available in BTD/PRIME:**
  - **Data modeling 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 support proposed shelf-life
    - 3 product-specific lots with minimum 6 months data

LIMITED BATCH PRODUCTION TO SUPPORT CLINICAL DEVELOPMENT

- **Limited number of batches (include representative development lots)**
- **Alternate approaches required for justification of specifications**

Options	Potential Challenge
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 VALIDATION TIMELINES ON CRITICAL PATH

- **Filing timeline driven by completion of PPQ campaigns**

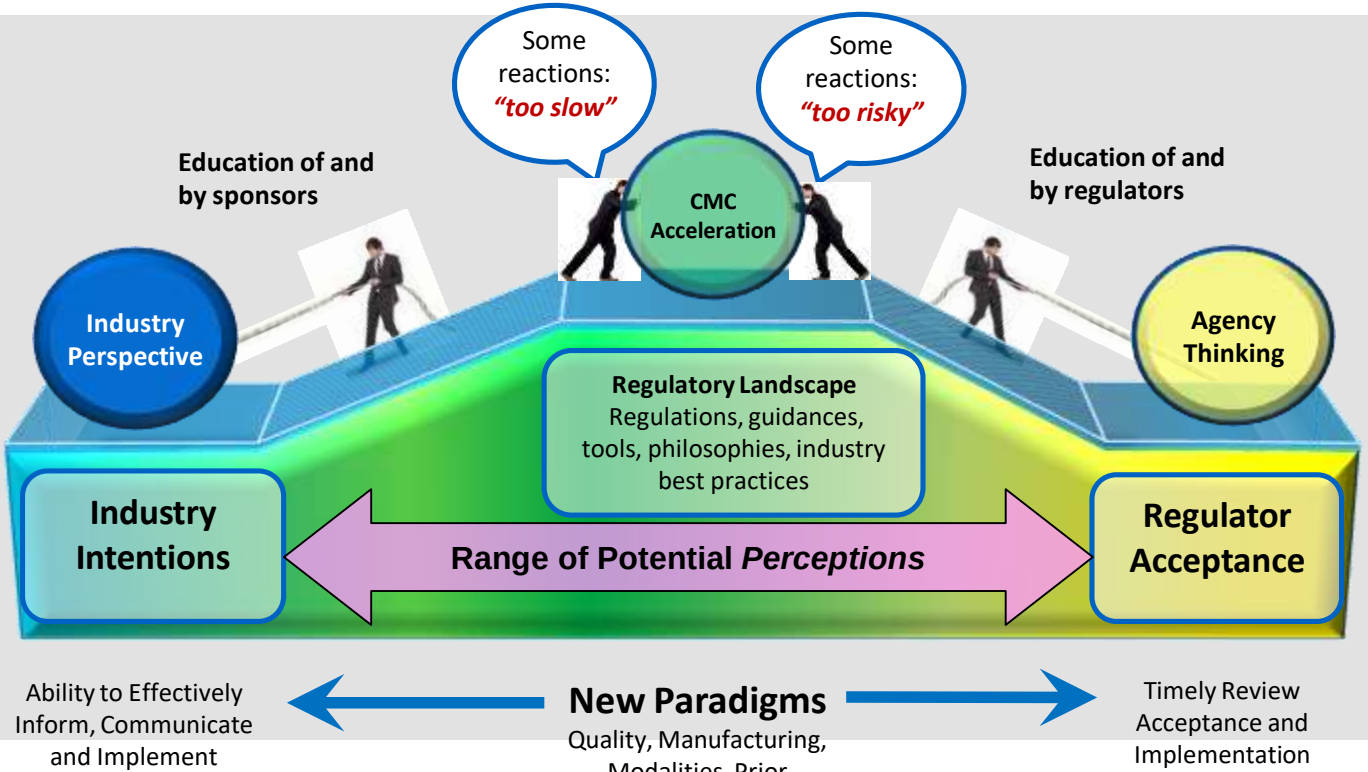
  - **Use of representative DS for DP PPQ considerations**
    - **Number of clinical DS lots needed**
    - **Types of changes made between pivotal process and commercial process**
    - **Comparability assessment, if needed.**
    - **Need for fully validated material for launch**

  - **Submission of protocol and data for 1-2 PPQ batches at time of filing and data for additional batch(es) provided later.**

SUMMARY CONSIDERATIONS IN DEVELOPMENT OF CMC STRATEGIES TO SUPPORT GLOBAL ACCELERATION

- CMC development planning links to clinical milestones
  - Timing of expedited pathway designation
  - Work must be performed at-risk
- Different CMC evidence may be required for submissions
  - Data requirements are the same
  - Level of evidence may be different and timing of deliverables may be negotiable
- Communication of CMC strategies to regulatory agencies
  - Importance of timing (right questions at the right time)
- Focus of CMC development programs on essential elements
  - e.g. may not need second supplier; may do less characterization work
- Ensure strategies and level of evidence is aligned with Global filings expectations

ADVANCING MEDICAL PRODUCT INNOVATION THROUGH CMC ACCELERATION REQUIRES BALANCED AGENCY AND INDUSTRY ENGAGEMENT



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