CMC for CAR-TCR Therapies Shifting the Quality Paradigm

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About ARM

- **International advocacy organization**
  - Dedicated to realizing the promise of safe and effective regenerative medicines for patients around the world
  - Cell and gene therapy, tissue engineering
- **350+ members**
  - Small and large companies, non-profit research institutions, patient organizations, and other sector stakeholders
  - Across 25 countries
- **Priorities:**
  - Clear, predictable, and harmonized **regulatory** pathways
  - Enabling market access and value-based **reimbursement** policies
  - Addressing industrialization and **manufacturing** hurdles
  - Conducting key stakeholder outreach, **communication**, and education
  - Facilitating sustainable access to **capital**

Alliance *for* Regenerative Medicine

Current Global Sector Landscape

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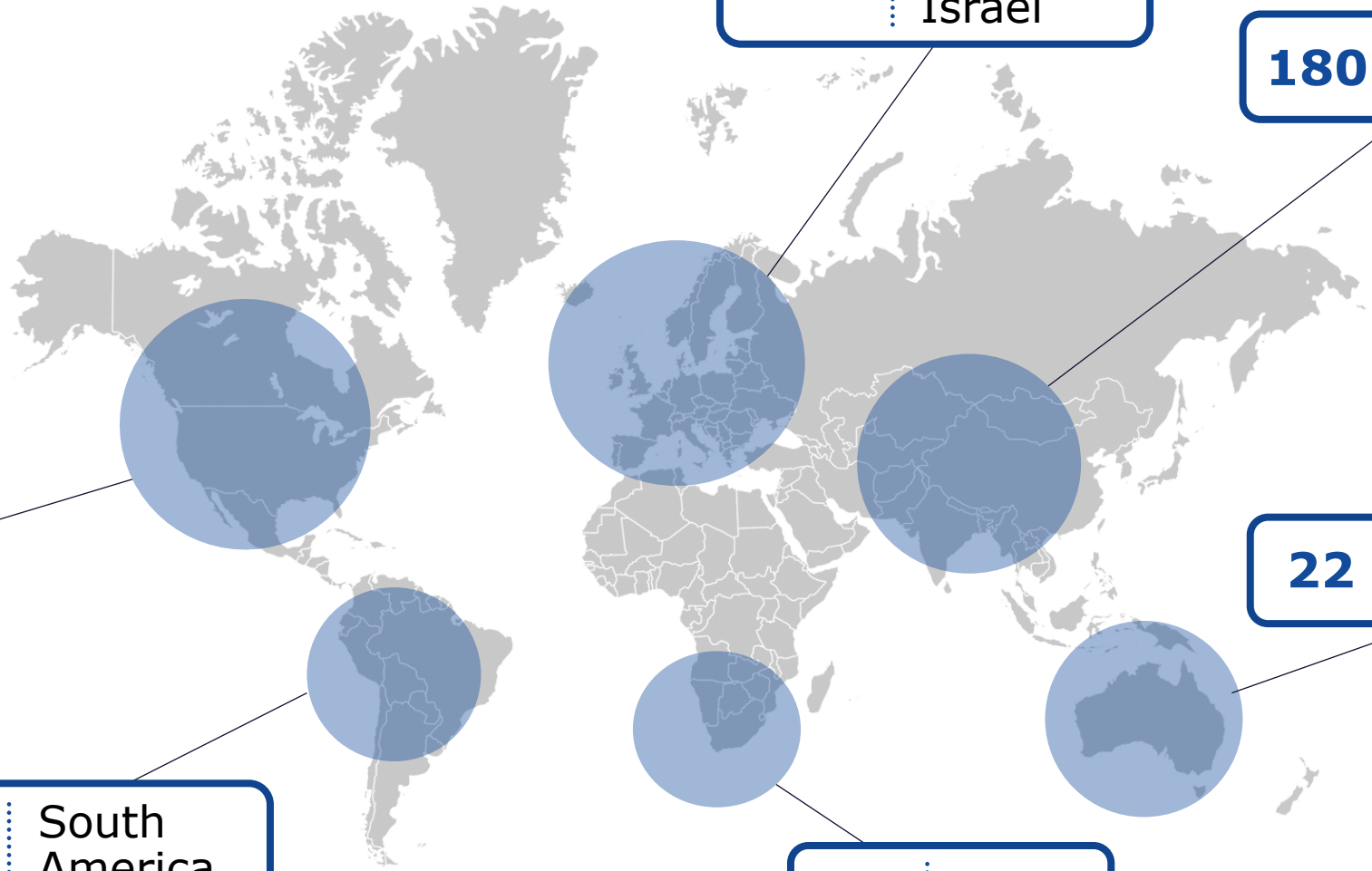
987+
Regenerative Medicine Companies Worldwide



237 Europe & Israel

180 Asia

534 North America

22 Oceania

Australia,
New Zealand,
Marshall Islands

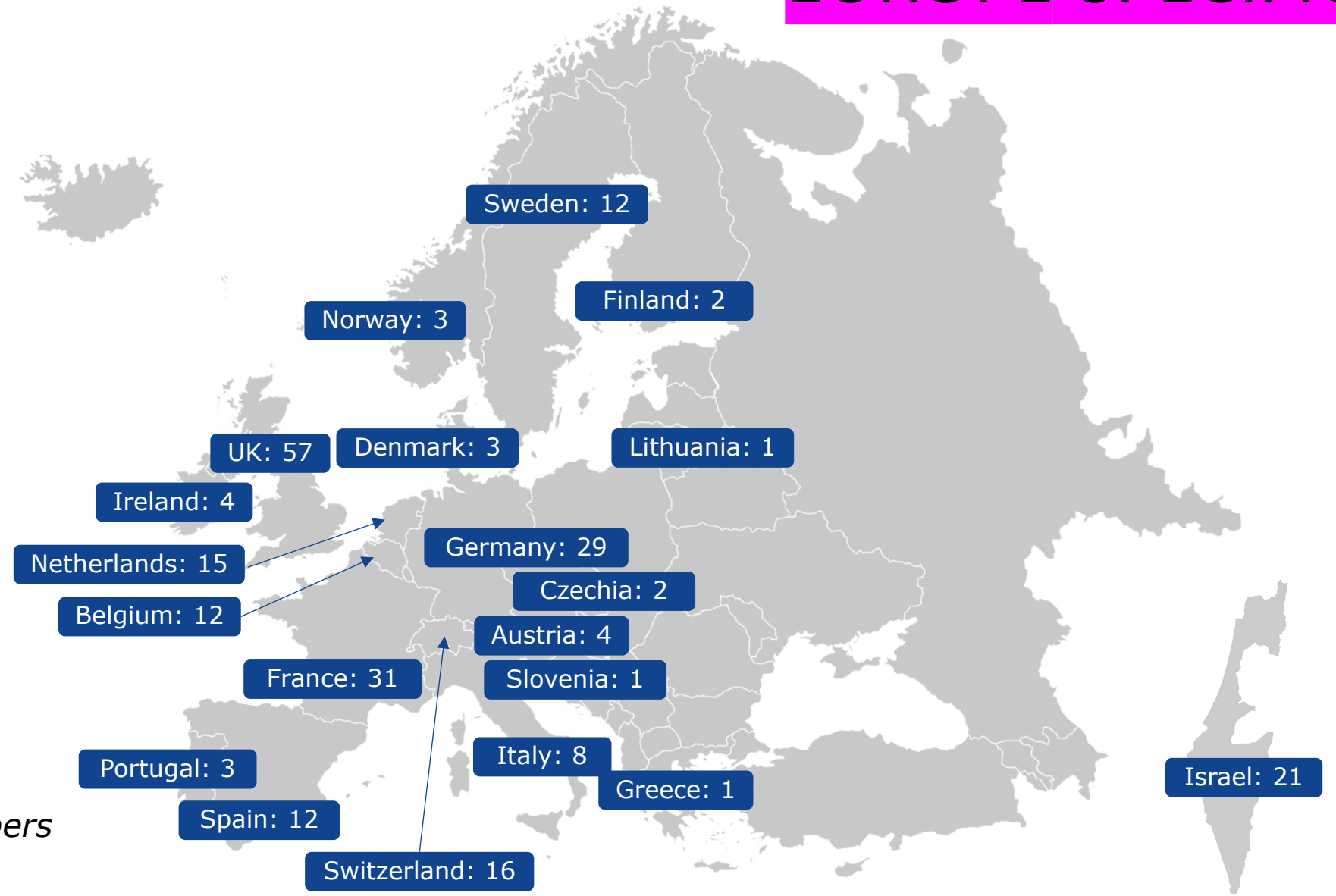
13 South America

1 Africa

European Sector Landscape

EUROPE-SPECIFIC

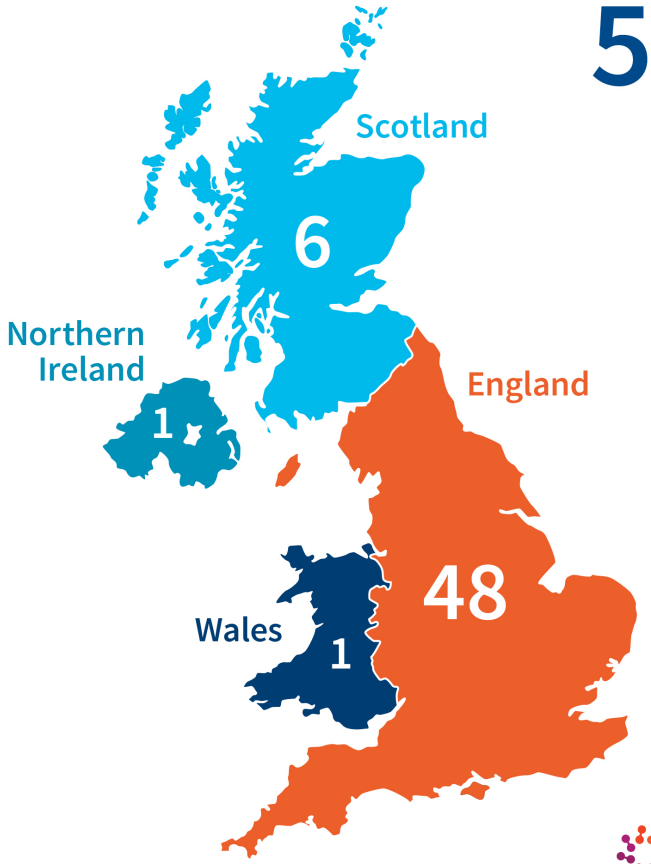
237+
Regenerative Medicine Companies HQ'd in Europe



Nearly ¼ of regenerative medicine therapeutic developers are headquartered in Europe

UK ATMP Developers

ATMP DEVELOPERS HEADQUARTERED IN THE UK



56 Total ATMP developers headquartered in the UK, with **70+ total companies active in the UK,** including gene therapy, cell therapy, and tissue engineering therapeutic developers

24	33	11
Gene Therapy	Cell Therapy	Tissue Engineering

**Some developers may be active in more than one technology area.*

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BIA UK BioIndustry Association

Global Sector Landscape

EUROPE-SPECIFIC

10

ATMPs Granted PRIME Designation in 2019

260

Ongoing ATMP Clinical Trials

$2.7B

Raised in Global Financings in 2019

2019 has been a significant year of growth for the advanced therapies sector

ATMP CMC paradigm

- PRIME Designation = accelerated regulatory timelines
- Accelerated regulatory timelines = less time for process development (accelerated CMC)
- “Traditional” approach of conducting heavy CMC lifting in parallel with stage 3 studies is not viable
- You must start CMC early, when you know the least!
- Requires a flexible risk based approach AND collaboration on standards and best practices

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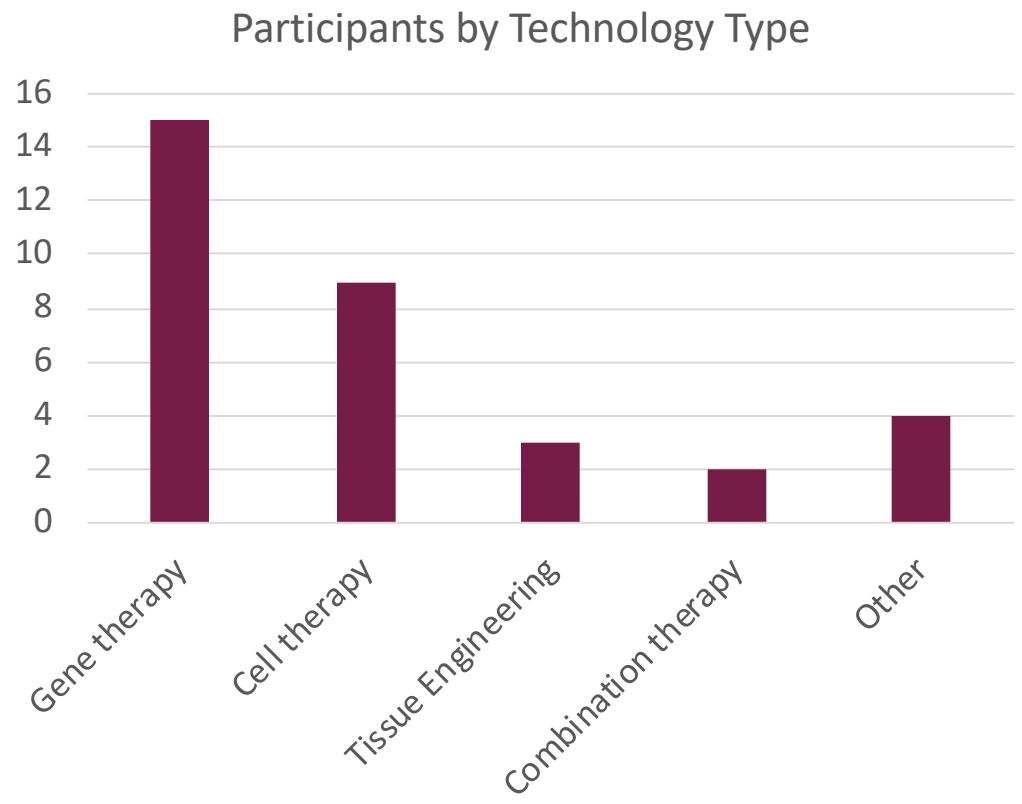
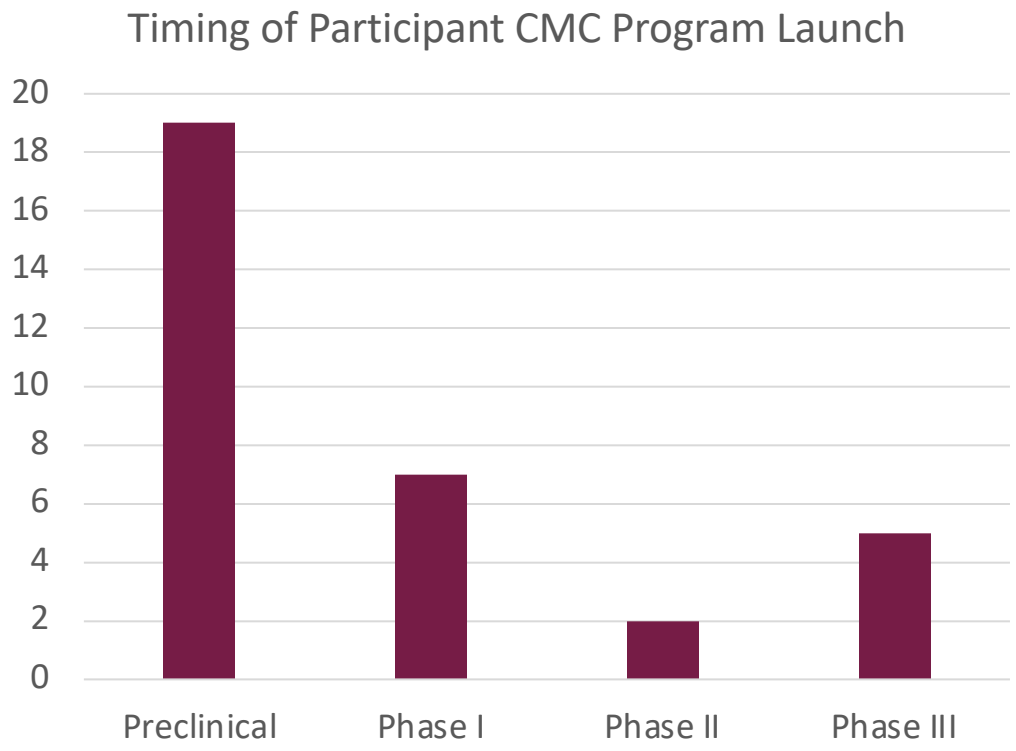
ATMPs Granted PRIME Designation in 2019

ARM CMC Summit survey

Are you producing a cell therapy, gene therapy, tissue engineered product, or a combination therapy?

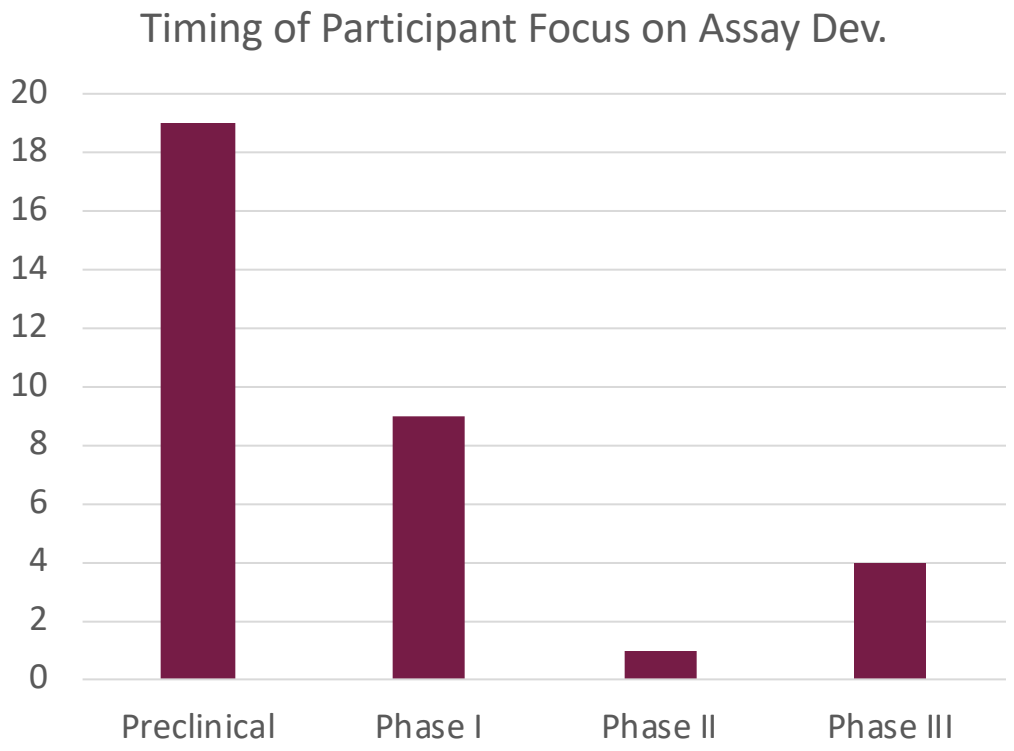


At what point in the development cycle did you begin to build out a CMC program?

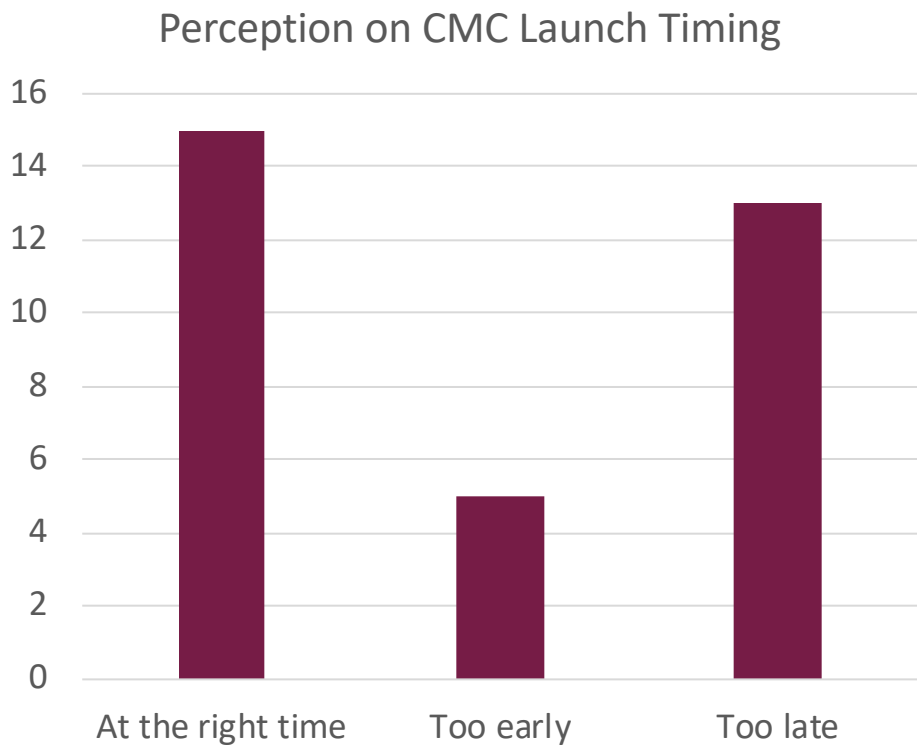


ARM CMC Summit survey

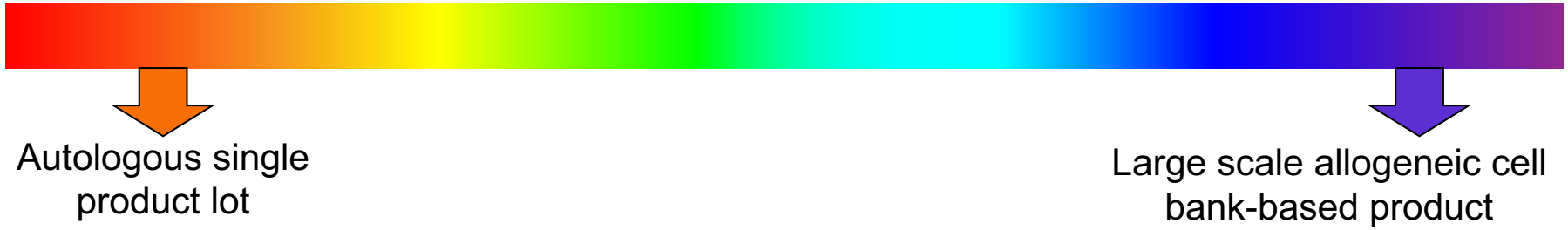
At what point in your development cycle did assay development become an area of focus?



Do you feel that your organization began building a CMC program:



CGTs encompass a wide spectrum of products, each with their own concerns



Common concerns

Mechanism of action, material qualification, challenges establishing specifications, manufacturing facility, product shipping/handling, major manufacturing changes

Specific concerns

- Product tracking and segregation
- High product variability (collection)
- Limited material or time for testing
- Short shelf life
- Manufacturing logistics
- Scale-out

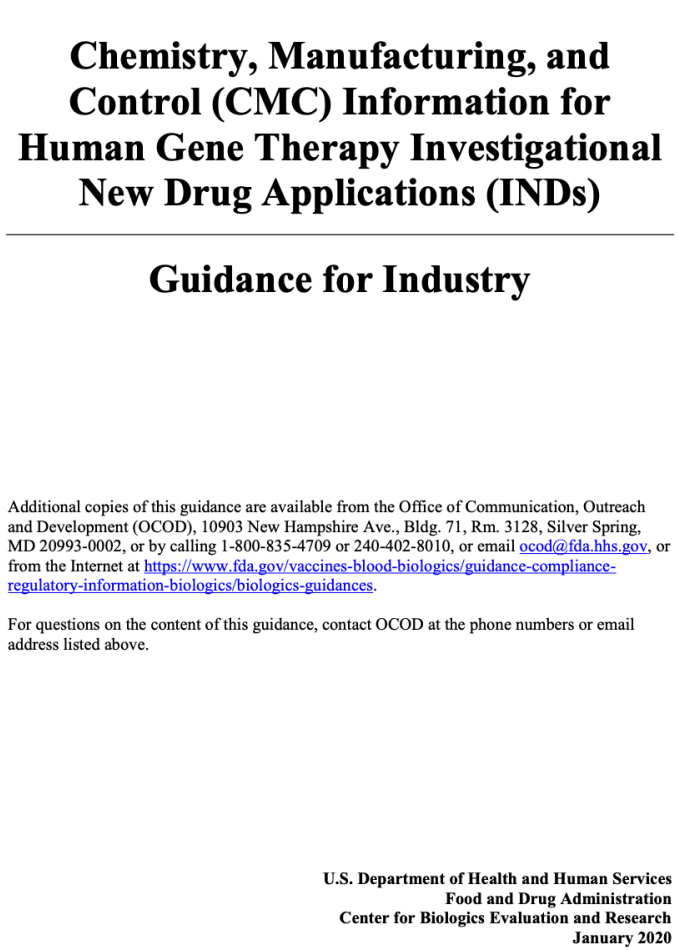
- Donor eligibility
- Qualification of cell banks
- Reproducibility of replacement bank
- Stability of cell banks and intermediates
- Scale up

Regulatory guidance

- ✓ *Recent FDA CMC Guidance*
- ✓ *EMA Comparability Q&A*
- ✓ *Significant differences FDA vs. EMA*

FDA Gene Therapy CMC Guidance

- Coverage includes gene therapies and gene modified cell therapies (e.g. CAR-T, TCR)
- Thorough coverage of manufacturing, characterization, and control of DS and DP
- Flexible language around CQA's, process validation, analytics
- Still primarily focused on IND stage
- **Draft CAR-T Guidance this year**



Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)

Guidance for Industry

Additional copies of this guidance are available from the Office of Communication, Outreach and Development (OCOD), 10903 New Hampshire Ave., Bldg. 71, Rm. 3128, Silver Spring, MD 20993-0002, or by calling 1-800-835-4709 or 240-402-8010, or email ocod@fda.hhs.gov, or from the Internet at https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-guidances.

For questions on the content of this guidance, contact OCOD at the phone numbers or email address listed above.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
January 2020

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/chemistry-manufacturing-and-control-cmc-information-human-gene-therapy-investigational-new-drug

Comparability

- Highlighted as a major issue by EMA, FDA and ARM members
- EMA Q&A* released December 2019
- "ATMPs are outside the scope of ICH Q5E guideline", however, " … the general principles of ICH Q5E can be applied to ATMPs"
  - "The comparability exercise should be conducted stepwise"
  - "The investigation should focus on the manufacturing process steps most appropriate to detect a change"
  - "Analytical methods should be suitable for purpose and sufficiently sensitive …"
  - A risk based approach
- Min # of batches "there is no one size fits all"

*(https://www.ema.europa.eu/en/documents/other/questions-answers-comparability-considerations-advanced-therapy-medicinal-products-atmp_en.pdf)

Comparability

- Suggestions from the regulators
  - Keep retains!
  - Measure multiple “potential CQA’s” at phase I
  - Use orthogonal assays – be prepared to abandon some assays as development proceeds
  - Qualify assays early, set specifications and validate later
- Other food for thought
  - Rely on risk assessments and quality systems for minor changes
  - Adding new methods to a comparability study that do not measure critical attributes may create unnecessary and potentially misleading data
  - With highly variable products, historical data may be a more meaningful control than a head to head comparison
  - Trend monitoring can mitigate against unknowns

FDA vs. EMA – Disharmony?

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Areas of Significant difference	Impact
1. Timing and extent of GMP implementation	Stage specific GMP program designed for US may not meet EU requirements
2. In the EU, a Potency Assay with Acceptance Criteria is required for Ph1/FIH trials	Delay to start of ph. 1 clinical trial in EU vs. US
3. In the EU, a Qualified Person must ensure GMP compliance and authorizes FP release	US sponsors must hire a QP. Logistical issues.
4. US Cleanroom Air Classification Standards differ from European Guidelines	EU requirement for Grade B vs. ISO 7 "background" disqualifies many US facilities
5. In the US, testing laboratories must be CLIA certified	Allogeneic cell line derived in EU not usable in US
6. Disease-specific donor testing requirements are not harmonized	Allogeneic cell lines

Source: IQVIA/ARM EU-US Regulatory Analysis

Standards & Best Practices

- ✓ *A-Gene and A-Cell*
- ✓ *Standards Coordinating Body Projects*

ARM A-Gene & A-Cell Projects

- Books of knowledge for best practices in the cell and gene therapy manufacture
  - Based on A-Mab model, a QbD approach to monoclonal antibody manufacturing (2009)
  - A-Gene follows the application of quality by design principles to a case study of a TT-HEK293/Sf9 AAV vector manufacture process
  - A-Cell scope will be general in nature with specific examples cited where appropriate (e.g. cell source selection – autologous vs allogeneic)
- Broad base of experienced contributors ~ 50 ARM member companies involved
- Collaborating with NIIMBL, SCB & USP
- A-Gene: Q1-Q2 2020 completion and release, A-Cell end of Q2
- What happens then?
    - ”Open source” on website and possible ‘print’ publication
    - Educational webinars and workshops
    - Continued maintenance and updates

A-Gene content

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Table of Contents

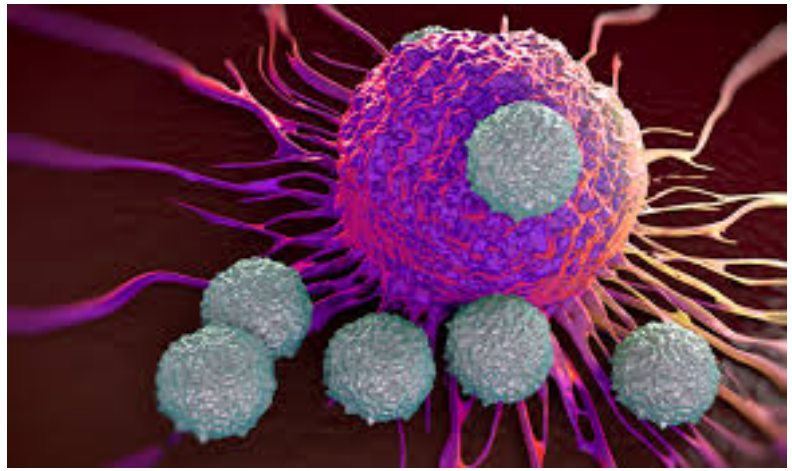
1. Introduction & Context
2. Generating a Quality Target Product Profile
3. Defining CQA & Performing Risk Assessment
4. Regulatory Considerations
5. Enacting Quality by Design & PAT
6. Managing Upstream & Downstream Processing
7. Formulation & Characterization of the Drug Product
8. Implementing a Process Control Strategy
9. Addressing Comparability
10. Development & Use of Standards

Table 1. Drug Substance and Drug Product Release Testing Panel

Quality Attribute	Analytical Test(s)	Rationale	Used for Drug Substance (DS), Drug Product (DP) and/or Stability (S)
Characteristics			
Clarity	Appearance	Compendial	DS, DP, S for both
Coloration	Appearance	Compendial	DS, DP, S for both
Visible Particles	Appearance	Compendial	DP, S
Sub-Visible Particles	Sub-Visible Particles	Compendial	DP, S
pH	pH	Compendial	DS, DP, S for both
Osmolality	Osmolality	Compendial	DS, DP
Extractable Volume	Extractable Volume	Compendial	DP
Viral Particle Titer	SEC-HPLC; ELISA	Measures total viral particles	DS, DP, S for both
Identity			
Capsid Identity	Peptide map by RP-HPLC; ELISA	Ensures intended capsid is present	DS, DP
Vector Genome Identity	qPCR, restriction map, sequencing	Ensures intended vector genome is present	DS, DP

Standards Coordinating Body:

Connecting the Regenerative Medicine Community to the Standards Development Process



- Launched in early 2017, SCB is an **independent 501(c)(3)** organization
- Occupies unique niche within field with **no vested interests in specific scientific, commercial, clinical or policy approaches**
- SCB is **not an SDO**, but rather **coordinates** the standards development process
- Serves as **communication vehicle** among all stakeholders, including government agencies, critical to the development of standards
- SCB works to **coordinate** standards activities, **engage** experts, and **educate** the regenerative medicine community.

CELL COLLECTION PROCEDURES

Bioprocessing and Production Standards

Establish cell collection requirements that ensure consistency, safety, and comparability in final products and reduced loss of cell material.

This standard is in the drafting phase. Experts are developing surveys for industry and apheresis centers to identify commonalities for standardization. This standard has begun development with FACT and PDA. This standard is expected in early 2023.

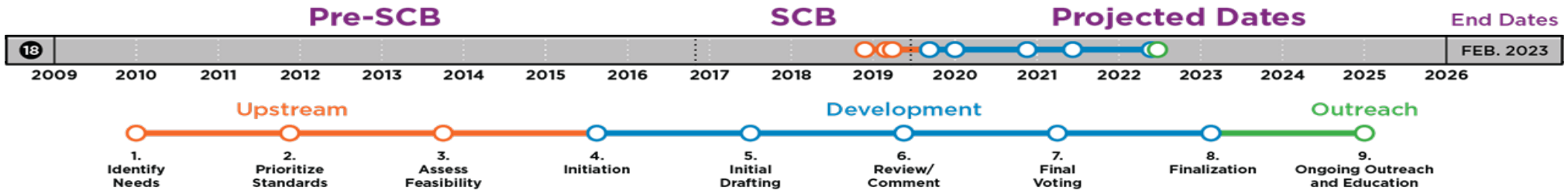
LABELING FOR APHERESIS PRODUCTS FOR REGENERATIVE MEDICINE MANUFACTURING

Logistics and Compliance

Standard Progress

This standardization will minimize confusion, mistakes, and production errors. This would integrate with FACT standards as it would be an update to ISBT 128 and will include:

This standard update to ISBT128 with sample labels is currently open for comments through ICCBBA. This standard is expected to be published in 2021 or 2022



COI/COC FOR PRODUCTS FOR REGENERATIVE MEDICINE MANUFACTURING

Logistics and Compliance

Experts have begun and effort to standardize Chain of Identity (COI) and Chain of Custody Identifiers (COC). This unique identifier will be on the standardized labels helping to streamline and simply the process from human medical materials, through the complex manufacturing processes, until reaching the patient in the final product.

In Total = Unique COI # for each product journey and each dose produced							
Core Chain of Identity (COI) [IDA].[123456].[5]				Chain of Custody (COC) [01].[AP1]-[01]-[01]			
Company Identifier	Product Identifier	Core Patient ID	Sum Check Digit	Product Journey #	Process Step Identifier	Sub-process identifier	Final Product Dose Number
3 alpha-numeric characters	3 alpha-numeric characters	6 alpha-numeric characters	1 numeric character	2 alpha-numeric character	3 alpha-numeric characters	2 alpha-numeric characters	2 alpha-numeric characters

Example 1

Examples Patient Use Cases								
Fred Smith DOB: 9-2-1988 with lung cancer enrolls in **Acme Cell Therapy's** clinical trial using T-cell therapy targeting CD133 that will have 2 aphereses performed 4 weeks apart and each aph will produce 4 frozen doses. All doses mfg successfully.	ACM	133	000123	1	01	FP4		01
	ACM	133	000123	1	01	FP4		02
	ACM	133	000123	1	01	FP4		03
	ACM	133	000123	1	01	FP4		04
	ACM	133	000123	1	02	FP4		01
	ACM	133	000123	1	02	FP4		02
	ACM	133	000123	1	02	FP4		03
	ACM	133	000123	1	02	FP4		04

Example 2

Carla Jones DOB: 2-3-1981 with Multiple Myeloma enrolls in the **XYZ therapy company's** clinical T-cell product trial with BCMA target and 2 doses are created from one apheresis; she had Aa failed apheresis on the first attempt due to venous access issues. The second aph and mfg were successful.	XYZ	BCM	123001	1	01	*APH fails and product journey ends with reason codes recorded in the traceability system for core COI with COC journey #1*		
	XYZ	BCM	123001	1	02	FP2		01
	XYZ	BCM	123001	1	02	FP2		02

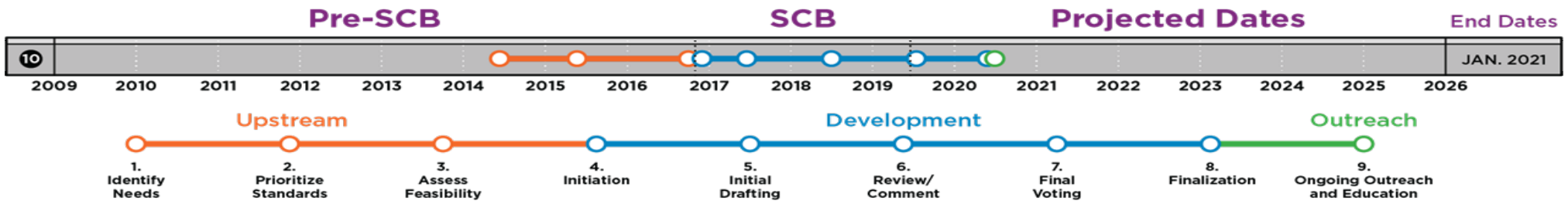
ISO/TC 276 21973 GENERAL GUIDE FOR TRANSPORTATION OF CELLS FOR THERAPEUTIC USE

Cell Therapy Gene Therapy Tissue Engineering

Standard Objective

Experts are standardizing transportation processes to ensure cell product quality that can ultimately affect product safety and effectiveness.

This Standard is currently open for DIS ballot. It has undergone many working group and committee ballots and revisions. It is open for a Draft International Standard Ballot currently. This ballot closes on November 25th. It expected to be published by late 2020.



Final thoughts

- Regulatory guidance is progressing, but more work is needed
- CMC harmonization (EU/US) would be beneficial
- A risk based approach is a double edge sword
  - Subjective in the absence of empirical data and experience
  - Humans possess inherent biases
- Collaboration is one solution to this quandary

For More

Visit **www.alliancerm.org** to access additional resources, including:

- Manufacturing web page - https://alliancerm.org/manufacturing/
- Quarterly sector data reports
- Upcoming near-term clinical trial milestones & data readouts
- Access to slides, graphics, and figures from ARM presentations
- Our weekly sector newsletter, a robust round-up of business, clinical, scientific, and policy news in the sector
- Commentary from experts in the field

For additional information, please contact:

- Michael Lehmicke, Director of Science & Industry Affairs
  mlehmicke@alliancerm.org

Thank You!

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