Regulatory Considerations to Accelerate Cell & Gene Therapy Development

Jiwen Zhang, Ph.D.

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Outline

- Global landscape for cell and gene therapy products
- Development challenges, uncertainties
- Regulatory considerations to accelerate product development
- It takes a village: stake holder initiatives

- **Dynamic landscape with challenges, uncertainties**

Recent Approvals in Global Market

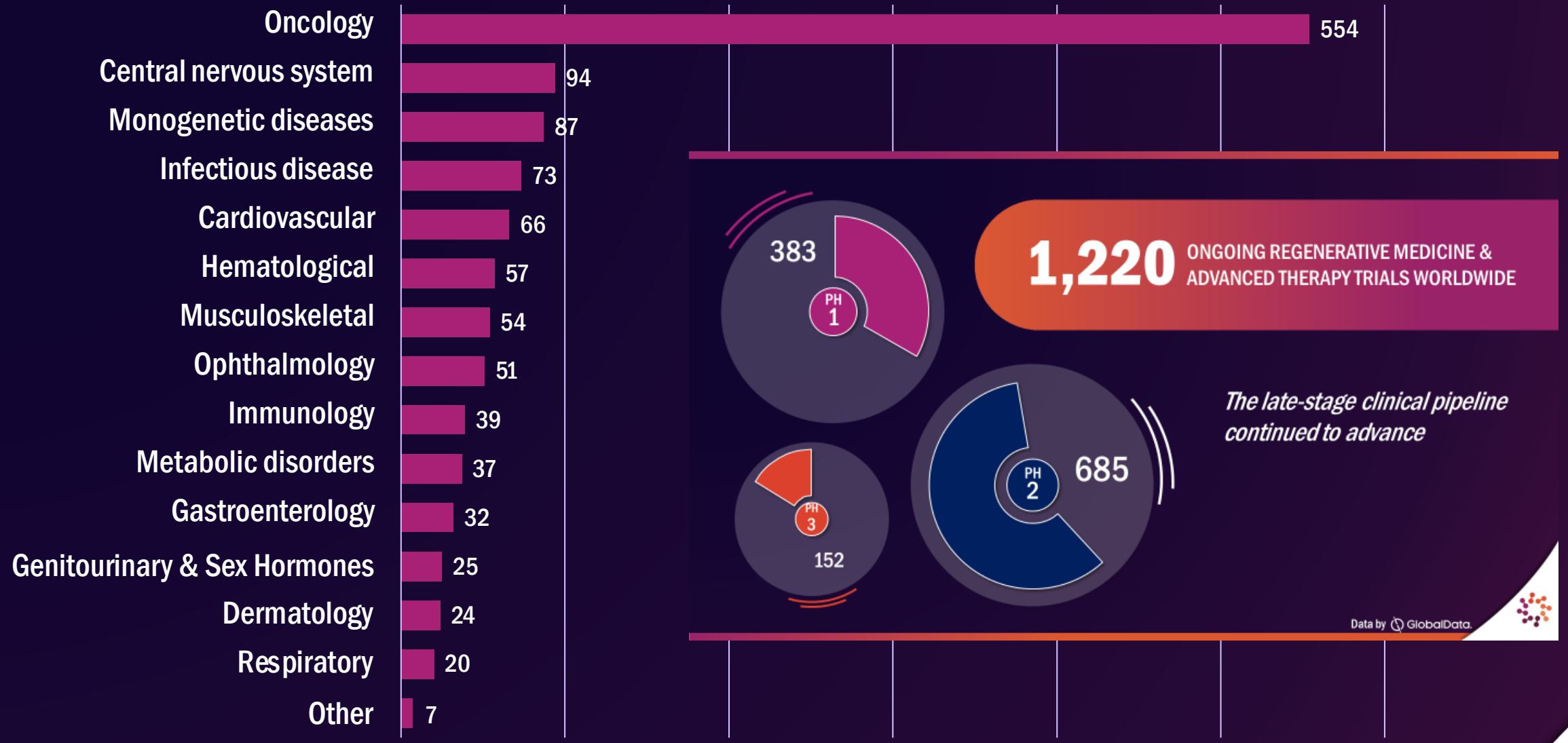
- Libmeldy (Orchard Tx) – Europe
- Tecartus(Kite, a Gilead company) – US
- Zolgensma (Novartis Gene Therapies) – Europe, Japan, Canada
- Luxturna (Spark / Roche) – Canada
- Abecma (Celgene/BMS) – US

US FDA approved products

Approved Cellular and Gene Therapy Products | FDA

Clinical Trials by Indication

Courtesy of Alliance for Regenerative Medicine



Data by GlobalData.

Regulations, guidelines – 2021 highlights

- US FDA: Human Gene Therapy for Neurodegenerative Diseases; Draft Guidance for Industry – Jan'21
- Spain: AEMPS authorises Hospital Clínic's CAR-T ARI-0001 for patients with acute lymphoblastic leukaemia (clinicbarcelona.org) – Feb'21
- Singapore's new regulations for cell, tissue and gene therapy products HSA | CTGTP – March'21

- FDA/CBER/OTAT 2021: Guidance Agenda: Guidance Documents CBER is Planning to Publish During Calendar Year 2021 (fda.gov)

Challenges, Uncertainties …

- Manufacturing capacity can not keep up with demand
- CMC often behind accelerated clinical development
- Early biomarker response may or may not predict clinical benefits
- There are still a lot of unknowns in terms of safety
- Regulatory standards are evolving as science and technology advance; regulatory requirements vary across countries, regions

- **Regulatory considerations to accelerate development**

Follow Regulatory Guidance

- **Understand intent**
- **Recognize ambiguity, flexibility**
- **Determine appropriate requirements**

- US FDA: Cellular & Gene Therapy Guidances | FDA
  - Guidance Agenda: Guidance Documents CBER is Planning to Publish During Calendar Year 2021 (fda.gov)
- EU EMA: Guidelines relevant for advanced therapy medicinal products | European Medicines Agency (europa.eu)
- Japan PMDA: Regulatory Science/The Science Board/Standard Development | Pharmaceuticals and Medical Devices Agency (pmda.go.jp)
- Health Canada: Guidance documents - Biologics, Radiopharmaceuticals and Genetic Therapies - Canada.ca

Consult with Agencies: Early, Frequent, Well Planned

Milestone Meetings

US FDA
- Pre-IND, EOP2, pre-BLA/NDA

EMA
- CHMP Scientific Advice

Japan
- PMDA consultations on quality, nonclinical, clinical, Cartagena protocol for gene therapy

National agencies
- Pre-CTA/submission meetings

Agency consultations are key components of regulatory strategy to de-risk development programs

Information Meetings

US FDA
- INTERACT for RMAT – pre-pre IND
- Type C meeting

UK
- Broader scope meeting

Brazil
- Information meeting

Consult local regulatory experts for country specific meeting types, formats, procedures, & timelines

Leverage Regulatory Mechanisms (US as Example)

Conventional mechanisms

- Intent to **expedite** drug development to treat **serious conditions**
- Frequent agency interactions
- May accept surrogate efficacy endpoints
- Criteria dictates when to request

- **Fast Track (FT)**
- **Breakthrough (BT)**

Cell & gene specific mechanisms

- **Similar intent and concept as conventional mechanisms**
- Specific regulatory framework and oversight for cell & gene products
- Take consideration of cell gene specific challenges and transformative nature

- **Regenerative Medicine Advanced Therapy (RMAT)**

Rare disease related

- Intent to encourage drug development to treat rare diseases
- Incentives more commercial or financial oriented
- **Serious nature of the rare diseases often eligible for other reg mechanisms**

- **Orphan drug designation (ODD)**

Comparison of US and EU Regulatory Mechanisms

• US	• EU
Fast Track (**FT**) Breakthrough Therapy (**BT**) Regenerative Medicine Advanced Therapy (**RMAT**)	**PRIME** Scheme
Priority Review	Accelerated Assessment
Accelerated Approval (based on surrogate or intermediate endpoints)	Conditional MAA (based on less complete clinical data)
(no equivalent)	Approval under Exceptional Circumstances
Expanded Access	Compassionate Use Early Access Schemes

Kymriah regulatory designations & pathways

US:

- Designations: FT, BT, RMAT (2020); Orphan, Rare Pediatric Disease
- Full approval (2017)

EU:

- Designations: PRIME; Orphan
- Full approval (2018)

Zolgensma: conditional approval in EU with a broader indication than US

Courtesy of NDA Group

Learn from Precedents

Evaluation of Devices Used with Regenerative Medicine Advanced Therapies | FDA

Feb, 2019

"If there is sufficient evidence that the safety and effectiveness of the RMAT would not be compromised when administered with the identified general class or specific subset of delivery devices, the RMAT could be approved with more general labeling rather than specifying a particular delivery device."

Luxturna approach – FDA Reviewer's comments:

- The applicant also notes that biocompatibility using Medallion® 1-mL syringe hasn't been tested because like the 1 ml Becton and Dickinson syringe, the Medallion® 1-mL syringe 510(k) # K875196 (Merit Medical Systems, Inc) mentioned in the surgical (b) (4) (b) (4) (b) (4) 113 manual, is an alternative to 1mL BD syringe and is manufactured using similar polycarbonate material. This is acceptable.
- The applicant also notes that **Spark does not propose to limit the device components to any specific brand** because of the use of P188 in the formulation and because of the compatibility data generated to date. **This is acceptable as there tends to be little variation in the materials used for ophthalmic instruments among various device manufacturers**

- **It takes a village**

Stake Holder Initiatives

- **Global regulatory convergence -** "FDA and EMA signal an opportunity to harmonize advanced therapy regulations"

- **Good Regulatory Practices** & **Good Reliance Practices (WHO Expert Committee Report 2021):** https://apps.who.int/iris/bitstream/handle/10665/340323/9789240020900-eng.pdf
  "The purpose of the **Good Reliance Practices** is to promote a more efficient approach to regulation, thereby improving access to quality-assured, effective and safe medical products. Reliance allows leveraging the output of others whenever possible while placing a greater focus at national level on value-added regulatory activities."

- **ARM/industry** initiatives on accelerating CMC development

- Developing and implementing standards for Regen Med products

- Patient engagement in cell and gene therapy development
- Natural history data as external control to support product registration
- …