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Applied Translational Medicine

Celerion's Symposia Series: Bridging the Gap from Phase I to Proof-of-Concept

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Applied Translational Medicine

Mind the Gap: Elements of a Bridging Strategy

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Managing Risk vs Reward in Drug Development

Discovery

Preclinical

Full Clinical Development

- FIH to Clinical Proof-of-Concept (CPoC)
- Where a new drug acquires real value
- Fail fast. Fail early
- The Valley of Death in drug development
- Where translational medicine is applied

Searching for More Efficient Ways of Managing Risk in Drug Development

Engineered Process

- Stepwise
- Early studies structured same as later studies – primary objectives and endpoints
- Influenced by “rules-based” regulations

Preclinical

- Phase I: safety, tolerance, PK (healthy participants)
- Phase II: dose response (small groups of patients)
- Phase III: safety and efficacy (statistically robust)
- Phase IV: post-approval surveillance
- Global filings to each market
- Filings for new indications

Adaptive Development

- Feedback loops to discovery (Translational Medicine)
- Early studies fused with multiple objectives and endpoints
- Influenced by emerging “risk-based”guidances

Learn

- Preclinical
  - Human Microdose - PK
- Early Clinical: safety, tolerance, PK (healthy subjects and patients)
  - Proof-of-Presence
  - Proof-of-Mechanism
  - Proof-of-Concept
- Dose Response

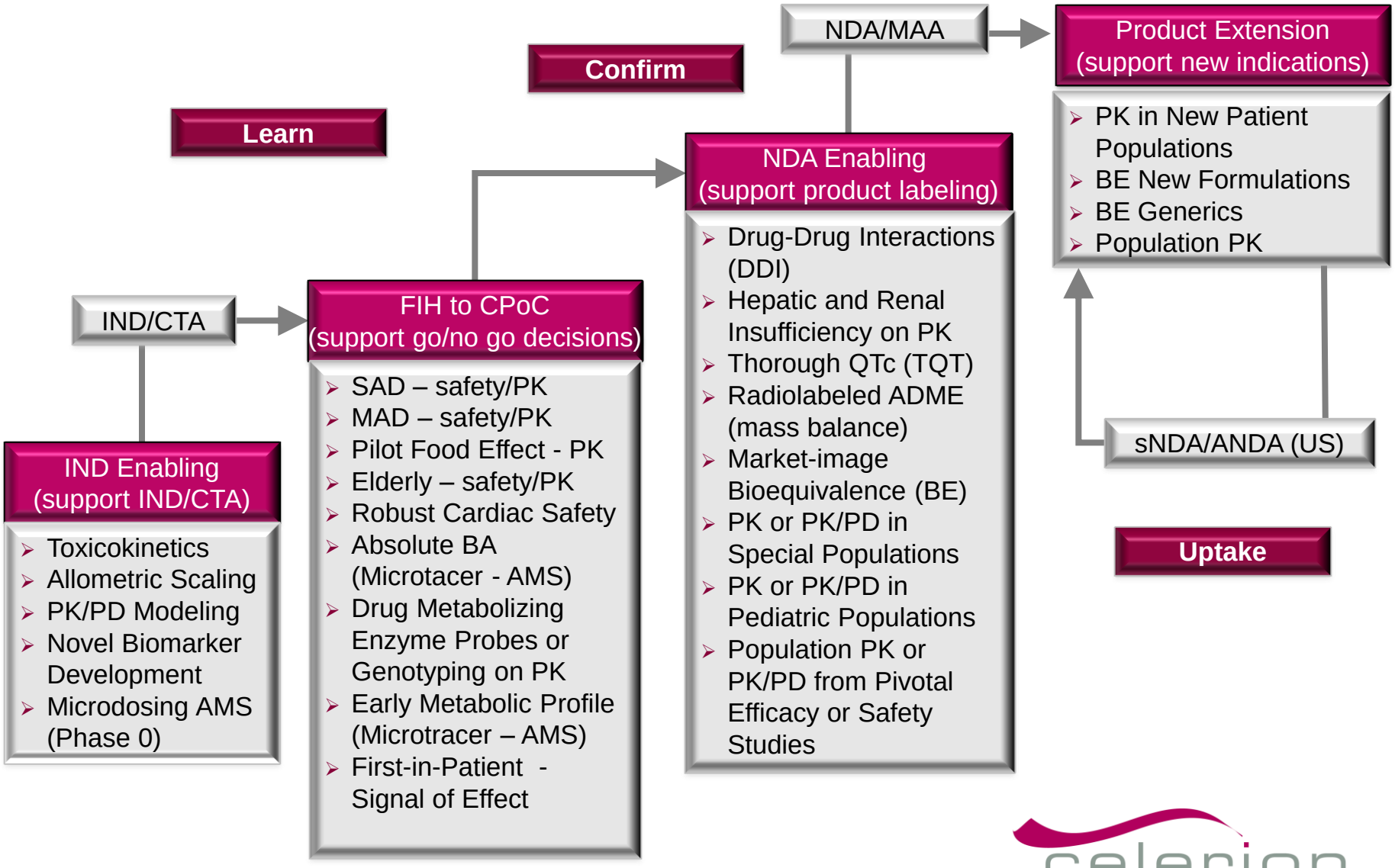
Confirm:

- Safety and efficacy (statistically robust)

Uptake:

- Simultaneous global filings
- Post-approval surveillance
- Filings of new indications

Clinical Pharmacology Impact Areas in Drug Development



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Clinical Pharmacology vs. Confirmatory Studies

Clinical Pharmacology Studies

- Small number of participants
- Few sites, usually single geography
- High density sampling
- Sampling logistics critical
- Specialized units with subject confinement capabilities
- Focus on “Proof-of-Presence”, “Proof-of-Mechanism”, “Proof-of-Concept” and specific product labeling needs.
- $$

Confirmatory Studies

- Large numbers of participants
- Many sites, many countries and geographies
- Low density sampling
- Study logistics critical
- Hospital or outpatient clinic settings
- Focus on pivotal efficacy and safety for regulatory approval and major product labeling claims
- $$$$$$$$

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What's Driving Change in Early Clinical Studies?

- Fail fast in Phase I
  - More information needed for early drug development decisions
- Clinical Pharmacology studies becoming more complex
  - Inclusion of patient cohorts
  - More biomarkers, more sampling
    - Sampling logistics challenges
  - Fusion and adaptive designs
  - More biologic drug candidates – immunogenicity
  - Earlier robust cardiac safety assessment

Bridging Strategy

Start design of CPoC study first

- What is “Proof”? Endpoints?
- What patients? How many?

How to get to CPoC?

- What can I do in healthy participants?
- Are biomarkers available?
- Develop novel biomarkers?
  - Biochemical assays
  - Imaging and imaging agents
  - MicroRNA panels
- Would microtracer studies be valuable?
- Can PK/PD modeling be applied?

What preclinical work is needed to support the early clinical program?

The Three Constraints

Bridging the Gap From Phase I to Clinical Proof-of-Concept

- **Diabetic Drugs – an Example of Learning Early**
  - **Helmut Steinberg MD**: Diabetes and Drug Development
  - **Clayton Dehn MS**: Techniques to uncover early signals of efficacy
- **Cardiovascular Safety – Changing Requirements**
  - **Joy Olbertz PharmD PhD**: Update on QTc Interval Assessments
- **Patients Earlier in Clinical Research**
  - **Fred Pritchard PhD:** Evolving Solutions

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Questions?