2021 Regulatory Roundup

Scott R. Burger, MD

ISCT 2021 Global Regulatory Perspectives Workshop
May 28, 2021

Impact of COVID-19

- Vaccines for COVID-19 represent the most rapid vaccine development program in history. Often overlooked, however, is that the worldwide vaccination campaigns are the most widespread use of advanced therapies ever.
- If these mRNA vaccines were not vaccines, they would be called gene therapies.
  - Clinical trials for gene therapies often exclude anyone who has received a gene therapy product in the past (similarly for cell therapy products).
  - Should this be considered in future clinical trials? All gene therapy products or just those using adenoviral vectors?
  - What proportion of the population would this exclude? If excluded from participating in trials for gene therapy products, wouldn't that mean final label of the gene therapy would specify excluding vaccinated individual? What are the risks, if any?

Advanced Therapy Product Development Worldwide

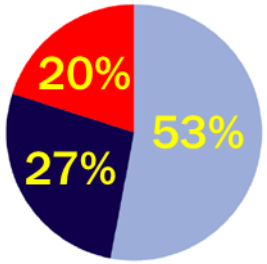
- CGT product development in 2020 continued at a brisk pace despite the pandemic

25 Phase III GT products
1-USA
2-China
3-UK

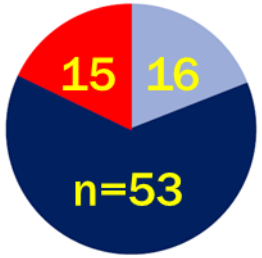
33 Phase III CT products
1-USA
2-China
3-South Korea,

19 Phase III RNA products
1-USA
2-Germany
3-Canada,

Products in Development Worldwide
n=3474, preclinical through pre-licensure



Approved Products Worldwide



American Society of Gene + Cell Therapy

: Pharmaprojects| Informa, April 2021

Approvals – May 2020 to May 2021

- Libmeldy (Orchard Therapeutics)
  - Autologous CD34^{+} cells transduced *ex vivo* with the human arylsulfatase A gene for pediatric metachromatic leukodystrophy
  - EMA approved December 17, 2020
- BREYANZI/lisocabtagene maraleucel (Juno Therapeutics-BMS)
  - CAR-T cell therapy for adult relapsed/refractory large B-cell lymphoma and follicular lymphoma grade 3B
  - FDA approved February 5, 2021
- TECARTUS/brexucabtagene autoleucel (Kite Pharma)
  - CAR-T cell therapy for adult relapsed/refractory mantle cell lymphoma
  - FDA approved February 24, 2021
- ABECMA/idecabtagene vicleucel (Celgene-BMS)
  - Autologous CAR T cell therapy for adult relapsed/refractory multiple myeloma, CAR specific for B cell maturation antigen
  - FDA approved March 26, 2021

Regulatory Feedback on Late-stage Products

- Regulatory feedback on CMC issues causing delays in clinical development of multiple gene therapy products
  - Freeline Therapeutics, Bluebird bio, BioMarin, Voyager Therapeutics, Sarepta Therapeutics, Iovance Biotherapeutics
- February 2021 - Bluebird Bio suspends sale of Zynteglo, autologous *ex vivo* gene therapy for β-thalassaemia already approved by EMA, due to safety concerns with related gene therapy for SCD – same lentiviral vector. Product put on clinical hold in US.

- Peter Marks, MD PhD, FDA-CBER Director:
  - "Just like manufacturers like consistency, FDA likes consistency in products… Many times, developers get very excited about the fact that their product produces an important effect and they don't worry as much about reproducibly making that product.“
  - "Pick something. Pick some quality of the cell. Pick something that you think might correlate and measure that. We'll take any offers that are reasonable."

Enforcement Actions

- FDA's enforcement discretion period for regenerative medicine therapies [stem cell clinics, *et al*.] will end on 31 May 2021.
  - "…despite all of the FDA's efforts to engage industry, there continues to be broad marketing of these unapproved products for the treatment or cure of a wide range of diseases or medical conditions."
    - Peter Marks, FDA-CBER

- Some enforcement actions already in progress.

Consumer Alert on Regenerative Medicine Products Including Stem Cells and Exosomes

WARNING LETTER

Invitrx Therapeutics Inc.

MARCS-CMS 581182 – MARCH 16, 2020

U.S. FOOD & DRUG ADMINISTRATION

March 10, 2021

VIA E-MAIL & UPS EXPRESS MAIL

Robert A. Eslinger, DO, HMD
Reno Integrative Medical Center
6110 Plumas St.
Suite B
Reno, NV 89519

Dear Dr. Eslinger:

The Office of Compliance and Biologics Quality in the Center for Biologics Evaluation and Research (CBER) of the United States Food and Drug Administration (FDA) has reviewed your website available at www.renointegrativemedicalcenter.com, as well as other information available to FDA.

Cancer immunotherapy product

On your website, you market an immunotherapy product to treat or prevent cancer. For example, in a video on Reno Integrative Medical Center's website, entitled "Dr. Bob on: Dendritic Cell Vaccine," www.renointegrativemedicalcenter.com/dendritic-cell-vaccine/, you state:

- "At Reno Integrative Medical Center, we use a simplified version of a dendritic cell vaccine. Well, what does that mean? It means we concentrate the specific type of white blood cell, called a T-cell or a T-lymphocyte…take it out of the body, concentrate it, …and technically educate or re-educate those T-cells in such a way that enables them to start killing cancer cells. And then the next day, we re-insert or inject it back into that patient's muscle. And all it is, is their own cells going back in so there is no complications or bad reactions that we have ever seen in years of doing this vaccine. The way that this works, is it's a very specific way to strengthen the person's own immune system to be able to start finding and killing abnormal or cancer cells, because that's what their normal job is. However, this technique of creating this vaccine enhances their ability to perform that function."

Similarly, your website further describes your cancer immunotherapy product:

- "Dendritic Cell Vaccine therapy offers a new promising immunotherapeutic approach for treatment of advanced cancer, as well as for secondary prevention of cancer."

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov