FDA Regulatory Considerations for NASH Clinical Trial Endpoints

Stephanie O. Omokaro, MD

Division of Gastroenterology & Inborn Errors Products (DGIEP)
U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
Office of Drug Evaluation III

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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
- A pediatric hematologist-oncologist by training; a regulatory expert in liver disease by design

Greetings from the FDA and DGIEP

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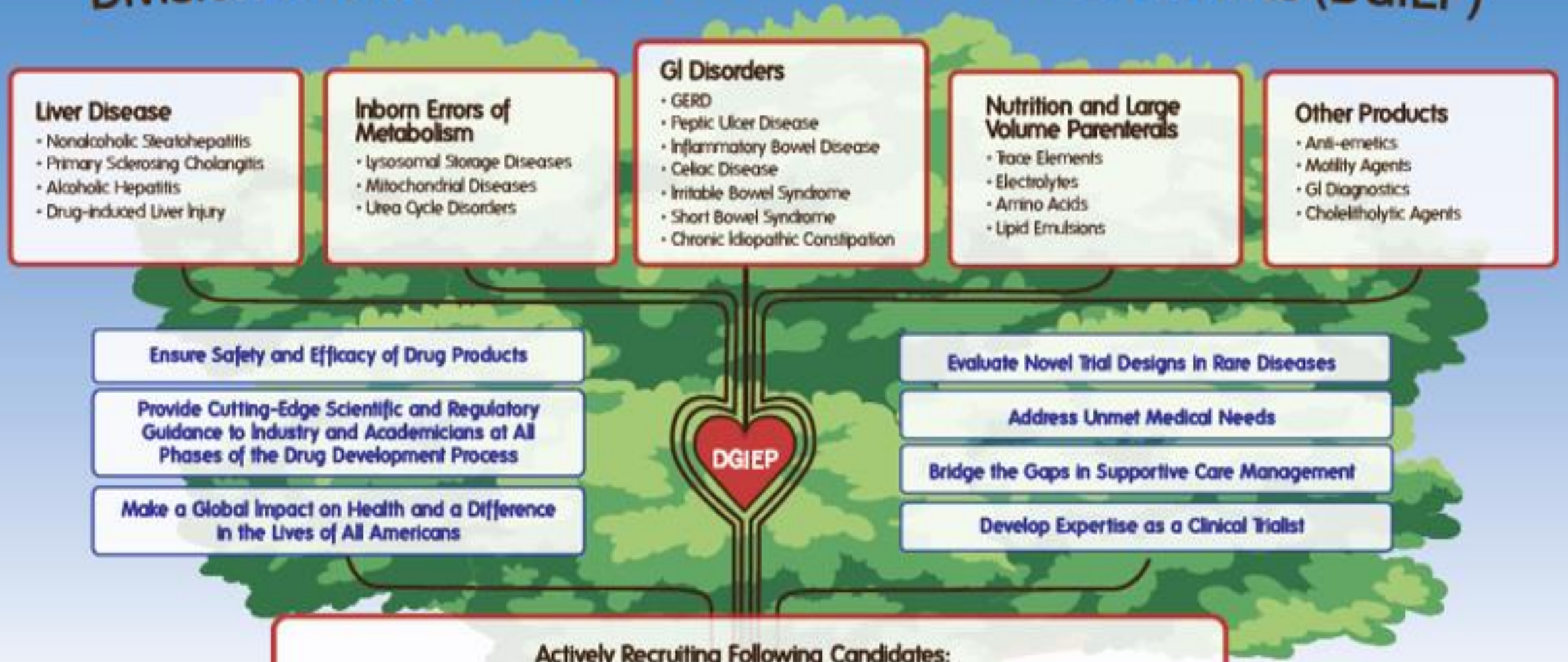
Division of Gastroenterology and Inborn Errors Products (DGIEP)



Actively Recruiting Following Candidates:

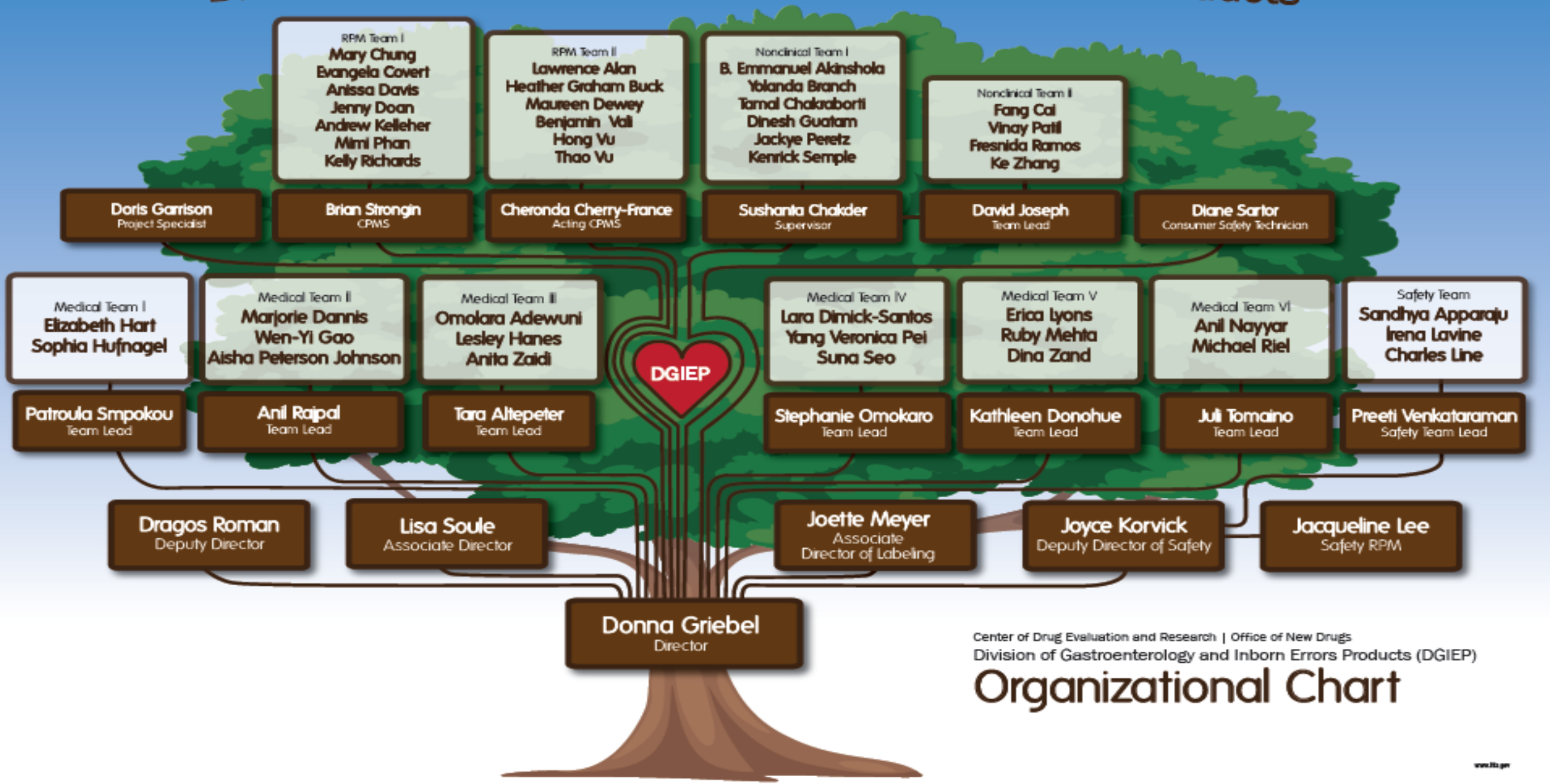
Nutritionists/Dieticians (PhD in Nutrition Science), Hepatologists and Gastroenterologists

Medical Geneticists, Pediatric or Adult Neurologists (esp. Related to Inborn Errors of Metabolism)

Other Specialized Backgrounds (e.g., Internal Medicine, Pediatrics, Preventive Medicine) are Also Encouraged to Apply

Division of Gastroenterology and Inborn Errors Products

U.S. FOOD & DRUG ADMINISTRATION



Center of Drug Evaluation and Research | Office of New Drugs

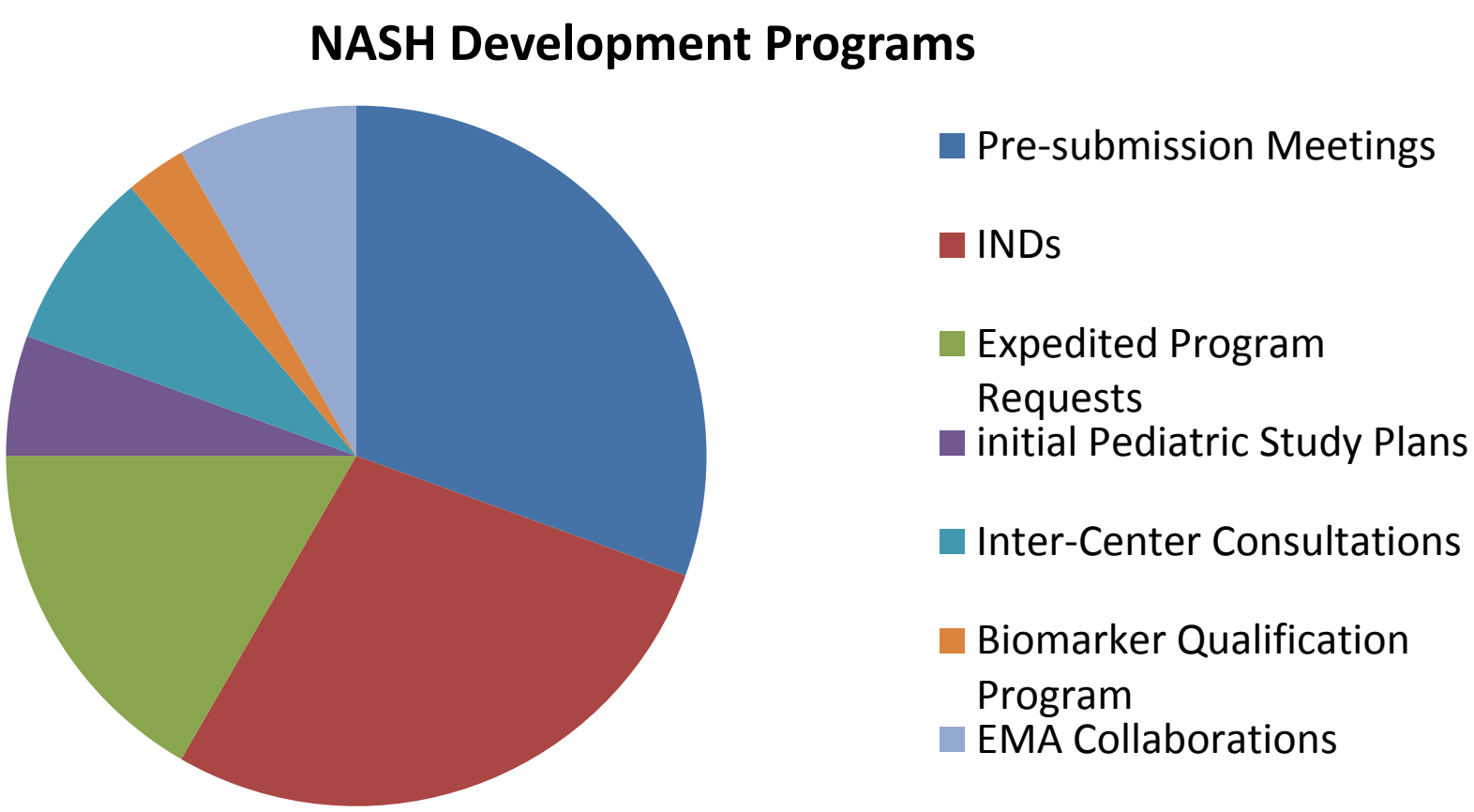
Division of Gastroenterology and Inborn Errors Products (DGIEP)

Organizational Chart

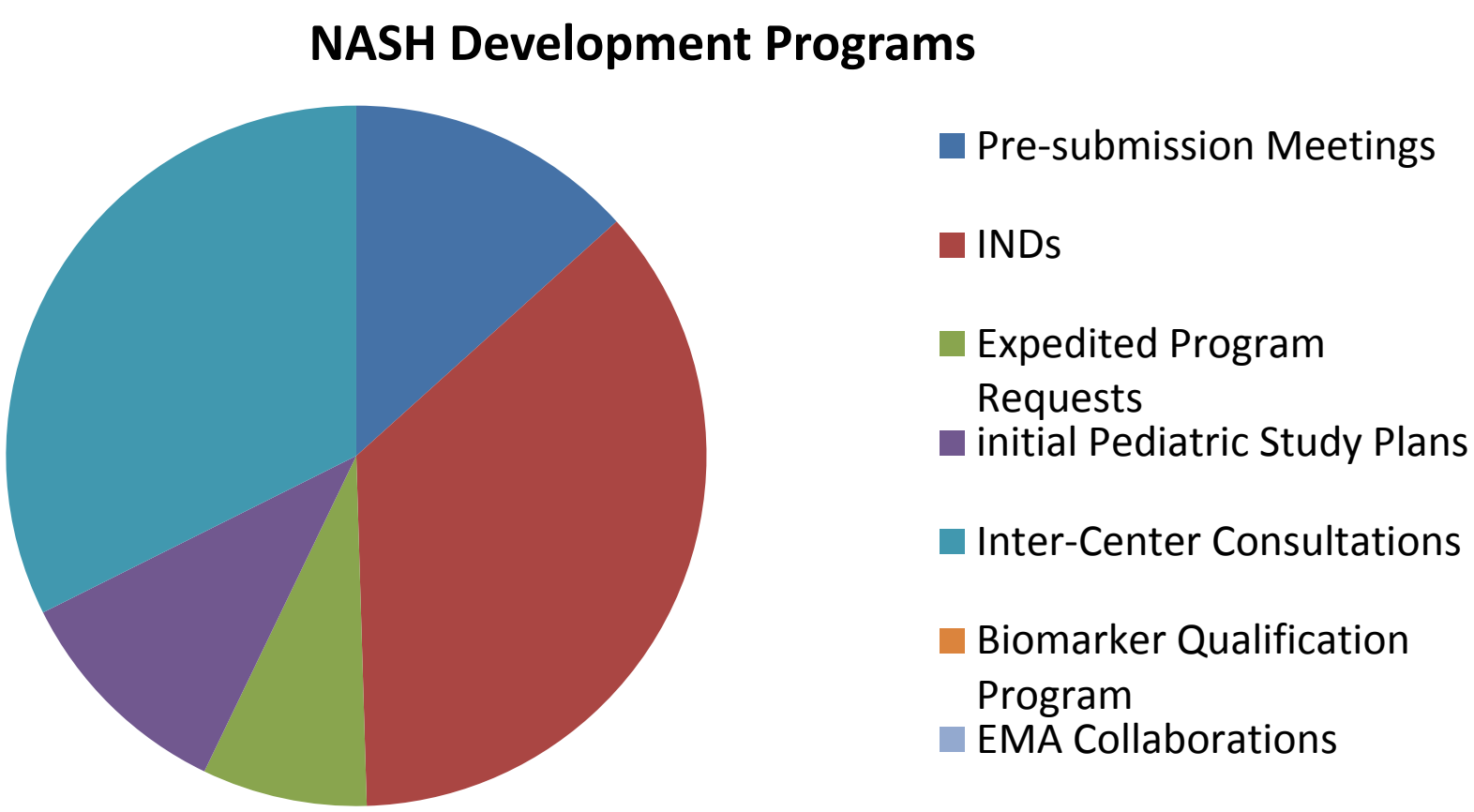
www.fda.gov

DGIEP NASH YEAR IN REVIEW

2016 in FDA NASH Review



2017 in FDA NASH Review



Overview

- FDA Regulatory Pathways
- Recommended Endpoints for Precirrhotic NASH
- Regulatory Considerations
- NASH Cirrhosis
- Pediatric NASH
- FDA Resources (for reference only)

FDA REGULATORY PATHWAYS

NASH

Significant Unmet Medical Need:

- Estimates that 25% of the adult population in the world has NAFLD and 3-5% with NASH
- Over 4 million people in the U.S. with NAFLD-associated advanced fibrosis
- Over 400,000 people in the U.S. with NASH-associated cirrhosis
- No approved therapies for NASH in the U.S.

Expedited Regulatory Pathway:

- Earlier drug approvals for safe and effective therapeutics for serious conditions with unmet medical need
- Use of endpoints reasonably likely to predict clinical benefit
- FDA requires that phase 3 trials for NASH enroll patients with liver fibrosis stage 2 or stage 3 (NASH/CRN Brunt/Kleiner scale)
- The benefit-risk balance of treating patients with earlier stage disease is not favorable as these patients are not at significant risk for the development of liver-related outcomes

Regular Approval Pathway

- Also known as traditional or full approval
- Evidentiary framework requires substantial evidence of effectiveness through adequate and well-controlled investigations (typically 2 or more trials)
- Efficacy endpoints are direct measurements of how a patient **feels, functions or survives** or validated surrogates:
  - Examples include overall survival (mortality), patient reported outcomes (PROs – valid symptom measurements) or disease free survival (morbidity).
- Noninferiority trial designs acceptable

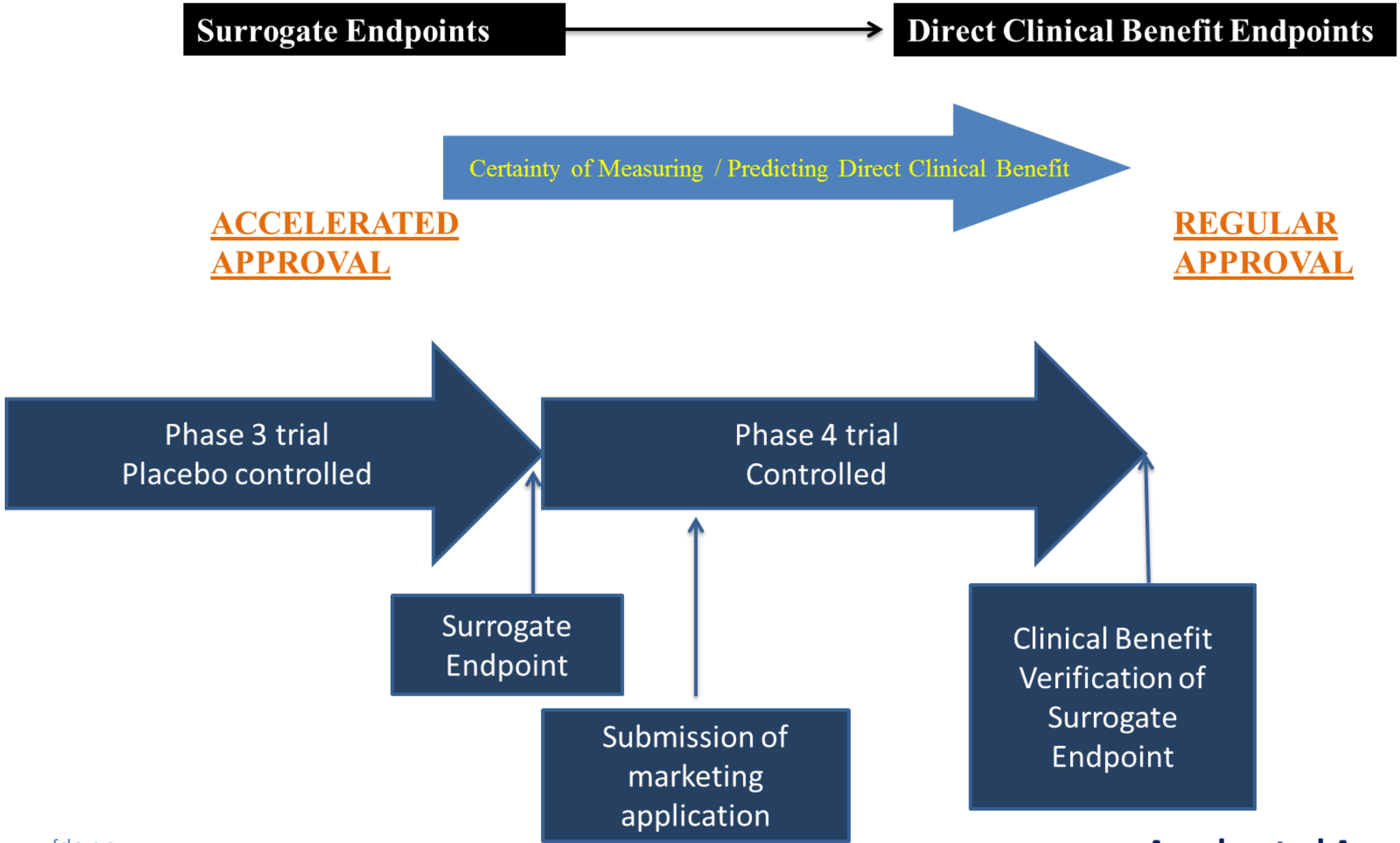
Accelerated Approval Pathway

- Section 506(c) of the FD&C Act, as amended by section 901 of FDASIA
- Subpart H - drugs (21 CFR 314)
- Subpart E – biologics (21 CFR 601)

For therapies that provide a meaningful advantage over available therapies (including no approved therapies as in NASH)

FDA guidance – Expedited Programs
http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf

- FDA expedited program intended to help ensure that therapies for serious conditions are approved and available to patients as soon as it can be concluded that the therapies' benefits justify their risks
- Evidentiary framework requires substantial evidence of efficacy through adequate and well-controlled investigations (typically 2 or more trials)
- Accelerated Approval may be granted based on surrogate endpoints that are "reasonably likely to predict clinical benefit" of a drug or on a clinical endpoint that can be "measured earlier than irreversible morbidity or mortality (IMM) that is reasonably likely to predict an effect on IMM or other clinical benefit (i.e., an intermediate clinical endpoint)"
- Requires Confirmatory postmarketing trials to verify the findings through clinical benefit endpoints
  - Should generally be underway at the time of accelerated approval



Accelerated Approval Pathway

ENDPOINT SELECTION

Types of Endpoints

- Clinical Benefit - Regular Approval
  - How a patient feels, functions or survives
- Validated Surrogate – Regular Approval
  - Recognized as validated through multiple definitive studies
- Surrogate – Accelerated Approval
  - Reasonably likely to predict clinical benefit

Definition of Surrogate Endpoint

"Biomarker, laboratory measurement or a physical sign used as a substitute for a clinically meaningful endpoint that is a direct measure of how a patient feels, functions, or survives and that is expected to predict the effect of the therapy"

(Temple 1999)

Pitfalls in Using Surrogate Endpoints

- Uncertainty about clinical benefit
- Potential for lack of correlation with outcome variable
- Lack of standardization or validation through multiple studies
- Missing long-term data
- Possibility of undiscovered risks
- Less information about the occurrence of rare or delayed adverse events

FDA Recommended Precirrhotic NASH Endpoints

Early Phase Trials:

Proof of Concept, Dose-ranging

Consider the mechanism and anticipated time course:

- Liver transaminases have been used; not predictive of histological changes in short duration trials
- Other non-invasive biomarkers (e.g., elastography, and/or serum biomarkers of disease activity); unclear if predictive or correlative with histology

Phase 2:

≥ 2 points reduction in NAFLD NAS:

at least a 1 point reduction in either lobular inflammation or hepatocellular ballooning

AND

no worsening of fibrosis stage

Phase 3:

Biopsy-based surrogate endpoints under Subpart H/E accelerated approval pathway:

- A complete resolution of NASH on overall histopathologic interpretation by an experienced pathologist with no worsening of fibrosis (Brunt-Kleiner scale)

AND/OR

- at least one point improvement in fibrosis with no worsening of NASH

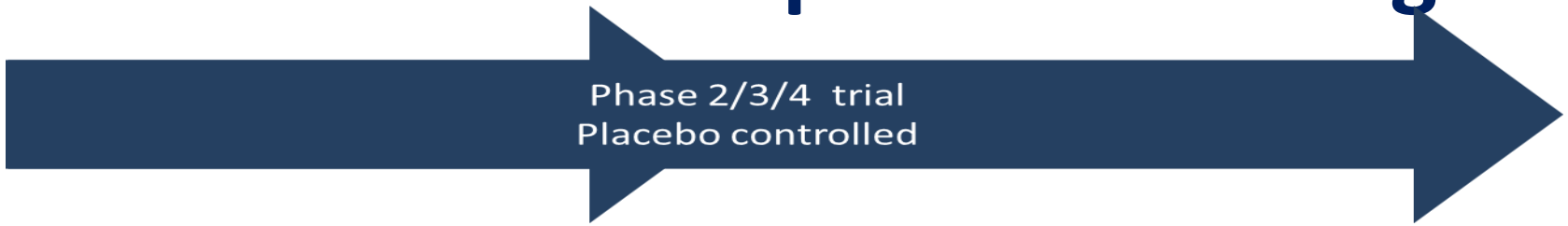
Phase 4:

Confirmatory clinical benefit trials

Composite of:

- All-cause mortality
- Liver transplant
- Hepatic decompensation events
- Histological progression to cirrhosis
- Increase of MELD score from below 12 to ≥15

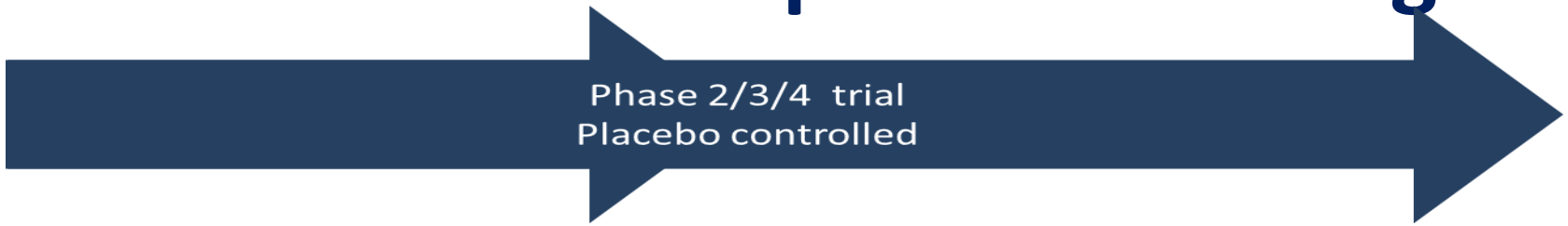
Seamless and Adaptive Trial Designs



- Using adaptive design in a clinical study allows opportunities for modifications in one or more aspects of the study design and hypothesis based on the interim data from subjects in the study
  - Potential modifications need to be prospectively planned

- Among all types of adaptations, a two or more stage (phase 2/3 or 3/4 or 2/3/4) seamless adaptive design could greatly speed up the NASH development process
  - Advanced planning and careful consideration of feasibility from both clinical and statistical perspectives are needed

Seamless and Adaptive Trial Designs



- Sponsors need to submit the statistical analysis plan including the key features of design and analyses for the entire two or three stage seamless study prior to trial initiation, in particular:
  - Procedures aimed to control the overall Type I error rate due to multiple stages for different purposes (claims)
  - Statistical methods to account for other sources of bias and possible type I error inflation from interim analyses, such as selection, sample size re-estimation, dropping doses, etc

REGULATORY CONSIDERATIONS

General Safety Considerations

- Safety should be considered in context of benefit
- Sources of safety information include: nonclinical data, early phase studies, later phase studies, other exposures of the same compound, different doses/populations in other development programs or experience in other countries, experience with similar compound (class effect)
- Signal detection (common, rare, severity)
- Association vs. causation (strength of signal, consistency, temporality, dose-response and mechanistic plausibility)
- Single arm safety data is of limited value; detection requires controlled, clinical trials of appropriate duration

Safety Considerations in NASH

- "For products intended for long-term treatment of non-life-threatening conditions, (e.g., continuous treatment for 6 months or more or recurrent intermittent treatment where cumulative treatment equals or exceeds 6 months), the ICH and FDA have generally recommended that 1500 subjects be exposed to the investigational product (with 300 to 600 exposed for 6 months, and 100 exposed for 1 year)."

- **Substantively more than the minimum of 100 subjects exposed for a year is expected for chronic use products in populations such as in NASH**

- "FDA recommends that the 1500 subjects include only those who have been exposed to the product in multiple dose studies, because many adverse events of concern (e.g., hepatotoxicity, hematologic events) do not appear with single doses or very short-term exposure. Also, the 300 to 600 subjects exposed for 6 months and 100 subjects exposed for 1 year should have been exposed to relevant doses (i.e., doses generally in the therapeutic range)."

http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126958.pdf

DILI in NASH Drug Development

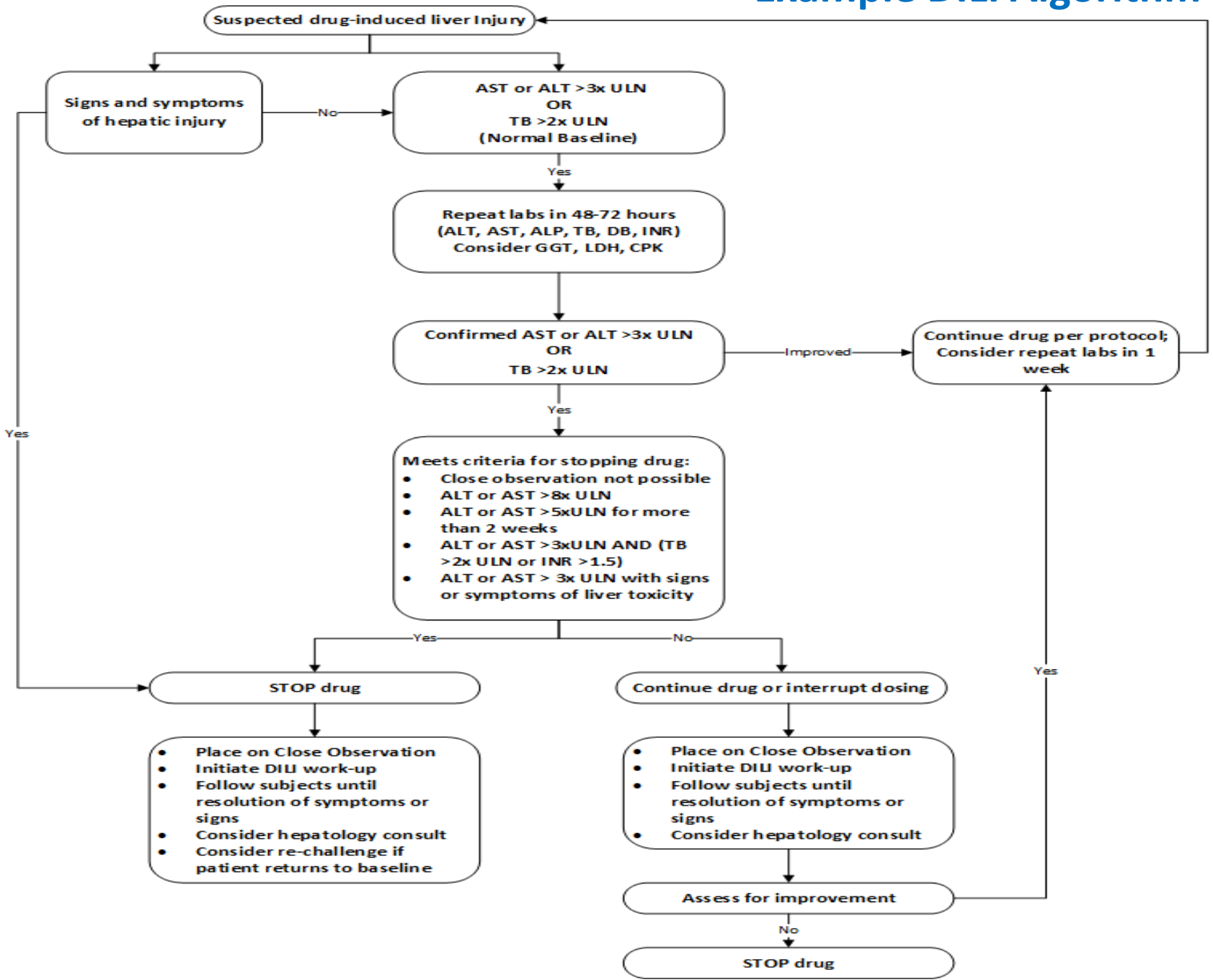
- Drug-induced liver injury (DILI) is the most frequent cause of acute liver failure requiring evaluation for transplantation
- “Hepatotoxicity has been the most common single adverse effect causing major drug problems, including withdrawals and refusals to approve.” – Robert Temple
- Hy’s Law (drug-induced hepatocellular jaundice) cases arise out of a background of increased incidence of transaminase elevations (Temple’s Corollary)
- Diagnosis of exclusion; need to gather data to rule out other causes

The Guidance for Industry - Drug Induced Liver Injury (Guidance for Industry-Drug Induced Liver Injury: Premarketing Clinical Evaluation at: http://www.fda.gov/downloads/Drugs/.../Guidances/UCM174090.pdf

DILI in NASH Drug Development

- Assess for DILI at all phases including preclinical, clinical and post-approval
- Perform early (e.g., after POC) dedicated hepatic impairment studies
- Establish a detailed response and management DILI algorithm
- Look for imbalance of liver injuries (enzyme rises) in randomized trials; describe severity and probability
- Closely monitor subjects with suspected DILI
  - Obtain PK and biopsy data
- Pre-specify rules for discontinuation
- Educate investigators and subjects about safety signals (update investigator brochure and reconsent subjects based upon emerging data)
- Explore mechanisms of toxicity (additional *in-vitro studies*, *in silico* modeling, nonclinical (animal), or clinical studies may be needed)

Example DILI Algorithm



21 CFR 300.50

Fixed Combination Prescription Drugs for Humans

- Two or more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effects
- The dosage of each component (amount, frequency, duration) is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy
- Often factorial studies are needed to show the contribution of each component of a fixed-combination drug
- The current rule is being proposed for revision. Although not yet finalized, the preamble to the proposed rule in the Federal Register notice describes FDA's longstanding policy on how applicants can demonstrate the contribution of each component

https://www.federalregister.gov/articles/2015/12/23/2015-32246/fixed-combination-andco-packaged-drugs-applications-for-approval-and-combinations-of-active

What is a Combination Product?

- A ***"combination product"*** is:
  - A product comprised of **two or more different types of medical products** (e.g., drug and device, drug and biological product, or all three together). (See 21 CFR Part 3)

- A combination product is **not**:
  - A product comprised of **only two or more of the same type of medical product** (e.g., drug and drug, device and device, or biologic and biologic).
  - A **medical product combined only with a non-medical product** (e.g., drug and food, drug and cosmetic). *See* 21 USC 353(g).

- ***"Constituent part"***: A drug, device, or biological product that is part of a combination product. *See* 21 CFR 4.1.

https://www.fda.gov/CombinationProducts/default.htm

Unsolved Clinical Development Issues in NASH

- **Investigational Agents:**
  - Pathophysiologic concepts of “purely antifibrotic” or “purely antiinflammatory” drugs. Is it possible in NASH to affect one without impacting the other?
  - Impact of early hepatotoxic signals on drug development in a population with underlying liver disease

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

- **Placebo/SOC:**
  - Precisely defining the placebo effect and exploring its mechanism and impact
  - Placebo arm sharing across multiple drug development programs and Sponsors
  - Incorporating standardized diet/exercise approaches 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
  - Burden and invasiveness to subjects

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

CIRRHOSIS CONSIDERATIONS

NASH Cirrhosis

- Early (e.g., after POC) dedicated hepatic impairment studies recommended
- First evaluate pre-cirrhotic population if the drug is intended for broad use
- FDA does not recommend combining pre-cirrhotic and cirrhotic patients in the same trial (currently considered 2 separate indications)
  - Laboratory inclusion/exclusion criteria differs
    - Pre-cirrhotic NASH patients should have ALT <5x ULN **and** normal bilirubin, platelets and INR
  - Monitoring and management of patients with cirrhosis differs
  - Trials with multiple sub-populations require independent power assumptions

NASH Cirrhosis

- The current standard for diagnosis remains histology and requires evidence of detailed histologic information to adequately characterize the findings
  - Currently, noninvasive evidence of cirrhosis may be acceptable in early phase trials but not in trials intended to support a marketing application
- Inclusion of fibrosis stage F4 patients with cryptogenic cirrhosis should be limited to less than 20%
  - Cryptogenic cirrhosis patients cannot be included for a primary endpoint that assesses improvements in NASH histopathology
- Cirrhosis specific DILI algorithm and considerations

PEDIATRIC CONSIDERATIONS

Pediatric NASH Development

- 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
- Challenges with developing clinical research outcomes that reflect benefit in pediatric studies
- Identification of high-risk sub-populations that may potentially benefit from earlier treatment such as in adult patients with fibrosis stage F2 and F3 fibrosis who are at higher risk for liver-related adverse events
- Due to current lack of comprehensive NASH natural history information in children, Sponsors need to collect, analyze, and submit natural history data to inform pediatric trial design:
  - Natural history studies should be incorporated into initial pediatric study plans (iPSPs)
  - Once natural history data become widely available, Sponsors may be able to rely (partially) on such data

PSP Basics

- Outline of the pediatric study(ies) the Sponsor plans to conduct
- The intent of the PSP:
  - Encourage Sponsors to identify pediatric studies as early as possible in product development
  - When appropriate, to conduct those studies prior to submitting the NDA/BLA
- PSP has replaced “Pediatric Plan” requirements
- Must be submitted within 60 days after an End of Phase (EOP2) meeting and no later than 210 days prior to submission of a marketing application
- Must be reviewed and agreed upon by FDA

Draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf.

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- DGIEP

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)


THANK YOU

FDA RESOURCES
(for reference)

FAST TRACK

- Expedited program for products with potential to address unmet need
- Qualifying criteria - includes a serious condition and a drug's potential to fulfill an unmet medical need
- Benefits – allows for early and frequent interaction with the review team; rolling submissions
- Submitted requests must be for the indication of: "Treatment of NASH with liver fibrosis"
- Level of evidence:
  - Nonclinical findings in an appropriate animal model that provides histologic evidence of a beneficial hepatic impact of the drug product on inflammation and/or fibrosis, with or without an effect on hepatic steatosis

  And/or

  - Human data demonstrating reduction in NASH disease activity

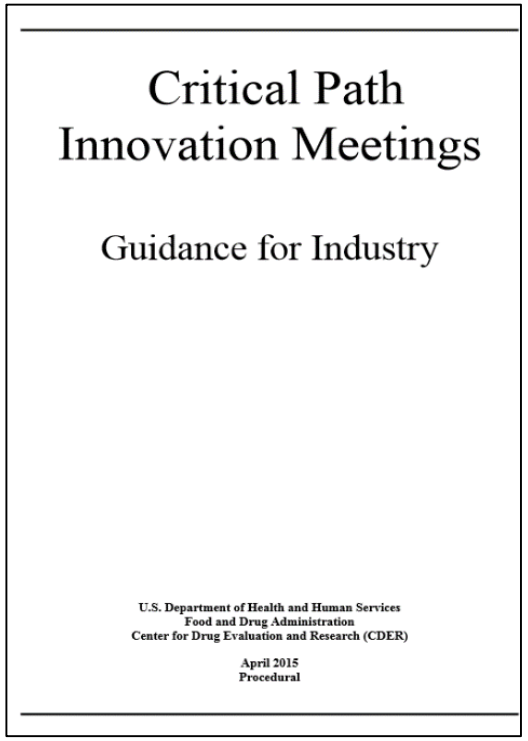
http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf

BREAKTHROUGH THERAPY

- Expedited program for products with potential to address unmet need
- Qualifying criteria - includes a serious condition and preliminary clinical evidence of substantial improvement over existing therapies on one or more clinically significant endpoints
- Benefits – intensive guidance on efficient drug development, organizational commitment, rolling review, other actions to expedite review
- Level of evidence:
  - Persuasive preliminary evidence of a substantial effect on either a surrogate histologic endpoint, or a clinical endpoint
  - Controlled data from a sizeable population for sufficient duration to characterize the chronic nature of NASH

http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf

CPIM


Critical Path
Innovation Meetings

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

April 2015
Procedural

- *http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformion/Guidances/UCM417627.pdf*

- Discussion of the science, medicine, and regulatory aspects of innovation in drug development
- Nonbinding meeting
- Not a meeting about a specific approval pathway
- Scope includes early biomarkers and clinical outcome assessments, natural history studies, technologies (not manufacturing), and clinical trial designs and methods

BEST Resource

- A glossary of terminology and uses of biomarkers and endpoints in basic biomedical research, medical product development, and clinical care
- BEST harmonizes terms and definitions and addresses nuances of usage
- Created by the NIH-FDA Biomarker Working Group
- Publicly available at: http://www.ncbi.nlm.nih.gov/books/NBK326791/
- Email biomarkers@ncbi.nlm.nih.gov

BIOMARKERS

- A defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions:
  - **Types**: Molecular, histologic, radiographic, or physiologic characteristics are types of biomarkers
  - **Examples**: blood glucose (molecular), biopsy-proven acute rejection (histologic), tumor size (radiographic) and blood pressure (physiologic)

BQP

Biomarker Qualification Process establishes the use of a biomarker for a specific context of use in drug development and makes information publicly available

- Qualification is a regulatory conclusion that means a biomarker:
  - Has adequate data to support the qualified context of use in drug development
  - Has evidence that supports the potential benefit for its use in clinical trials to aid in developing new therapeutics
  - Can be used in any drug development program under the qualified context of use
  - Has qualification recommendations and FDA review documentation publicly available on the Biomarker Qualification Program's website

BQP

- Biomarker qualification is a tool for drug development and **not for approval/clearance of diagnostics or for companion diagnostics for use in clinical practice**
- **Requestor** can be a person, a group, organization (including the federal government), or consortium that takes responsibility for and initiates a BQ proposal using the procedures described in the DDT guidance
- **No fees** for submissions to the BQ program
- Biomarker qualification is **voluntary**
- Once qualified for a specific **context of use**, a biomarker can be used by drug developers for other applications for the qualified context, without re-review
- Biomarkers considered for qualification are conceptually **independent of the specific test or device** performing the measurement

https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/BiomarkerQualificationProgram/ucm535383.htm

CLINICAL OUTCOME ASSESSMENTS TO ASSESS HOW PATIENTS "FEEL" OR "FUNCTION"

The FDA encourages the development and implementation of patient-focused clinical outcome assessments (COAs) in clinical trials to support drug approvals and labeling claims.

Clinical outcome assessment (COA) can be made through report by a clinician, a patient, a non-clinician observer (e.g., caregiver) or through a performance-based assessment. There are four types of COAs:

- **Clinician-reported outcome**
- **Observer-reported outcome**
- **Patient-reported outcome**
- **Performance outcome**

There may be limited value for COAs in NASH since symptoms may not occur until late in the disease course

- **FDA COA Staff Website: http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm349031.htm#Endpoints**
- **COA Qualification Website: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm284077.htm**
- **COA Compendium Website: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm459231.htm**
- **PRO Guidance (2009): http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf**

CDRH Device Development

- Medical devices premarket requirements are based on the level of control necessary to assure the safety and effectiveness of the device (for example, 510(k), PMA)
- Qualification of medical device development tools (MDDT) in the Center for Devices and Radiological Health (CDRH) is available through the voluntary MDDT program
  - Program only for medical devices
- The Pre-Submission program allows applicants to request specific feedback from FDA prior to an intended submission to CDRH
- Additional information about medical device regulation is available at CDRH Learn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BACK-UP SLIDE with HYPERLINKS

CDRH Device Development

- Medical devices premarket requirements are based on the level of control necessary to assure the safety and effectiveness of the device (for example, 510(k), PMA)
- Qualification of medical device development tools (MDDT) in the Center for Devices and Radiological Health (CDRH) is available through the voluntary MDDT program https://www.fda.gov/medicaldevices/scienceandresearch/medicaldevicedevelopmenttoolsmddt/default.htm
- The Pre-Submission program allows applicants to request specific feedback from FDA prior to an intended submission to CDRH https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf
- Additional information about medical device regulation is available at CDRH Learn https://www.fda.gov/Training/CDRHLearn/default.htm

PSP Basics - Content
High-Level Summary (10-12 pages)

1. Overview - Disease Condition
   a. Indication of 'NASH' in pediatrics
2. Overview - Drug/Biologic Product
3. Plan for Extrapolation
4. Plan to Request Waiver(s)
   a. Formal requests are made at the time of the NDA/BLA submission
5. Summary of Planned Nonclinical and Clinical Studies
6. Pediatric Formulation Development
7. Nonclinical Studies
8. Clinical Data to Support Design and/or Initiation of Studies
9. Planned Pediatric Clinical Studies
10. Timeline of the Pediatric Development Plan
11. Plan to Request Deferral
12. Agreements with Other Regulatory Authorities

Draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf.