What is New on the Regulatory Front?

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Outline

- Innovation in regulatory science
- Regulatory challenges in NASH
- Opportunities for innovation

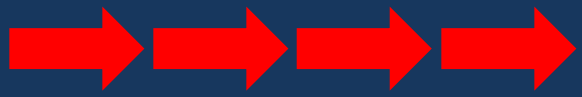
Innovation in Regulatory Science

What is regulatory science?

- The development and use of tools, standards and approaches to more efficiently develop products and to more effectively evaluate product safety, efficacy and quality

Innovation

- Tools
- Standards
- Approaches



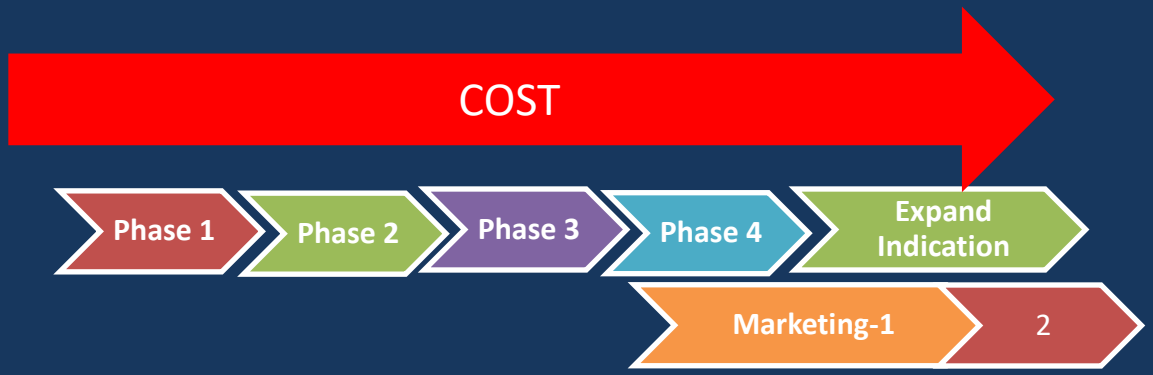
More efficiently
More effectively

- Products
- Product safety
- Product efficacy
- Product quality

Where is there room for innovation?

- Use all evidence
  - "Totality" of evidence
  - Integrate RCT and real-world data
- Improve efficiency
  - Study size
  - Study duration
  - Earlier combination studies when needed
- Improve study output
  - Make better use of data
- Prevent drug failures
  - Better safety signal detection

Traditional development path



- Discreet phases (start/stop/start)
- Requirement for placebo arm throughout
- “Single-use” data points

21st Century Challenge

- Maximizing benefit of treatment while decreasing safety risk
- Context:
  - ↑ understanding of biology and disease
  - ↓ development of new therapeutics
  - ↑↑ cost of bringing new therapeutics to market

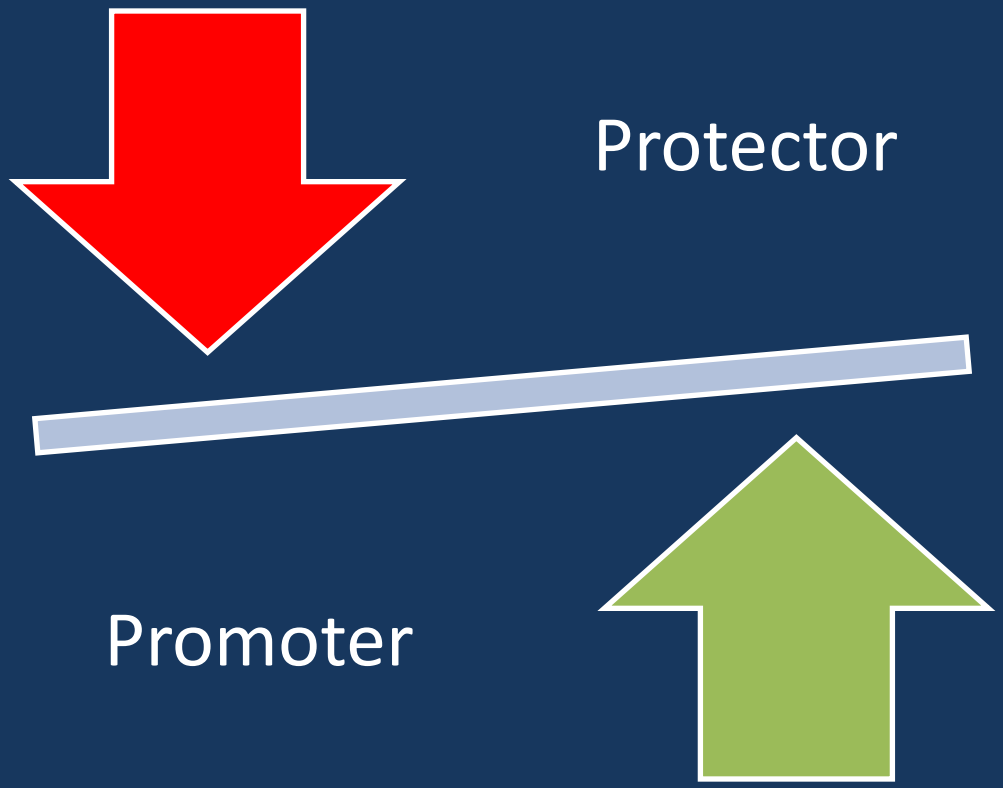
Evolution at the FDA: From the Age of Safety to the Age of Development – PDUFA VI and 21st Century Cures Act

Peter P. Stein, M.D.
Deputy Director
Office of New Drugs
Center for Drug Evaluation and Research

May 2017

2nd International NASH Biomarker Workshop, Washington DC

The 21st Century Regulator



Evolution at the FDA: "The Age of Development" - PDUFA VI and the 21st Century Cures Act

- 21st Century Cures and PDUFA VI increasingly places FDA as an *active participant* in drug development, broadening our traditional regulatory role
- Requires expanded efforts to enhance drug development
  - *Patient-focused drug development*: collect / analyze patient experience, to use in designing drug development programs (endpoints), and in regulatory decision making (endpoints and risk/benefit considerations)
  - *Novel, innovative trial designs*: use of complex adaptive and other novel trial designs – and how such clinical trials can be used to satisfy the substantial evidence standard
  - *Real world evidence*: using data regarding use or potential benefits and risks of a drug derived from sources other than randomized clinical trials – in support of new indications and post-approval study requirements
  - *Drug development tools: biomarkers and COAs*

NASH

REGULATORY CHALLENGES

Challenges: The List

10. Lack of awareness of disease (recruitment)
9. Slow progression of disease
8. Don’t know enough about natural history/disease progression
7. Multifactorial disease
6. Need for combination therapies
5. The liver is just too complicated
4. Concurrent development of biomarkers and therapeutics
3. Sampling and operator error -- liver biopsy based diagnosis
2. Invasiveness of diagnosis
1. Can’t clone Pierre Bedossa

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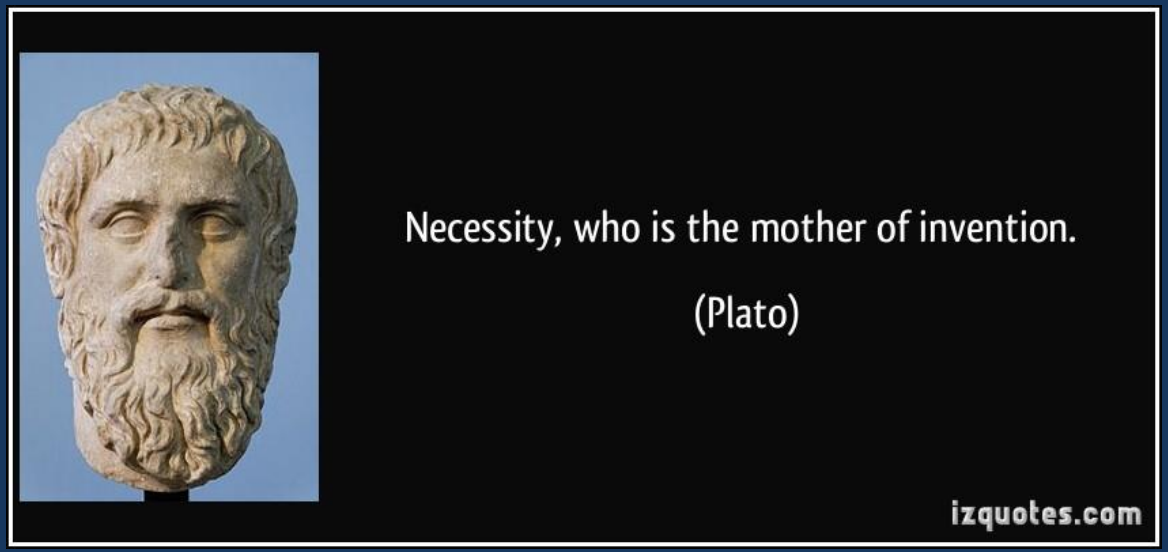


*either Plato (Republic), or an old English proverb

** Necessity = Unmet medical need
** Invention = Innovation

Can NASH lead the way to paradigm change?

FROM CHALLENGE TO OPPORTUNITY

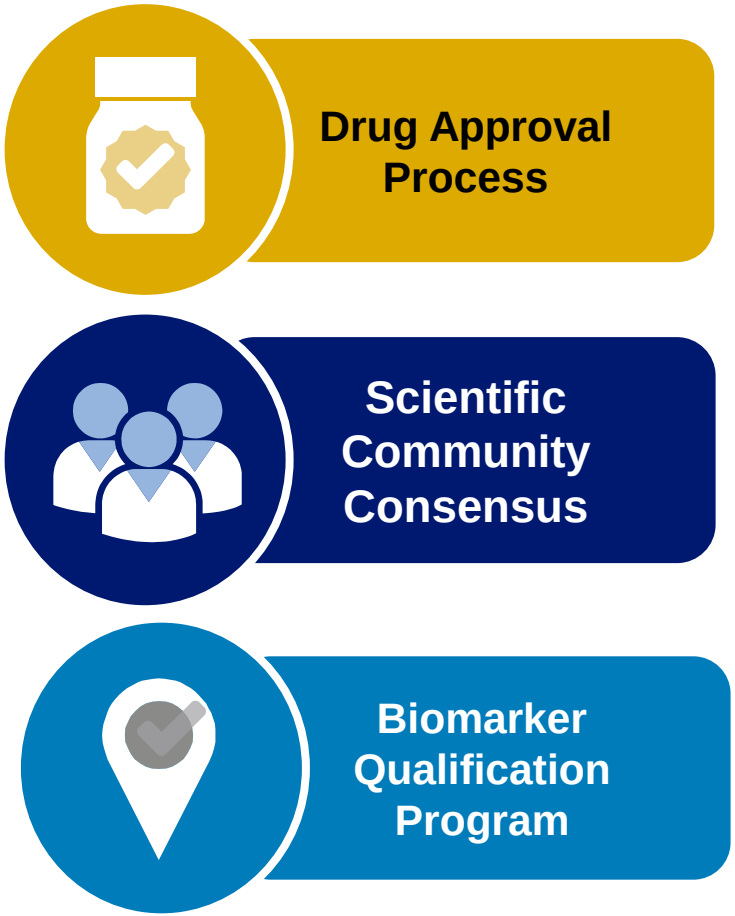
The Liver Forum: Assets

- Cross-Atlantic regulatory, industry and academic perspectives
- Safe/neutral space to allow consensus to evolve
- Infrastructure for collaborative efforts within Liver Forum
- Infrastructure for coordination across efforts among Liver Forum members and partners

Biomarkers

TACKLING CHALLENGES THROUGH INNOVATION

BIOMARKER INTEGRATION INTO DRUG DEVELOPMENT



Note: These pathways do not exist in isolation and many times parallel efforts are underway within or between pathways. All share common core concepts, are data-driven, and involve regulatory assessment and outcomes based on the available data.

Chris Leptak, Washington DC

Facilitating Biomarker Development: Strategies for Scientific Communication, Pathway Prioritization, Data-Sharing, and Stakeholder Collaboration; Published June 2016, Duke-Margolis Center for Health Policy

Existing Collaborations for NASH Biomarker Qualification

Qualification programs

- LITMUS (IMI)
- NIMBLE (FNIH)

Scientific Community Consensus

- E.g. Liver Forum dialogue/deliberation process

Natural history

TACKLING CHALLENGES THROUGH INNOVATION

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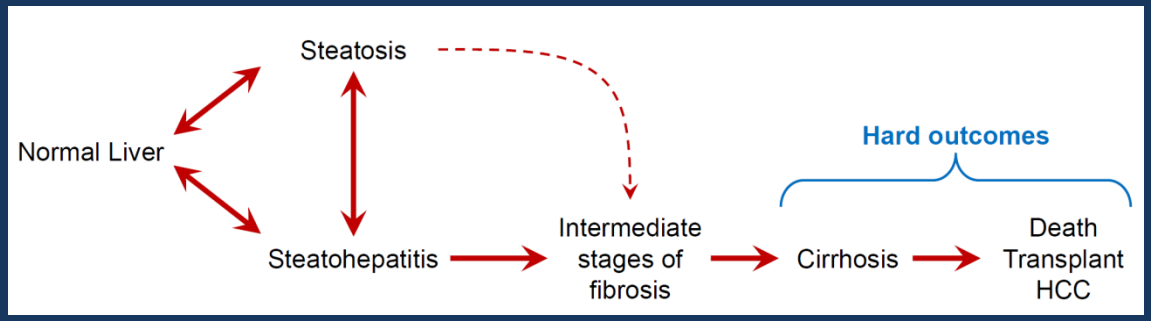
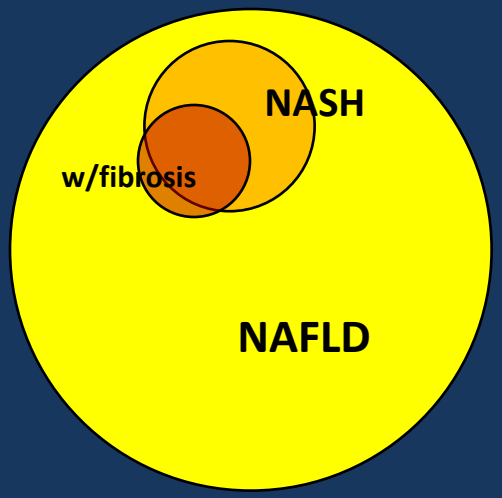




- Waxing and waning of disease
- Need for long-term placebo exposure

Figures courtesy of Brent Tetri, 2nd International NASH Biomarker Workshop

Increasing Natural History Knowledge

Liver Forum proposal

- Establish placebo arm cohort
  - Completed and un-blinded phase 2 and 3 studies
- Apply novel analytic approaches to identify risk factors for “waxing and waning” of disease
  - Disease progression
  - Disease resolution

Placebo Arm Cohort

- Growing cohort
  - Cumulative data from phase 2 and 3 trials in real time
  - Maintain relevance wrt improvements in standard of care over time
- Benchmark placebo arm cohort against a trial's own placebo
  - Know outcome of intervention effect in trial
- Test utility of placebo arm cohort to partially replace future placebo arms
  - Reduce exposure by reducing number of patients in placebo arms
  - Reduce exposure by reducing follow-up time on placebo

Expected Contributions

- Modeling of disease progression
  - Increase efficiency, improve clarity, increase confidence in results
- Precision powering, sample size estimation
- Reduction in placebo arm size/duration
  - $25-70K/patient
- Benefit to patients
- Ethical use of patient contribution to clinical research

New trial design options

TACKLING CHALLENGES THROUGH INNOVATION

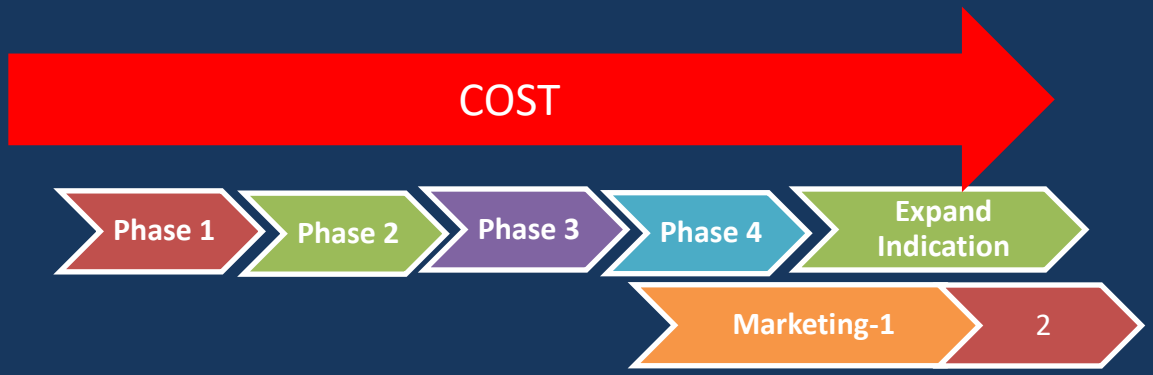
Adaptive Trial Designs

- Seamless trial designs
  - Moving from phase 2 through phase 3
  - More efficient post-marketing assessments
- Patient enrichment trial designs
  - E.g. subpopulations responding differently to treatment
- Dose adjustment
- Randomization probabilities

Potential impact

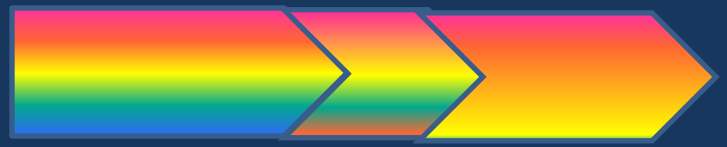
TACKLING CHALLENGES THROUGH INNOVATION

Traditional development path



Innovative development paths

1st in human | PoC | Dose finding | Confirmatory | Post marketing



+ Novel Analytics (e.g. Targeted Learning)
+ Placebo arm cohort (multiple use datapoints)

Building blocks

TACKLING CHALLENGES THROUGH INNOVATION

Start from ground up

- Common language
  - ✓ Disease Case Definitions (Baseline)
    - ✓ Siddiqui et al (under review)
  - ✓ Resolution of NASH (definition)
    - ✓ Under construction
- Common Elements
  - ✓ Standardization of Baseline Parameters
    - ✓ Patel et al (Gastroenterology, 2017)

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Acknowledgement & Disclaimers

- Presentation informed by Liver Forum deliberations
- Any opinions expressed are my own and do not necessarily represent Liver Forum views

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