Response to Subcommittee Review:
Nanotechnology, Bioanalytical and Bioimaging

Presented by:
Dr. Laura Schnackenberg
Research Chemist, Division of Systems Biology
Dr. Anil Patri
Director Nanocore, Office of Scientific Coordination
U.S. Food and Drug Administration

First - Thank You!

We appreciate the careful review and suggestions by the Subcommittee provided in the report. We thank the group for their expert analysis and suggestions. We take the advice seriously and will consider the comments in these areas in order to focus the research on FDA programmatic needs.

Common Themes Identified

- Cross Training and Core Imaging Facility:
  - Would be difficult to train someone in the diverse technologies (electron microscopy (EM), mass spectrometry (MS), magnetic resonance imaging (MRI), etc) and expect them to be proficient .
  - It may be possible to train someone in common, overlapping areas and this option will be explored.
  - Progress is being made in the infrastructure needed to support an image repository and software.

Common Themes Identified - Continued

- Adding to Existing Staff – Three areas could benefit from additional efforts:
  - Recruitment of individual with expertise in the technologies.
  - Post-docs that are well-suited to work on specific projects.
  - Staff that handles data storage are sufficient but additional training and infrastructure may be needed.
- Outreach:
  - Ongoing collaborations with multiple groups and continuing efforts to reach out to others at FDA and in academia.

Specific Areas Reviewed

- Imaging Assessment
- Image Analysis, Modeling, and Computational Analytics
- Nanotechnology and Nanomaterial Assessment

Imaging Assessment – General

- Subcommittee encouraged cross-Center and cross-FDA collaborations to meet future regulatory needs of the FDA.
  - Will help develop analysis tools and more specifically, provide molecular probes for positron emission tomography (PET).

Imaging Assessment – Biomarker Translation

- Subcommittee particularly noted that efforts should be made to translate T2 magnetic resonance (MR) imaging from animal models to human.
  - A Letter of Intent to the Biomarker Qualification Program at CDER is being prepared to consider T2 MR imaging as a qualified biomarker of neurotoxicity in preclinical context of use.
  - Will provide guidance on how to continue the program and bridge the methodology to a clinical setting.

Imaging Assessment – Imaging Processing and Analysis

- Noted by the Subcommittee as “a significant challenge to increasing the impact of imaging at NCTR” with need for image co-registration capabilities between platforms emphasized.
  - We agree that this capability would make it better to assess and understand adverse responses or disease pathways.
- Additional computing power and storage will be needed especially with the recent purchase of a Bruker ScimaX mass spectrometer that provides higher resolution imaging.

Image Analysis, Modeling and Computational Analytics – PK/PD

- Dr. Fisher appreciates the comments and support of the committee towards the pharmacokinetics/pharmacodynamics (PK/PD) modeling & simulation.
- The committee noted and it is agreed that there is a lack of strategic thinking about modeling & simulation that needs to be addressed moving forward.

Image Analysis, Modeling and Computational Analytics – Imaging Tools

- We appreciate the recommendations for improving the repertoire of imaging tools, management and storage, which are common issues among all the imaging technologies.
  - We continue to work with the research laboratories to determine current and projected storage requirements.

Image Analysis, Modeling and Computational Analytics – Data Storage

- The information requested from the groups includes:
  - Estimated size of imaging data to be collected over the next two years (in terms of gigabytes or terabytes)
  - Vendor or commercial software applications used to acquire, view and analyze images
  - Where is imaging analysis done? Desktop computer, server, high performance cluster, other?
  - Are images typically analyzed one at a time or in batches?
  - Other relevant information

Image Analysis, Modeling and Computational Analytics – Data Storage

- External bandwidth increase to 10 gigabits
- Additional storage purchased
- Budgeting for general purpose graphics processing units (GPU's)
- Evaluate cloud storage cost/ feasibility as available to FDA

- Engaging research staff to understand infrastructure requirements:
  - Volume of data anticipated in 2-3 years
  - Software used to acquire, view and analyze images
  - Hardware used for analysis
  - Analysis workflow
- Evaluating image repository and analysis applications

Nanotechnology Core Facility

- Thank you for the wonderful comments on the leadership, in-depth evaluation, detailed recommendations through horizon scanning. We appreciate the input on the new areas of emerging needs that NCTR Nanocore should explore.

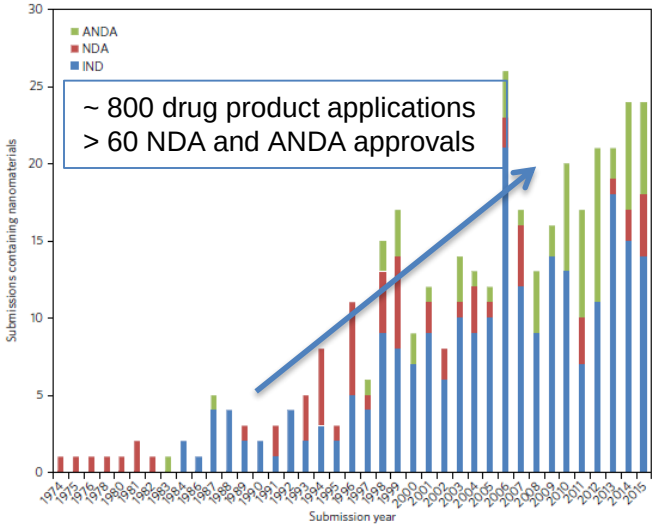
SAB Subcommittee advice

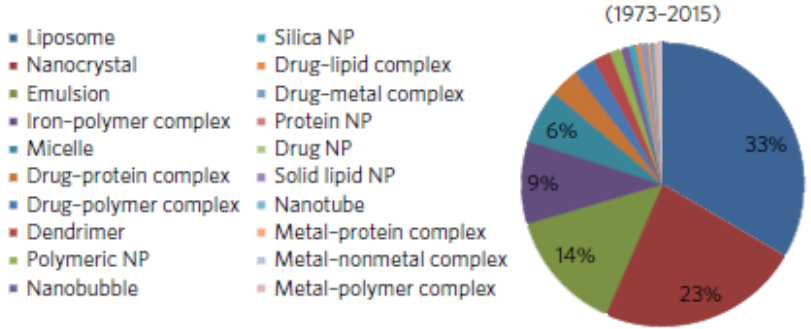
- EM Laboratory needs
- Staffing
- Horizon scanning advice for Nanocore

Electron Microscopy

- For Electron Microscopy, the sub-committee suggested a sharing of analytical resources, implementation of multi-purpose image storage, and analysis technology software, owing to the fact that it has state of the art EM instrumentation but suffers from lack of analytical capability and personnel
- We appreciate the in-depth analysis and suggestions. Due to budget limitations to recruit personnel, we will pursue the possibility for cross training in image analysis within NCTR and utilize collaborations with the Advanced Biomedical Computing Center at the Frederick National Laboratory for Cancer Research. This Center has software, hardware and image analysis experience that can address the EM image analysis needs.

Submissions to the US FDA of Drug Products





- Evolution from simpler drug delivery systems to highly complex, multicomponent, multifunctional structures and devices
- Liposomes make up 1/3rd of the submissions. Nanocore currently has a significant project on liposome based products to understand the nuanced differences in properties and how they influence efficacy

D'Mello S. et al. Nature Nanotechnology DOI: 10.1038/NNANO.2017.67

New areas of emerging needs

- Assessment of nanomaterial physico-chemical attributes, Quality by Design, and how they impact biological response
  - We are currently pursuing two projects
    - Liposome products
    - Ligand targeting
- Macrophage phagocytosis
- Nitric Oxide Production
  - These two assays are current work items we proposed at ASTM to develop standards. We will continue to investigate and expand the research into this area as suggested by the SAB Subcommittee

New areas of emerging needs

- Nanomaterial based vaccines
- Immunotherapy
- Complement activation
- Generic biologics and exosomes

- We are planning to develop a complement activation assay as a guide/standard test method.
- We will consult with product centers on emerging challenges and priorities to set up research projects to address regulatory science needs.

Staffing of Nanocore

- SAB Subcommittee recommendations
  - Transient nature of post-docs, loss of ‘corporate memory’ without permanent staff hampers
  - NCTR will need to judiciously hire new permanent scientists to stabilize this program and to maintain institutional experience

- Thank you for the recommendations. We will take action on prioritizing the projects, discuss with regulatory Centers on emerging needs to recruit a few permanent staff
- We will extend collaborations with other government agencies and academia to address emerging needs in Nanotechnology

Thank you!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