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Liver Forum Cirrhosis Working Group

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DRUG DEVELOPMENT PATHWAYS

- Regular approval pathway:
  - **based on demonstration of clinically meaningful benefit:**
    - Clinical outcomes that affect patient survival, functional status or quality of life
    - Use of surrogates generally accepted to reflect a meaningful change in health status

CLINICALLY MEANINGFUL BENEFIT

- Based on how a patient feels:
  - symptoms
  - quality of life
- Based on how a patient functions:
  - functional status (impairment or improvement in ability to lead a normal active life)
- Based on how a patient survives:
  - survival
  - liver-related outcomes
  - rates of hospitalization (resource utilization)

DRUG DEVELOPMENT PATHWAYS

- Accelerated pathway (subpart H)
  - Based on use of surrogate endpoints that are reasonably likely to reflect changes in clinically meaningful outcomes
  - Requires post-approval completion of long-term study to objectively document improvement in clinically meaningful outcomes or changes in surrogates generally accepted to reflect changes in clinically meaningful outcomes.

SURROGATE ENDPOINTS

Generally accepted

- Substantial body of literature available
- Quality of data is strong
- Surrogate should reflect:
  - Survival
  - Other clinical outcomes
- Surrogate should have:
  - Content and face validity
  - Sensitivity to change

Reasonably likely

- Less amount of data available
- Quality of data not as strong
- Surrogate should have:
  - Reasonable likelihood of reflecting change in health status based on its relationship to biology of disease
  - Sensitivity to change

Biomarkers that are still under development are unlikely to be accepted as endpoints

THE FDA-AASLD NASH WORKSHOP 2013: A TURNING POINT

- Two major barriers to therapeutic development for NASH are:
  - lack of noninvasive tools to evaluate the disease
  - lack of a clear regulatory pathway for drug or diagnostics approval for NASH

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CONCEPT OF THE LIVER FORUM

A platform for ongoing multi-stakeholder dialogue to identify barriers, prioritize research and identify solutions to accelerate therapeutic development for NASH and progressive fibrosis

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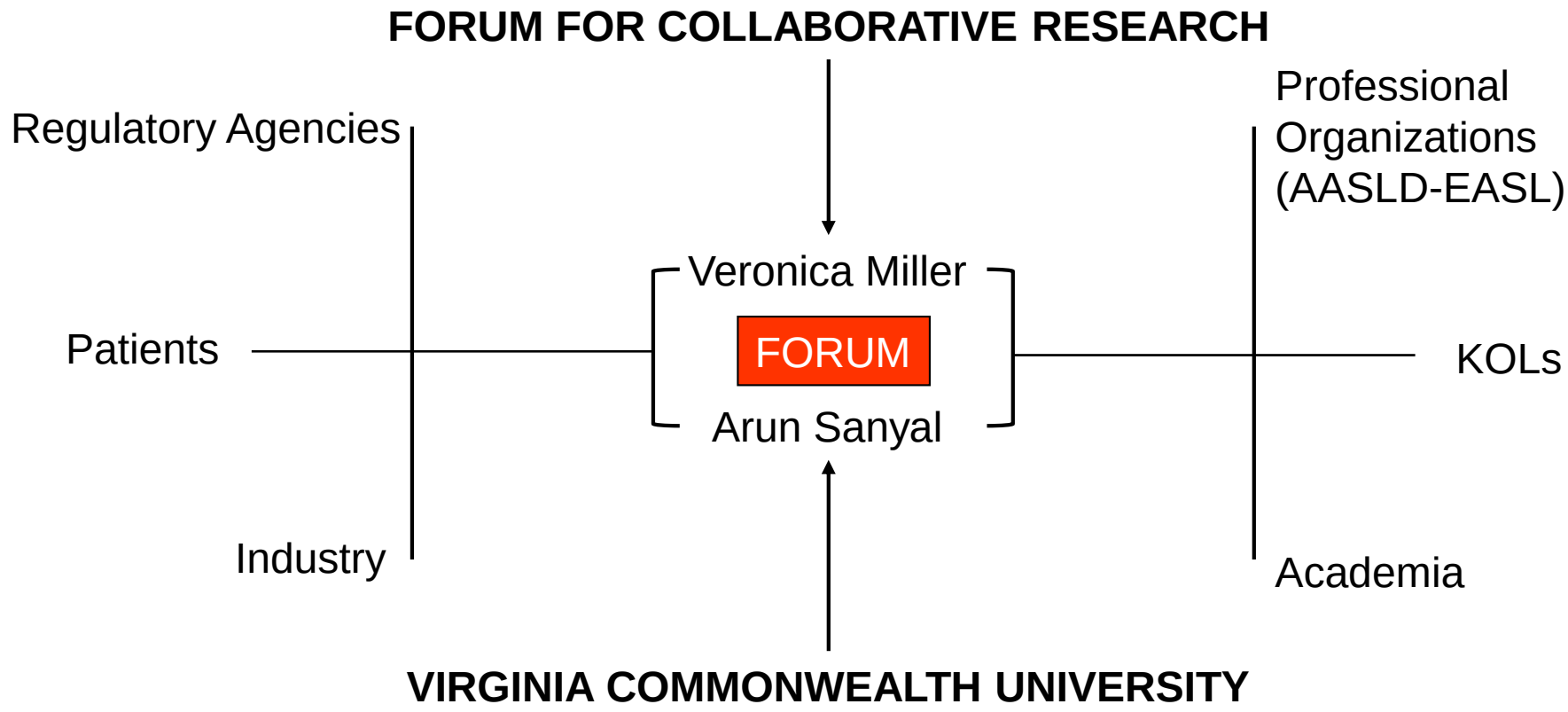
LEVERAGING THE DRUG RESISTANCE ACTION GROUP TO FORM THE LIVER FORUM



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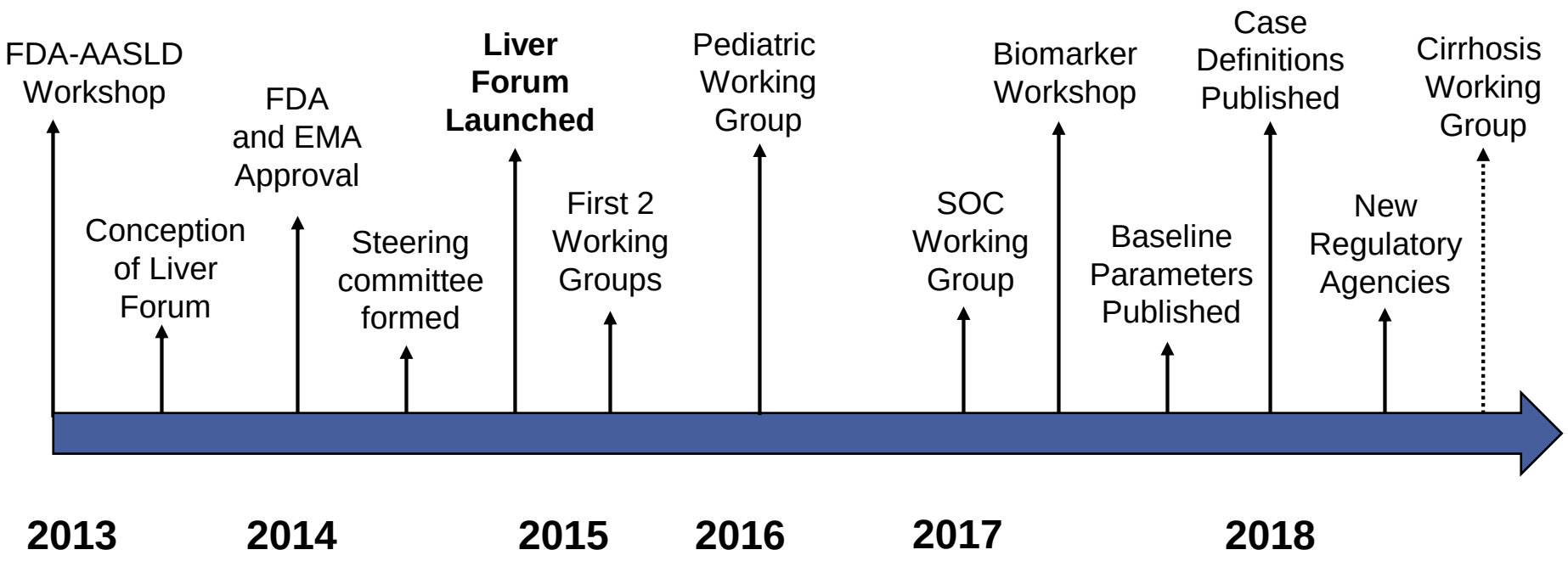
THE LIVER FORUM TIMELINE



HOW REGULATORY SCIENCE DIFFERS FROM TRADITIONAL SCIENCE

- Defining the population:
  - is this the right population for a given drug and MOA
  - are there subpopulations with different risk profiles
  - are there standardized, implementable case definitions that are translatable to practice
  - Additional forum perspective- what is the burden to patient for diagnostics and burden to payer and what is the value proposition for the diagnostic
- Endpoints:
  - Clinically meaningful or surrogate
  - Biological plausibility
  - Objective or subjective
  - Quantifiable
  - Robustness of measure
  - Sensitive to change
  - Best practices in interpreting changes in the endpoint

POTENTIAL UNMET NEEDS

- Defining the populations and aligning with natural history
  - case definitions (from regulatory perspective)
  - alignment with biology
  - alignment with clinical course
  - rigorous analysis of the validity of methods
- Defining clinically meaningful benefit
- Developing endpoints: is mortality a good endpoint?

AGENDA FOR TODAY

- Review key unmet needs and identify top two priorities for the working group (compensated and decompensated cirrhosis working groups)
- Rules of engagement:
  - composition of working groups
  - integration of activities
  - how multi-stakeholder consensus is developed
  - policies
  - establish timelines and milestones