U.S. FOOD & DRUG ADMINISTRATION

Center for Biologics Evaluation and Research

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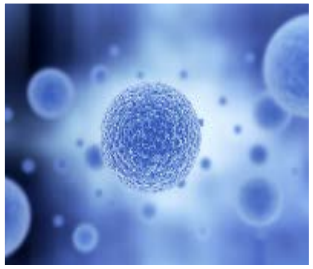
My comments are an informal communication and represent my own best judgment.

These comments do not bind or obligate FDA.

Products Regulated by CBER



- Allergenics
- Blood Products
- Devices Related to Biologics
- Gene Therapies
- Human Tissues and Cellular Products
- Vaccines (preventative and therapeutic)
- Xenotransplantation Products

CBER Regulated Products: Vaccines for Disease Prevention

>150 million doses of influenza vaccine given in 2016-2017

	Annual US disease, 1900s	US disease in 2013
• Smallpox:	29,005	0
• Diptheria:	21,053	0
• Pertussis:	200,752	28,639
• Polio:	16,316	1
• Measles:	530,217	187
• Mumps:	162,344	584
• Rubella:	47,745	9
• H. Influenzae:	20,000	31

Challenges:
Probiotic therapeutics
Vaccines for infectious diseases of global importance/EIDs

https://www.cdc.gov/vaccines/pubs/pinkbook/downloads/appendices/e/impact.pdf

CBER Regulated Products: Keeping the Blood Supply Safe

Need for continued vigilance against emerging threats

Successes*:

- HIV: 1 per 2,435,000 units
- HBV: 1 per 1,565,000 units
- HCV: 1 per 2,680,000 units
- Pathogen reduction technology –approved for platelets

Ongoing Challenges:

Continued low rates of bacterial contamination

Pathogen reduction technology – apply to rbc/wb

Agents of TSE

EIDs, especially arboviruses (Dengue, Chikungunya, Zika)

Malaria-causing species; *Babesia microti*

*Crowder, et al. Transfusion 2017; 57 (suppl3):47A (abstract from AABB)

CBER Regulated Products: Advanced Therapies at the Leading Edge

Ex vivo or *In vivo* gene editing to treat various conditions

FDA News Release

FDA approval brings first gene therapy to the United States

CAR T-cell therapy approved to treat certain children and young adults with B-cell acute lymphoblastic leukemia

FDA approves CAR-T cell therapy to treat adults with certain types of large B-cell lymphoma

Yescarta is the second gene therapy product approved in the U.S.

For Immediate Release

October 18, 2017

Challenges:

Preparing for new and evolving technologies, such as gene editing

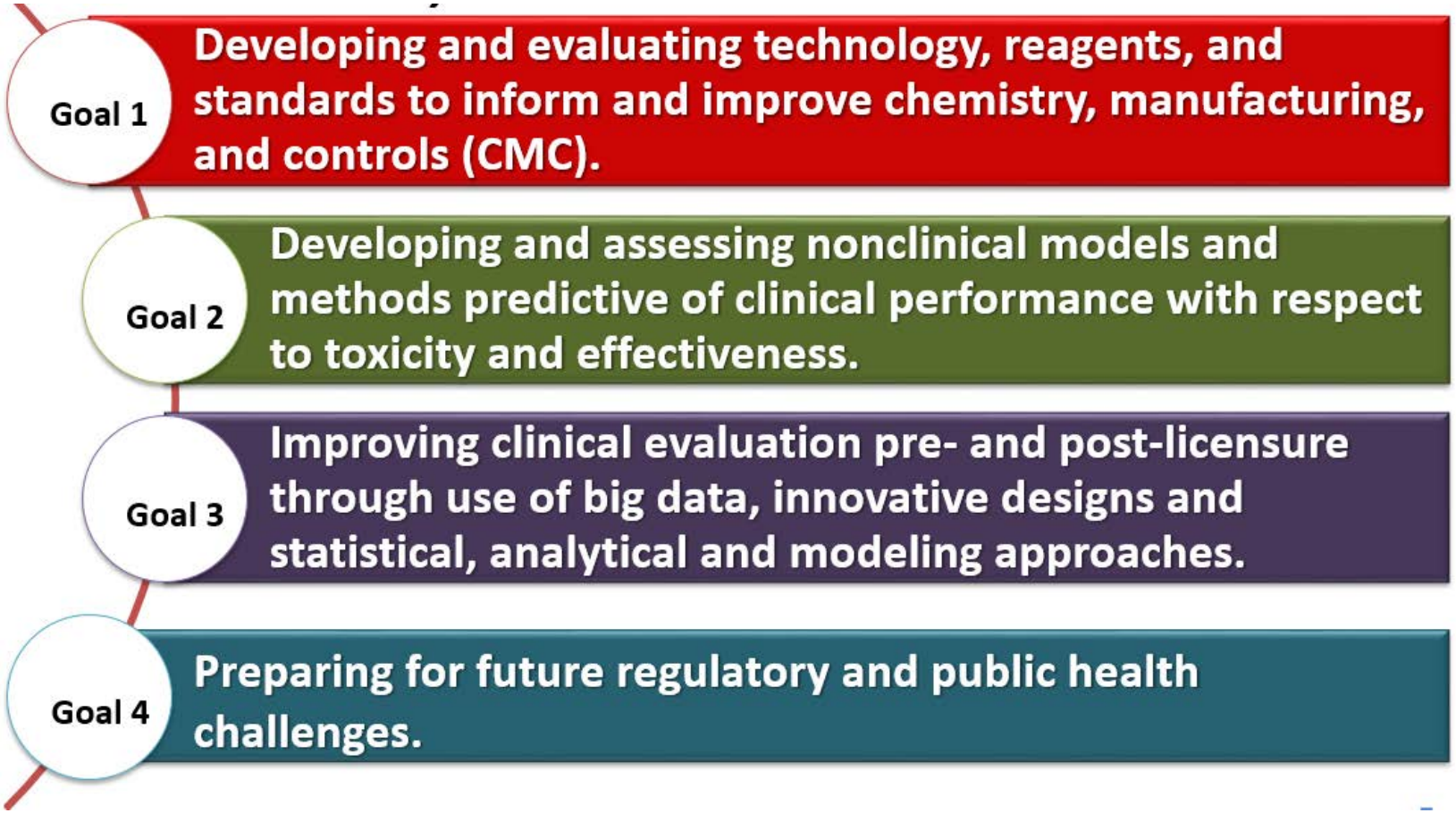
Manufacturing scale-up – applying continuous manufacturing?

Stem cell-derived products

Cells combined with devices (i.e. 3D-printed scaffolds)

CBER Research Goals

Advancing the scientific basis for regulation of biologics, human tissues and blood by:



NCTR Collaborations Supporting CBER Research Goals

- Goal 1: CMC
  - *Improved methods/development of standards to characterize products*
- Goal 2: nonclinical
  - *Develop novel approach to evaluate impact of non-synonymous mutations*
  - *Bioreactor model to simulate C. difficile-host interactions*
  - *Detect off-target mutations of gene editing*
  - *PK and biodistribution of novel adjuvants (n=2)*
  - *Support development of animal model to support norovirus vaccine development*

CBER Collaborations Supporting NCTR

- Mechanisms of norovirus-*Salmonella* coinfection
  - CBER developing enteroid and animal model
- Functional screening of candidate molecules identified by NCTR SDAR for anti-trypanosomal activity

Selected Updates and New NCTR Collaborations Supporting CBER Research Goals

FMT-related projects (2)

Assays to evaluate genome editing

Use of NGS and ribosome profiling to evaluate codon optimization impact on therapeutic proteins

Fecal Microbiota Transplantation (FMT)

Donor Screening/sample testing

What should we test for?

How good are the tests used for pathogen screening?

Does the manufacturing process alter efficacy?

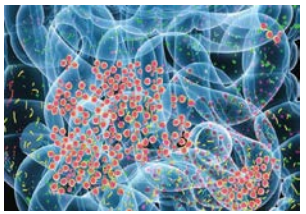
- Oxygen exposure
- Lyophilization
- Freeze/Thaw

Product characterization:

- Potency?
- Efficacy?
- Manufacturing consistency?

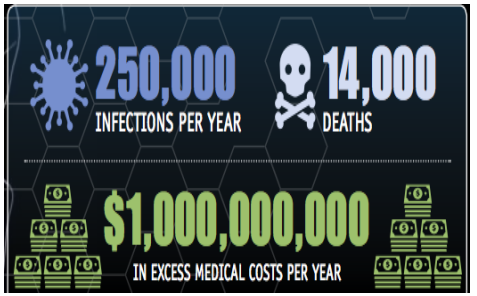
- **Disease/conditions associated with dysbiosis:**
  - Bacterial infection/colonization
  - Inflammatory Bowel Diseases
  - Obesity
  - Metabolic Disorders
  - Autism
  - Parkinson's Disease

CBER Goal 1: *Update*
Pathogen Detection in FMT



- *Need:* Evaluate assays typically used to screen clinical samples for relative sensitivity when used to screen FMT products.
- *Why NCTR:* Experience with bioreactors that produce "stool cultures" by inoculating a base medium with human stool under controlled growth conditions.
- *Approach*: Bioreactors with active stool cultures will be inoculated with various levels of pathogen alone or pathogen plus FMT, and plating and NGS methods used to determine if pathogen can colonize. In vitro results will be expanded in mouse model of infection.
- *STATUS*: Research protocol approved; testing initiated
- *Potential Impact*: Improved understanding of assay applicability and identifying assays that need improving to ensure the safety of FMT products.

CBER Goal 2:Update Clostridium difficile- host interactions



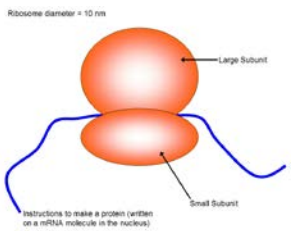
- *Need*: Improved understanding of how commensal bacteria impact host dendritic cell responses to *Clostridium difficile*
- *Results:* Co-culture system (developed by CBER) with epithelial cells has been implemented at NCTR. Expanding to work on dendritic cells.
- *Potential Impact*: Improve our understanding of how microbiota impacts the immune response against *C. difficile*. May provide insights into how to regulate FMT, vaccine development for treating *C difficile.*

CBER Goal 2: New

Off-target mutations in genome editing technologies

- *Need:* Address safety evaluation of advanced therapies involving CRISPR-mediated genome editing. In particular, to develop new methods and evaluate existing methods for off-target mutation detection.
- *Why NCTR:* Well-equipped with NGS facility and extensive experience.
- *Approach:* Whole genome sequencing will be applied to enhance sensitivity of detection. Genomes of single-cell-derived clones treated with CRISPR will be compared. Performance compared to other published approaches to detect DNA breaks.
- *Potential Impact:* Additional methods for detecting potential off-target mutations caused by genome editing. Valuable information on advantages and limitations of existing off-target detection methods.

CBER Goal 2, New
Bioinformatic workflows for NGS data generated form ribosome profiling



- *Need:* Codon-optimization is employed more commonly. We know that it may impact protein structure-function in unexpected ways. Need better tools to assess.
- *Why NCTR:* NCTR scientists have experience with ribosome profiling data and analysis.
- *Approach:* Ribosome profiling will be used to identify codons that induce changes in ribosome movement across transcript; may identify how synonymous codon changes impact translation kinetics and protein conformation.
- *Status:* on-going (CBER does experiments; NCTR analysis)
- *Potential Impact:* This method may prove useful to assess impact of codon sequence changes on protein conformation as a consequence of codon optimization in regulated therapeutic proteins.

Acknowledgments

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