Address the Need of Standards Development in the CGT Space: SCB & Standards Initiatives

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STANDARDS COORDINATING BODY

Outline

- CMC challenges and need of standards
- SCB and standards initiatives
- Rapid Microbiology Testing Method (RMTM) project

Unique Challenges in Cell and Gene Therapy - Manufacturing, Control, Testing (CMC)

Remarks by Commissioner Gottlieb to the Alliance for Regenerative Medicine's Annual Board Meeting, May 22, 2018

"We're at a key point when it comes to cell and gene therapy. These therapies have the potential to address hundreds, if not thousands, of different rare and common diseases. For a long time, they were largely theoretical constructs. Now they're a therapeutic reality. And it's my expectation that they will soon become the mainstay of how we treat a wide range of illness."

"In contrast to traditional drug review, where 80 percent of the review is focused on the clinical portion of that process, and maybe 20 percent is focused on the product issues, I'd say that this general principal is almost completely inverted when it comes to cell and gene therapy. "

CMC Challenges – in Need of Standards

Comparison of Specifications

Products	Identity	Purity/impurity	Safety	Potency
Gleevec (NCE)	IR, HPLC,. XRPD, assay (HPLC)	impurities (HPLC), residual solvents (GC), water content (KF), sulphated ash (Ph Eur) and heavy metals (Ph Eur); methanesulphonic acid content (potentiometric titration)	microbiological quality (pharmacopeia)	Dissolution (pharmacopeia)
Kymriah (Autologous gene-modified cell therapy)	presence of CAR19 transgene	# viable cells*; % Viable CD19+ B cells*; % viable T cells*; Cell viability*; Transduction efficiency*; Residual Beads	Endotoxin; Sterility; mycoplasma; Presence of VSV-G DNA	CAR expression (potency); IFN-γ Release

Role of Standards

Standards to reduce cost, streamline development, support commercialization & patient access

"Mass production became possible through standardization. By the turn of the 19th century, standardization was already recognized in industrialized countries as a powerful tool to increase productivity through interchangeability and reduction of variety.

After the First World War, standardization, through reduction in variety, was established as a useful management tool for reducing costs."

Role of standards by UNITED NATIONS INDUSTRIAL DEVELOPMENT ORGANIZATION

https://www.unido.org/fileadmin/media/documents/pdf/tcb_role_standards.pdf

From Need of Standards to SCB

2009: Need for standards recognized during discussions with FDA and ARM

2013: ARM stake holder survey identified the need for standards

2013: ISO Biotechnology Committee TC276 initiated

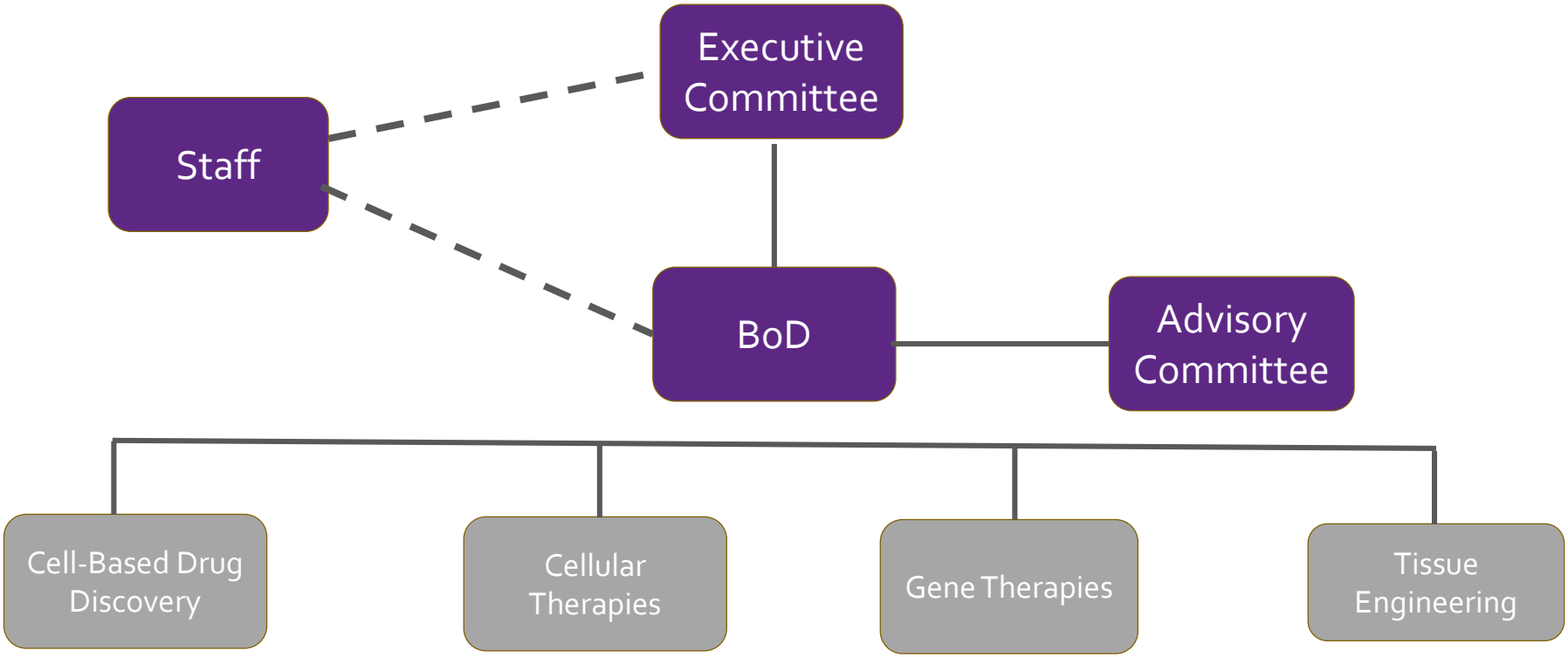
2014: FDA workshop: Synergizing standards efforts
2014: Standards were strategic focus of ARM S&T Committee

2015: ARM S&T Committee proposal to create a **standards coordinating body**; ARM annual fly-in

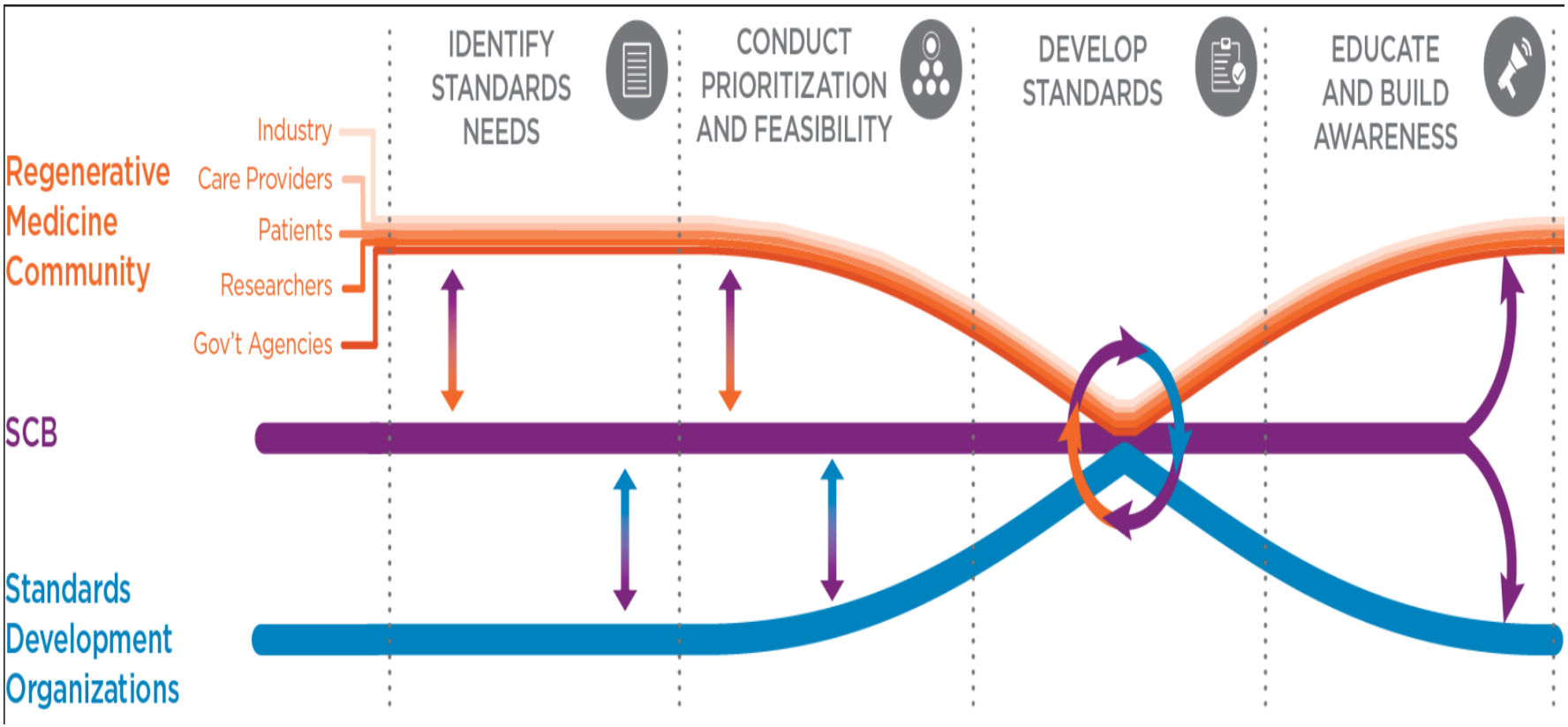
2016: January – Senate bill; March – House Bill
2016: Dec – 21st Century Cures Act, Section 3036

2017: January – SCB inception
2017: Sept – FDA awarded 1 year contract to Nexight/SCB under Cures Act Section 3036

SCB Organizational Structure

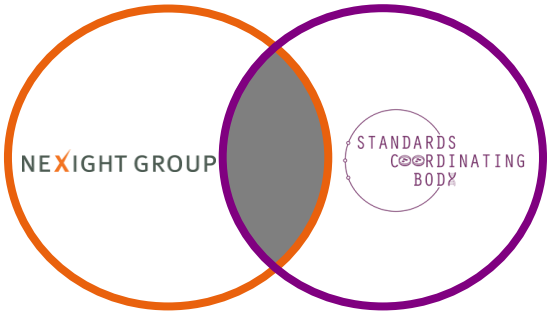


SCB: Coordinate Standards Efforts From Upstream to Downstream



FDA Standards Development Project

SUPPORTING THE DEVELOPMENT OF STANDARDS FOR REGENERATIVE MEDICINE THERAPIES



SEP 2017 — SEP 2018

KEY PRODUCTS

1. Report on the current landscape for regenerative medicine therapy standards
2. Three, educational webinars on standards
3. Report that specifies processes and criteria to identify and prioritize standards
4. Report that specifies processes and criteria to determine the feasibility of standards
5. Report outlining a roadmap for operationalizing identification, prioritization, and feasibility for standards

On Track to Complete Projects By Sept

Webinars

- 1st Webinar completed December 12, 2017
- 2nd Webinar: March 13
- 3rd webinar: June 26
- Webinar recordings available on SCB website

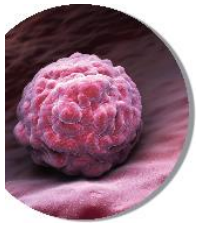
Reports in progress

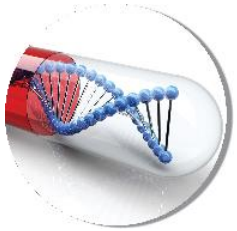
- Standards identification and prioritization
- Feasibility assessment
- A Roadmap to Improve Processes and Criteria to Advance Standards Needs for Regenerative Medicine

- **Standards landscape report**
  - 194 standards identified
  - Summarized by sectors, by functional areas
  - Standards gaps and needs identified, eg. Cell counting, cell characterization, raw materials, sterilization and sterility testing, reference materials

https://static1.squarespace.com/static/58a331b0db29d63c7fb64528/t/5a9ee032e2c483767c878be9/1520361532848/Landscape+Report_3-2-2018.pdf

SCB Supporting Stake Holder Projects

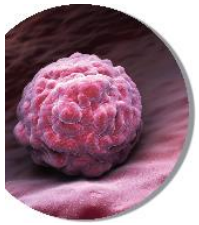




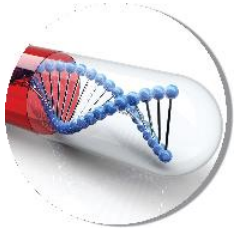
- **Seven** projects in progress
  - Rapid microbial testing methods
  - Microphysiological paper
  - **Characterization of fibrous scaffolds (along with ASTM, NIST, BioFabUSA)**
  - Pre-existing immunity standards
  - **ARM S&T A-gene project**
  - Cell transportation
  - Cell therapy manufacturing equipment
- **Five** projects proposed
  - Cell potency assays for cell therapy & tissue engineering
  - Fluorescence intensity measurements in cell based assays
  - Characterization for various cell types (e.g., neurons, pancreatic beta cells, cardiomyocytes)
  - **Cell Tracking Project (in collaboration with HESI)**
  - **Training Programs with Northeastern University (NEU)**

SCB Supporting ISO TC276

- Leading **three** standards projects
  - Rapid Microbial Testing Methods (being presented at ISO meeting June 2018)
  - **Cell transportation (ISO 21973)**
  - **ISO 23565 TS - General requirements and considerations for equipment systems used in manufacturing of cellular therapeutic products**



- Supporting **seven** standards projects
  - **ISO 20391-1:2018 Cell Counting Part 1: General guidance on cell counting methods – published January 19, 2018!**
  - ISO 20191-2 Cell counting Part 2
  - ISO 20395-1 Quantification methods nucleic acid – qPCR & dPCR
  - ISO 23033 Cell characterization
  - ISO 20399 Technical Specifications (TS) Ancillary Materials for Cell Therapy
    - Part 1: General Requirements
    - Part 2: Best practice for suppliers
    - Part 3: Best practice for users
    - **To be published late 2018!**
    - **SCB will be leading a new project to develop IS document by combining 3 TS documents**



SCB Supporting ASTM F04

ASTM F04 Medical and Surgical Materials and Devices

- F04.41 – Classification and Terminology for TEMPs (tissue engineered medical products)
- F04.42 – Biomaterials and Biomolecules for TEMPs
- F04.43 – Cells and Tissue Engineered Constructs for TEMPs
- F04.44 – Assessment for TEMPs
- F04.45 – Adventitious Agents Safety
- F04.46 – Cell Signaling

Please contact SCB Technical Program Manager, Dawn Henke (dhenke@regenmedscb.org), if you would like to participate in these efforts.

RMTM Project: the Need of the CGT Field

Regulatory/FDA requirements:

- 21 CFR 610.12 Sterility Testing
- 2012 sterility rule encourages sponsors to develop and validate alternative methods

Current standards testing methods:

- Pharmacopia (USP 71/EP/JP) growth method
- Limitations and gaps
  - CART products released and administered to patients before test results available

Request from Stake holders

- Rapid testing methods
- Standardized methods to ease validation requirements by individual sponsors

RMTM Project: SCB Addressing the Need

- **June 2017: project initiation, establishing steering committee**
  - Steering committee: KOLs from U. Penn, Georgia Tech, MSKCC, MIT, Celgene, CCRM, Novartis, NIST

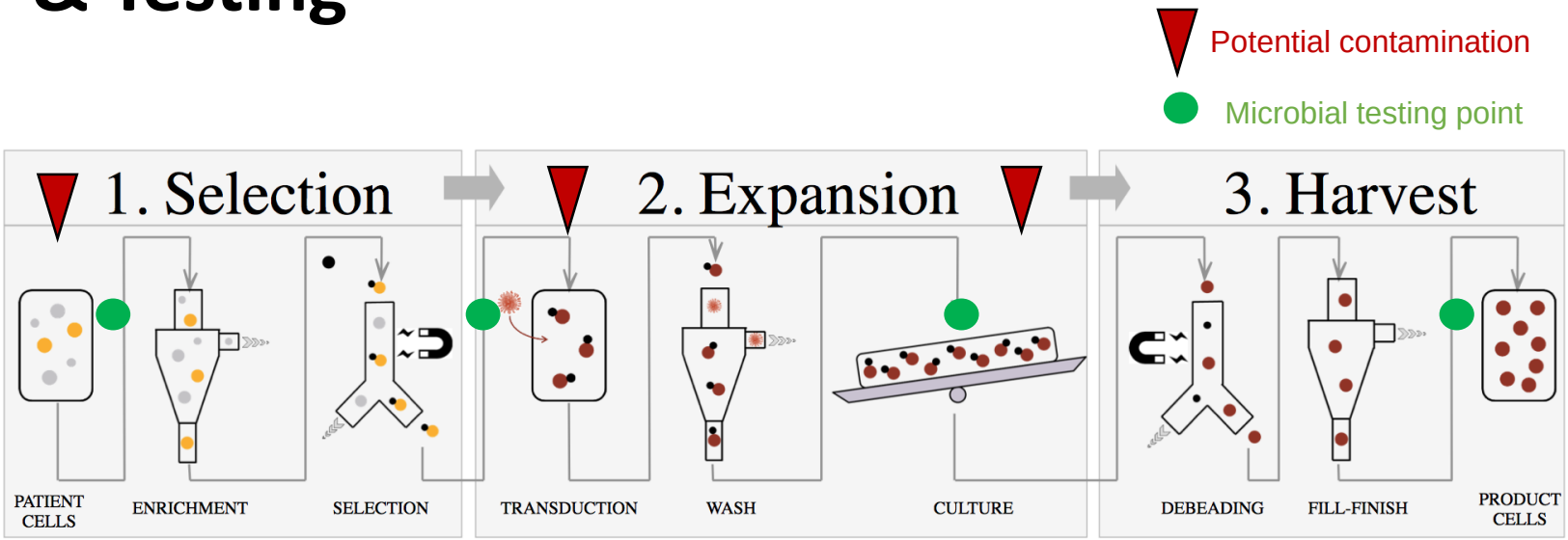
- **July 2017: responded to NIIMBL quick start project call to develop standardized RMTM**
  - Overall project plan
  - Preliminary input from the FDA
  - Decision to organize a stake holder workshop

- **April 10, 2018: stake holder workshop co-sponsored by SCB, NIST, BiofabUSA, and NIIMBL**
  - Project roadmap
  - Initial documentary standard: risk based control and testing strategy

RMTM Project Road Map: Technology and Standards Development

July 2017 Project initiated	1H 2018 Workshop	2H 2018	2019 & Beyond
• Project proposal & roadmap • Support from stakeholders, NIST, NIIMBL, Biofab	• URS for technologies • Whitepaper: risk based, scenario associated guiding principles	• Publish whitepaper • Initiate standards projects	• Methods validation • Standards release, dissemination, adoption, education, implementation
• Standards Development	• Draft documentary standards	• Initiate projects at ISO, ASTMi	• Overarching standard • Compendial method standards
• Technology Development	• Specific testing methods and kit products development		• Commercialize testing kits • New technology development

RMTM Standards Workstream: Risk Based Control & Testing



ISO/TC276

Risked based control & testing

- Expert support at June'18 meeting
- Initiate NWIP for Dec discussion

ASTM F04

Rapid detection in biological preparations using scaffolds

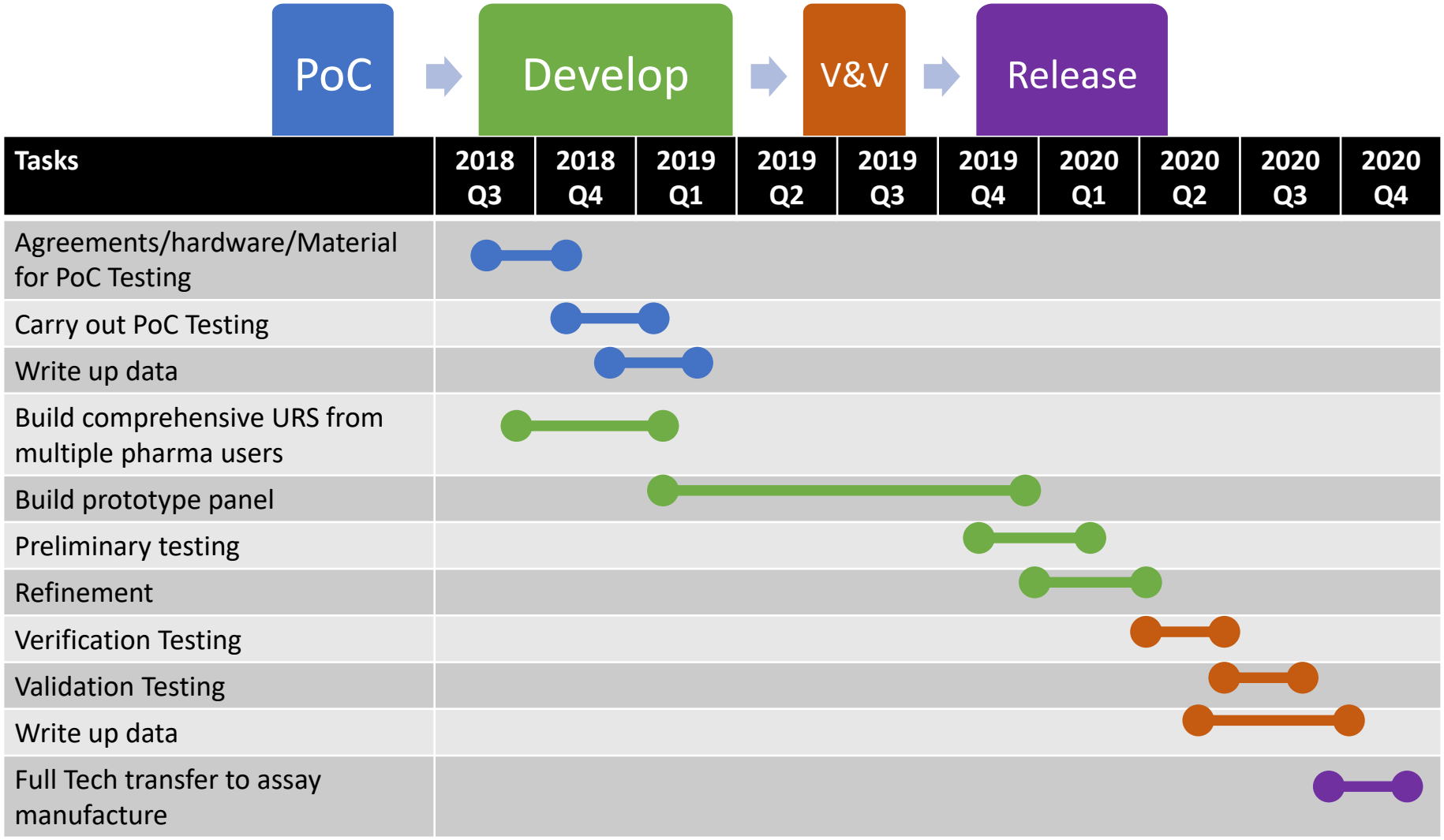
- Expert support at May'18 meeting
- Drafting document for next meeting

Reference Standards

Determine, develop, & source reference standards

- Develop process
- ID resources

RMTM Technology Development Workstream



Engage, Participate, Contribute

For general information on the SCB, visit
standardscoordinatingbody.org

For general SCB inquiries or to sign-up for regular SCB communications, contact SCB Program Manager, Allison Getz
agetz@regenmedscb.org

To participate in SCB sector activities or ISO/ASTM projects, contact SCB Technical Program Manager, Dawn Henke
dhenke@regenmedscb.org

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THANK YOU!

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