U.S. FOOD & DRUG ADMINISTRATION

Center for Biologics Evaluation and Research

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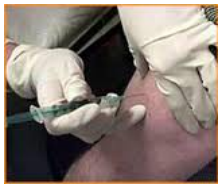
CBER Regulates Complex Products

- **Cell & Gene Therapies**
- **Tissues**
- **Blood, blood components, derivatives**
- **Vaccines: Preventive and therapeutic**
- **Live biotherapeutics**
- **Allergenic products**
- **Related devices**

2016 CBER Regulatory Science and Research Goals

- Advance the scientific basis for regulation of biologics, human tissues and blood to enhance safety, effectiveness, quality and consistency through development and evaluation of new concepts, methods, models, and reagents.
- Develop and assess nonclinical models and methods with improved predictive value, and, as feasible, reduce, refine, or replace the use of animals, for evaluation of safety and effectiveness of CBER-regulated products.
- Improve clinical evaluation related to CBER-regulated products through the use of new biomarkers, large scientific and healthcare datasets, and innovative design and analysis of clinical studies by applying new statistical, epidemiological, and mathematical modeling approaches, and considering patient input to inform benefit-risk assessment of general and special populations.
- Prepare for future regulatory and public health challenges through investments in emerging science and technology, and develop and sustain varied scientific expertise.

Current Regulatory and Research Areas and Collaborations



- CBER-initiated: PK/PD of vaccine adjuvant
  - *Need:* Lack of well-designed studies to address pharmacokinetics of squalene oil-in-water (SQ/W) emulsion with influenza vaccine antigen. Inform modeling and simulation for adjuvants in humans.
  - *Why NCTR:* Experience with PK using in vivo imaging and quantification techniques.
  - *Results:* pharmacokinetics and biodistribution of SQ/W with and without H5N1 vaccine; rapid clearance from site of administration with minimal systemic exposure (except liver); developed data-driven *in silico* model for IM administration
    - M.A. Tegenge, et al, 2016. Regulatory Tox. And Pharm.
  - *Impact:* Provides mode of action for this class of adjuvants; results suggest little systemic accumulation. Informs benefit-risk assessment of vaccines
  - *Future:* Continuing to analyze data and evaluate model prediction for newer generation of SQ/W emulsion (i.e., alpha-tocopherol, AS03)

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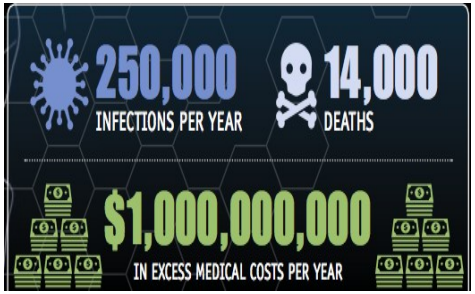


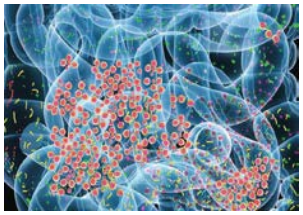
NCTR Initiated/CBER scientist is consultant

- *Need*: Improved understanding of how commensal bacteria impact host dendritic cell responses to *Clostridium difficile*
- *Results:* Establishing co-culture system developed by CBER.
- *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.*

Current Regulatory and Research Areas and Collaborations

- Joint CBER/NCTR developed
  - *Need:* Lack of quality control metrics to support de novo assembly validation protocols for next generation sequencing used to support Precision Medicine approaches.
  - *Why NCTR:* Experience with MAQC, SEQC, and now SEQC2 to work with stakeholders to develop consensus around application of new technologies.
  - *Results:* HIVE providing environment for SEQC to run extra-large de-novo assembly protocols. Protocols for assessing quality of assemblies are being developed.
  - *Potential Impact:* Standardized approaches for data assembly will allow more robust application of NGS to diagnose and treat human disease

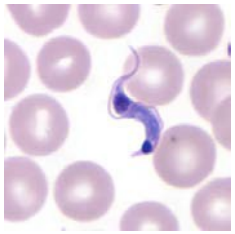
Future Regulatory and Research Areas and Collaborations



Jointly developed: pathogen detection in FMT

- *Need:* Evaluate assays typically used to screen clinical samples for relative sensitivity when used to screen fecal microbiota transplant (FMT) products.
- *Why NCTR:* Experience with bioreactors that produce "stool cultures" by inoculating a base medium with human stool.
- *Approach*: Test will be performed on pathogens spiked into stool at various levels and compared to plating and NGS detection. Bioreactors with active stool cultures will be inoculated with pathogen alone or pathogen plus FMT to see if the pathogen can colonize. In vitro results will be expanded in mouse model of infection.
- *STATUS*: concept paper approved
- *Potential Impact*: Improved understanding of assay applicability and identifying assays that need improving to ensure the safety of FMT products.

Future Regulatory and Research Areas and Collaborations

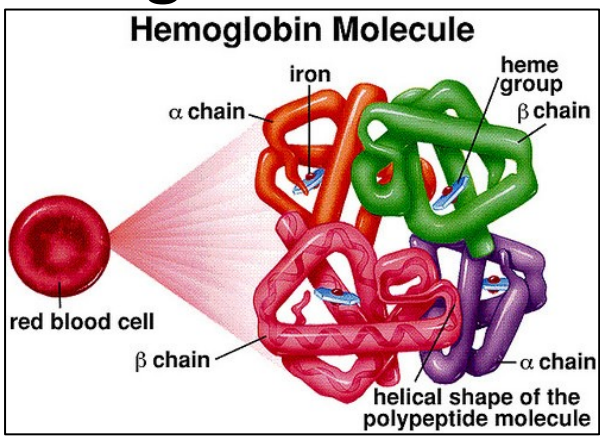


- NCTR-initiated:
  - NCTR: Use SDAR to model new anti-parasitic drugs (*Trypanosoma cruzi)*
  - CBER: Evaluate candidate drugs for anti-parasite activity
  - STATUS: Concept paper

CONCEPTS for Future Regulatory and Research Areas and Collaborations

CBER seeking NCTR collaboration

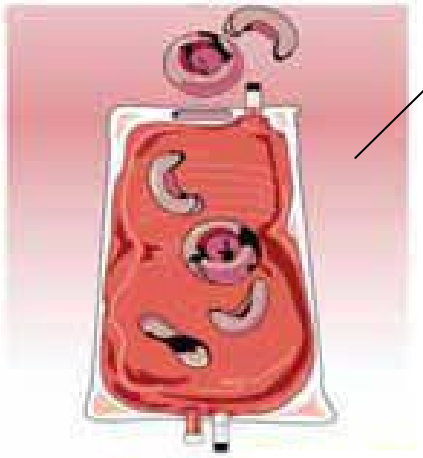
- *Need*: Clinical development of HBOCs impeded by oxidation-mediated toxicity. Need to further investigate toxicological consequences of Hb in relevant animal models.
- *Why NCTR*: Extensive experience with mouse models to evaluate toxicity *in vivo*.
- *Potential Impact*: Improved understanding of mechanisms of toxicity may allow development of HBOCs with reduced toxicity.

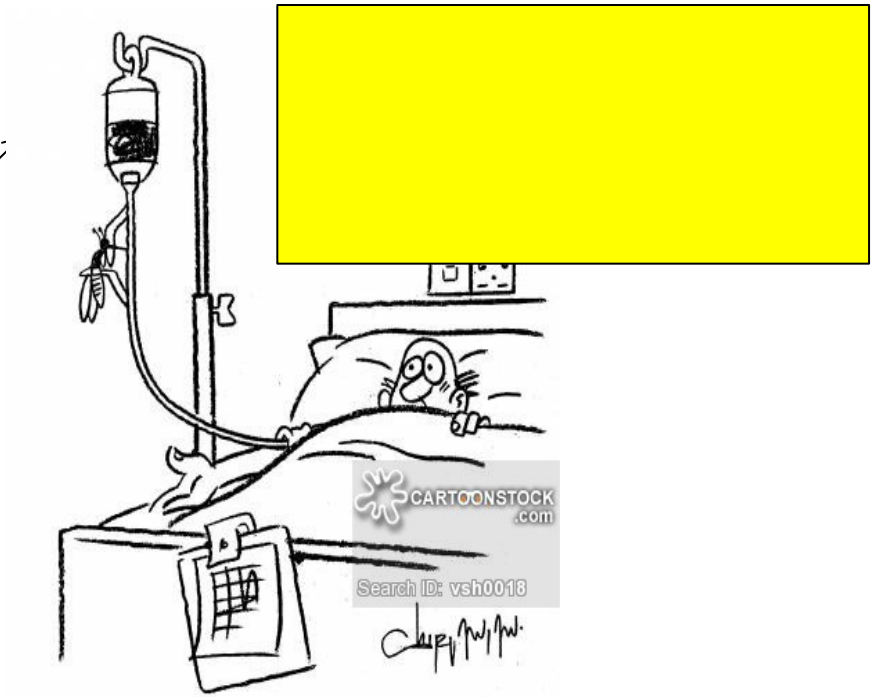


CONCEPTS for Future Regulatory and Research Areas and Collaborations

Need: Small Animal Model to Understand how RBC-Storage Lesions cause AEs*?

Ex Vi





***"B**

RBC

are collectively known as RBC storage lesion"

Acknowledgments

- Million Tegenge, OBE
- Paul Carlson, OVRR, DBPAP
- Alain Debrabant, OBRR, DETTD
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- CD Atreya, OBRR, DHHR