U.S. FOOD & DRUG ADMINISTRATION

FDA Introductory Remarks

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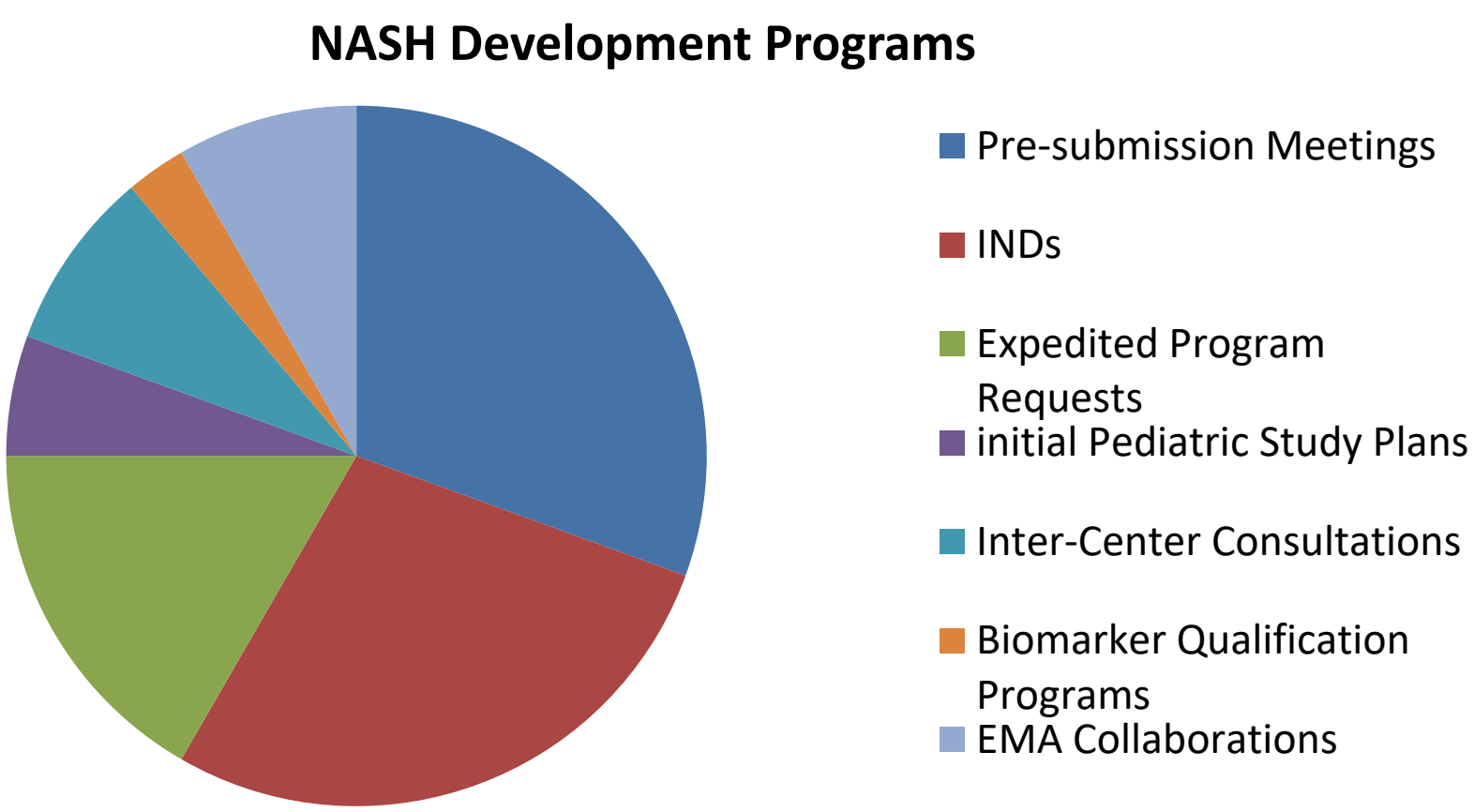
Disclosure Statement

- No conflicts of interest
- Nothing to disclose
- This talk reflects the views of the author and should not be construed to represent FDA's views or policies


Greetings from the FDA and DGIEP

2016 in FDA Review



Regulatory Considerations for Endpoints

Early Phase Trials (e.g. proof of concept, dose-ranging):

- Consider the mechanism and anticipated time course for changes when selecting endpoints and design
- Liver transaminases have been used; however, changes in transaminases have not been found to be predictive of histological changes in short duration trials
- Other non-invasive biomarkers (e.g., elastography as measured by MRI, and/or serum biomarkers of disease activity based on drug mechanism) also have been used
  - May reflect the activity of the drug and its effect on the underlying disease process; however, unclear if predictive or correlative with histology

Phase 2 Trials:

- Approach that has been used and found acceptable is histological evaluation
  - Histologically-based NAFLD Activity Score system (NAS) with a decrease of ≥ 2 points with at least a 1-point reduction in either lobular inflammation or hepatocellular ballooning and with no concurrent worsening of fibrosis stage

Regulatory Considerations for Endpoints

Phase 3 Trials:

- Use of biopsy-based surrogate endpoints :

  – A complete resolution of NASH on overall histopathologic interpretation by an experienced pathologist (with a NAS of ballooning of 0 and an inflammation score of 0-1) AND no worsening of fibrosis (NASH/CRN Brunt-Kleiner scale)

  – At least one point improvement in fibrosis score (Brunt-Kleiner scale) AND no worsening of NASH (defined as no worsening in ballooning or inflammation by NAS)

  Choice of either as a primary endpoint and the other as a key secondary endpoint or assessment of both changes as a co-primary endpoint

  Subpart H or E generally requires that a trial (phase 4) to verify and describe clinical benefit be ongoing at the time of marketing approval

Regulatory Considerations for Endpoints

Phase 4 Trials:

- For confirmatory trials, clinical benefit endpoints of:
  - All-cause mortality
  - Liver transplant
  - Hepatic decompensation events
  - Histological progression to cirrhosis
  - Increase of MELD score from below 12 to ≥ 15

  Acceptable and reflect a meaningful change in clinical status associated with morbidity and mortality.

Issues with HCC as a Component of a Clinical Benefit Composite Endpoint

- Multifactorial etiology and complex pathophysiology
- Majority of events in the endpoint analyses will be primarily cirrhosis events
- Few events relative to the other components (e.g. death, liver transplant, and MELD score increase) of the composite
- Not expected to have a significant impact on endpoint analysis
- Issues of implying that drug reduces HCC when not assessed and shown independently from other components to do so
- Need for appropriate screening at enrollment (liver ultrasound and alpha fetoprotein) and adequate assessments during the trial

Unsolved Clinical Development Issues in NASH

- **Investigational Agents**:
  - Pathophysiologic concepts of “purely antifibrotic” or “purely antinflammatory” drugs. Is it possible in NASH to affect one with out impacting the other?
  - Impact of early hepatotoxic signals on drug development in a population with underlying liver disease

- **Population**:
  - Appropriately defining high risk F1 subjects for trial inclusion

- **Placebo/SOC**:
  - Precisely defining the placebo effect and exploring it’s mechanism and impact
  - Placebo arm sharing across multiple programs and Sponsors
  - Incorporating standardized diet/exercise programs modeled from obesity clinical trials

Clinical Development Issues in NASH

- **Histology Based Endpoints:**
  - Necessity of additional liver-trained pathologists
  - Standardization of the overall histologic interpretation for use across the spectrum of pathologists
  - Understanding of intra- and inter-rater validity to better design clinical trials

- **Role of Non-Invasive Biomarkers**:
  - Standardizing methods and protocols for diagnostic imaging
  - Establishing clinically meaningful thresholds
  - Increasing measurement frequency of endpoints (i.e. more data to assure validity)
  - Validation via concurrent biopsies

Pediatric Development Considerations

- Enrollment of minors under 21 CFR 50 subpart D requires the investigator demonstrate prospect of direct benefit to the subject as a result of the drug intervention
- Treatment of fatty liver alone is inadequate to support direct benefit in minors
- Identification of sub-populations that may benefit from potential treatment such as in adult patients with F2 and F3 fibrosis who are at higher risk for liver-related adverse events
- Need for pediatric natural history data and incorporation of natural history studies in the initial pediatric study plans (iPSPs)

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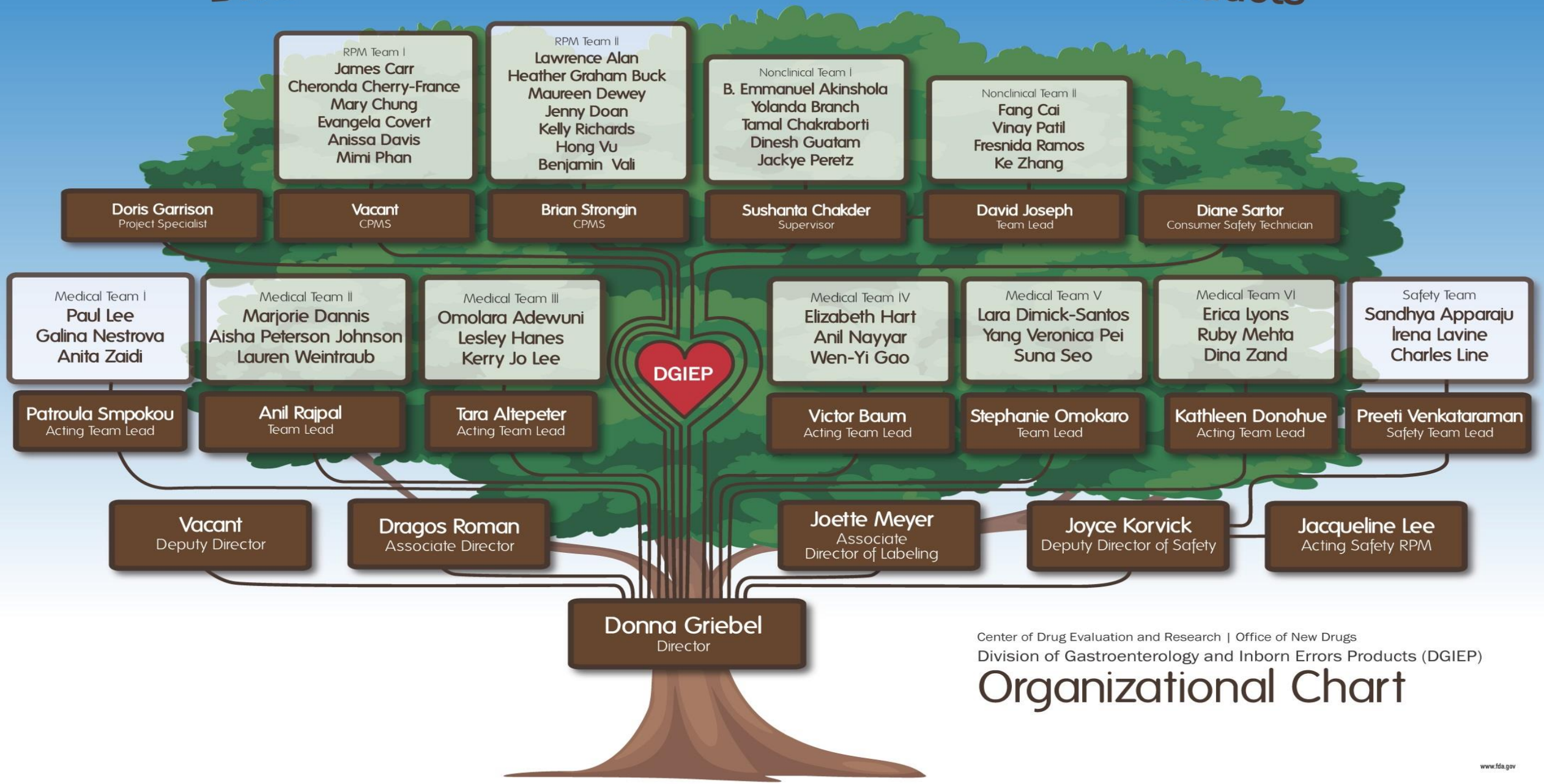

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Organizational Chart

Future Workshops Planned

Trial Design, Baseline Parameters and Endpoints for Clinical Trials:

- Alcoholic Liver Disease (AH)
- Pediatric Chronic Idiopathic Constipation (CIC) and Irritable Bowel Syndrome (IBS)

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THANK YOU


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