

Biomarker Applications and Development

Accelerating Therapies for Rare Diseases
October 2010

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The views expressed are those of the author, and do not necessarily represent an official FDA position

Definition of Biomarker

- A characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes (abnormal biologic processes), or biological responses to a therapeutic intervention
- Any measurable characteristic that is not a measure of the patient's clinical functional status
- Clinical measures are those indicating how a patient feels or functions, or survival

Types of Biomarkers (1)

- Prognostic biomarker
 - Indicates future clinical course of the patient with respect to some specified clinical outcome, in the absence of a Tx intervention
 - ❖ Except Tx interventions incorporated in the data that established the biomarker
 - No relationship to any particular new Tx
 - Applying a new Tx may invalidate the preTx inference
 - ❖ Marker-outcome relationship can change with new Tx

Types of Biomarkers (2)

- Predictive biomarker
 - Measured prior to an intervention
 - Identifies patients who are relatively susceptible to a particular drug effect versus less susceptible patients
 - ❖ Benefit or harm
 - ❖ Exists only for a Tx with some effect
 - Developed Tx by Tx
 - Not necessarily prognostic of the Post-Tx clinical course

Types of Biomarkers (3)

- Pharmacodynamic biomarker
 - Response-indicator biomarker
 - Post Tx measurement
 - ❖ Stand alone
 - ❖ Pre vs post Tx comparison
 - Marker that reveals whether, or how large, a biological response has occurred in that particular patient
 - May or may not be Tx-specific
 - ❖ Development occurs in a Tx by Tx manner

Types of Biomarkers (4)

- Efficacy-response biomarker
 - ❖ Efficacy-surrogate biomarker, Surrogate endpoint
 - Subset of general pharmacodynamic biomarkers
 - Predicts the clinical outcome of the patient at some later time
 - ❖ Sometimes just a low-variance alternative measure indicating the current state of function
 - Usually some prognostic utility or else placebo group measurements cannot be interpreted
 - Developed Tx by Tx

Biomarkers in Clinical Development Programs (1)

- Patient selection tool for enrollment
 - Prognostic biomarkers
 - Predictive biomarkers
- Patient stratification tool
 - To ensure balance between randomized groups
 - Prognostic or unconfirmed predictive biomarkers

Biomarkers in Clinical Development Programs (2)

- Phase 1 study outcome assessment
 - Pharmacodynamic biomarkers
 - Demonstrate drug is bio-active
 - ❖ May indicate actions on early cellular effects rather than clinical outcome
 - Aid in selection dose / regimen for later studies
 - Justify putting resources into further development

Biomarkers in Clinical Development Programs (3)

- Phase 2 study outcome assessment
 - Pharmacodynamic biomarkers
 - Evaluate dose-response relationship
 - Identify other patient characteristics that are predictive
 - Design of A&WC studies
 - ❖ Selection of doses
 - ❖ Selection of patient population
 - ❖ Estimation of sample size
 - Can be critical to efficient and successful development program

Biomarkers in Clinical Development Programs (4)

- A&WC Studies (Phase 3)
 - Pharmacodynamic biomarkers
 - Secondary endpoint
 - ❖ Supportive of primary EP findings
 - ❖ Objective, precise
 - Primary Endpoint
 - ❖ Surrogate endpoint
 - ❖ Well established relationship to clinical outcome
 - Conventional marketing approval
 - ❖ “reasonably likely to predict...” relationship
 - Accelerated approval provisions of regulations

Potential Advantages of Pharmacodynamic biomarkers

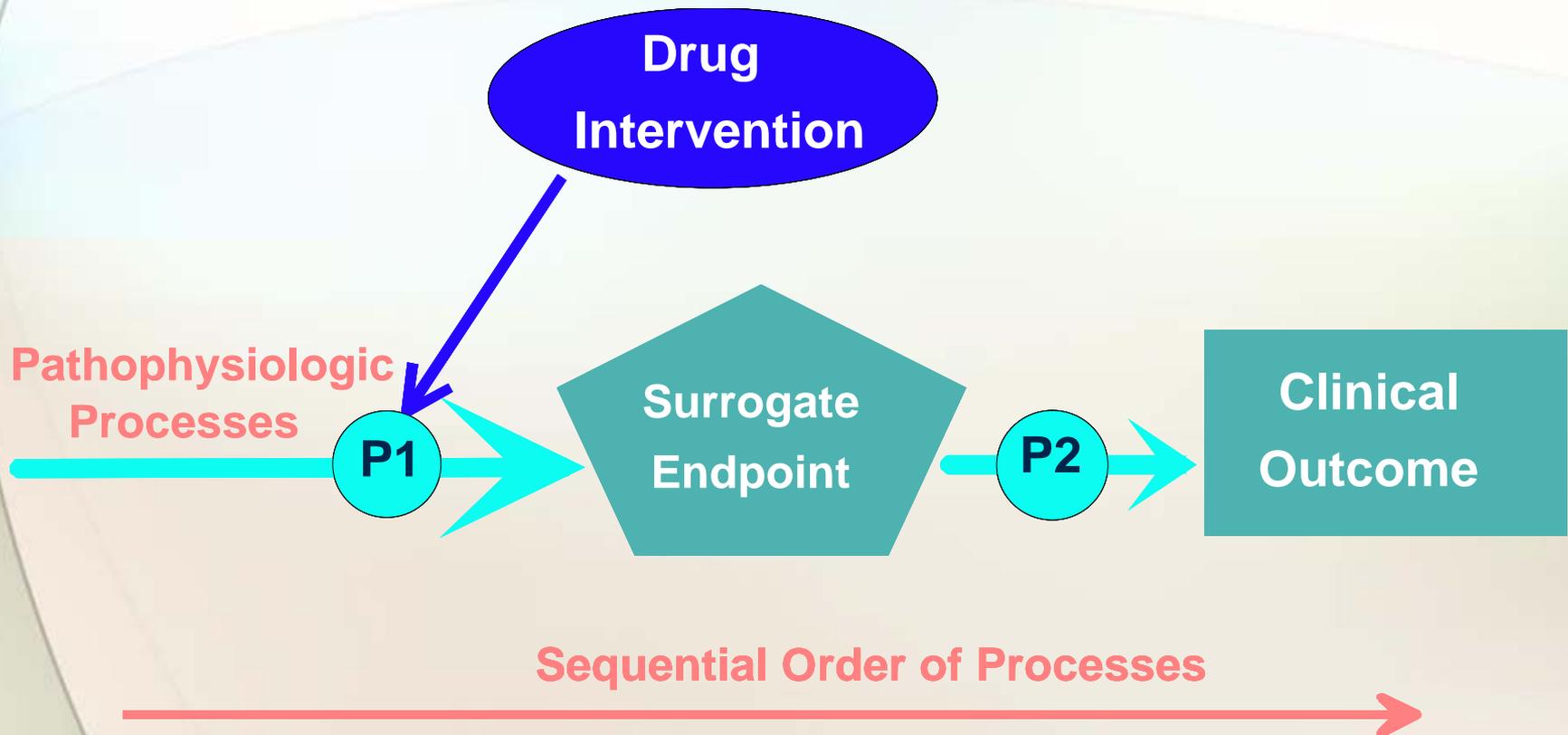
Compared to clinical outcome measures:

- More rapidly observed
- More easily measured
- Less intrinsic variability
- More objective measurement
- Less costly to measure

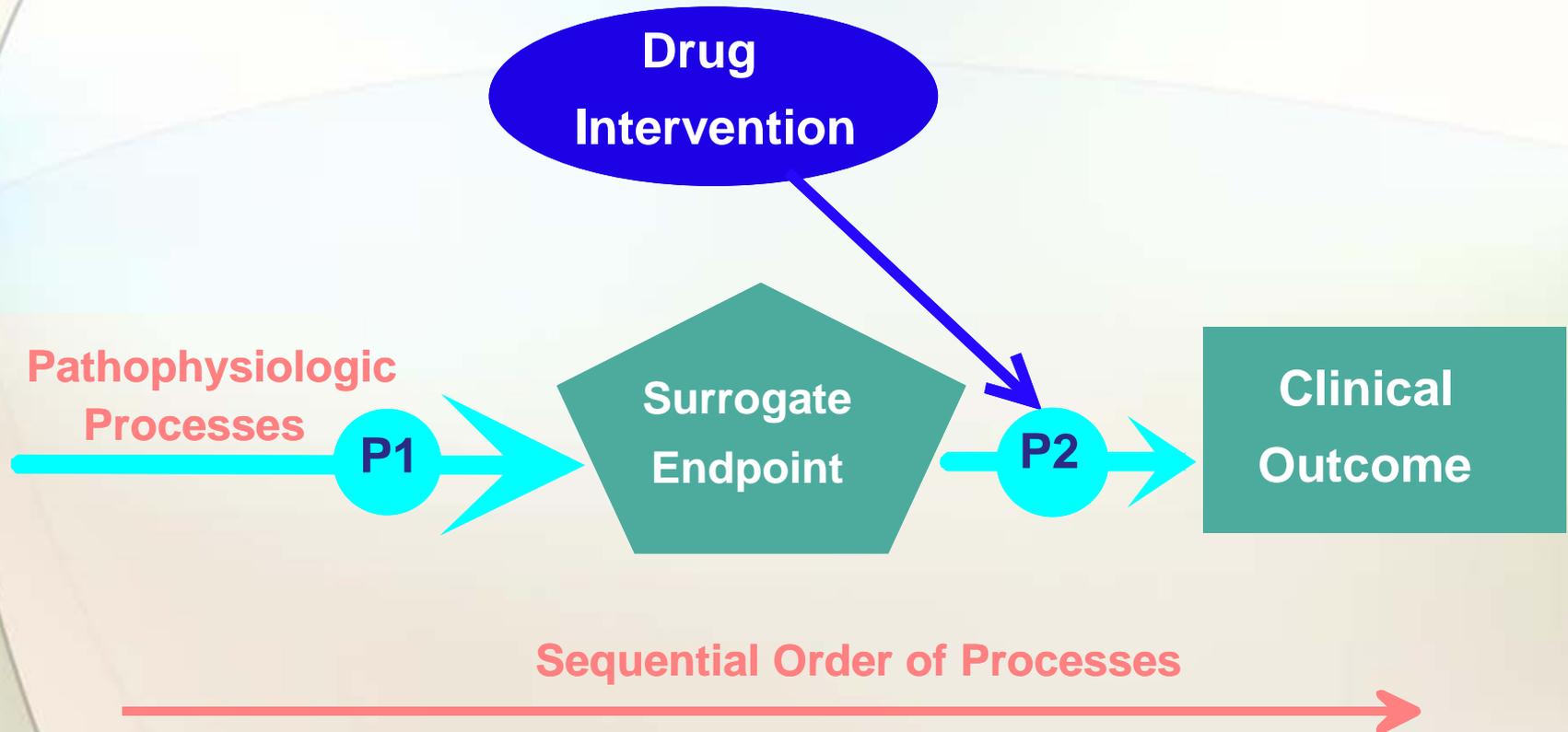
Potential Hazards of Pharmacodynamic biomarkers

- May mislead if discordant with clinical outcome
 - False indication of presence or absence of benefit
 - False optimization of dose / regimen / population
 - Inaccurate estimate of size or frequency of benefit
- May result in a failed next trial for an effective drug

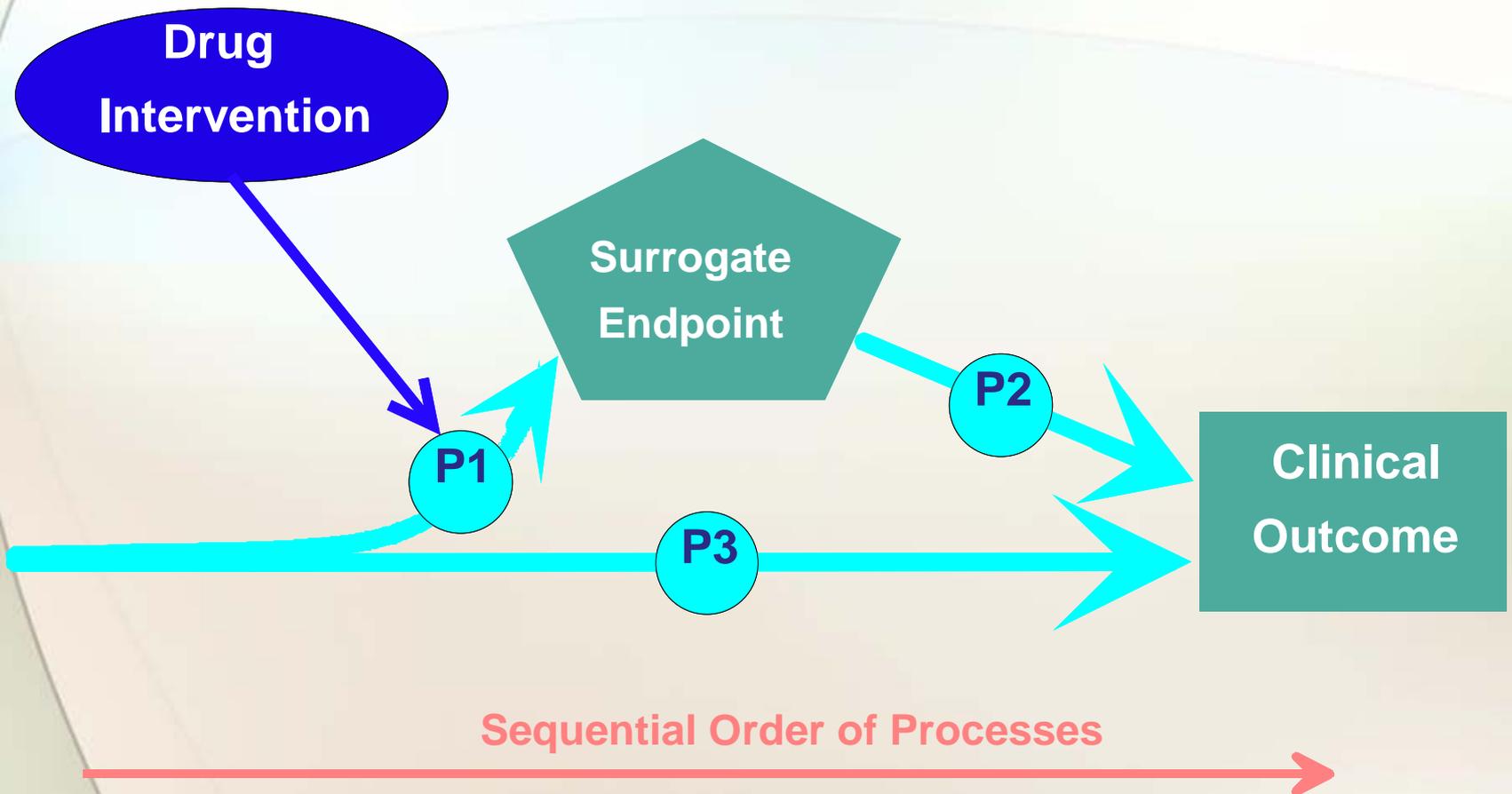
Understanding the Surrogate Measure: Idealized



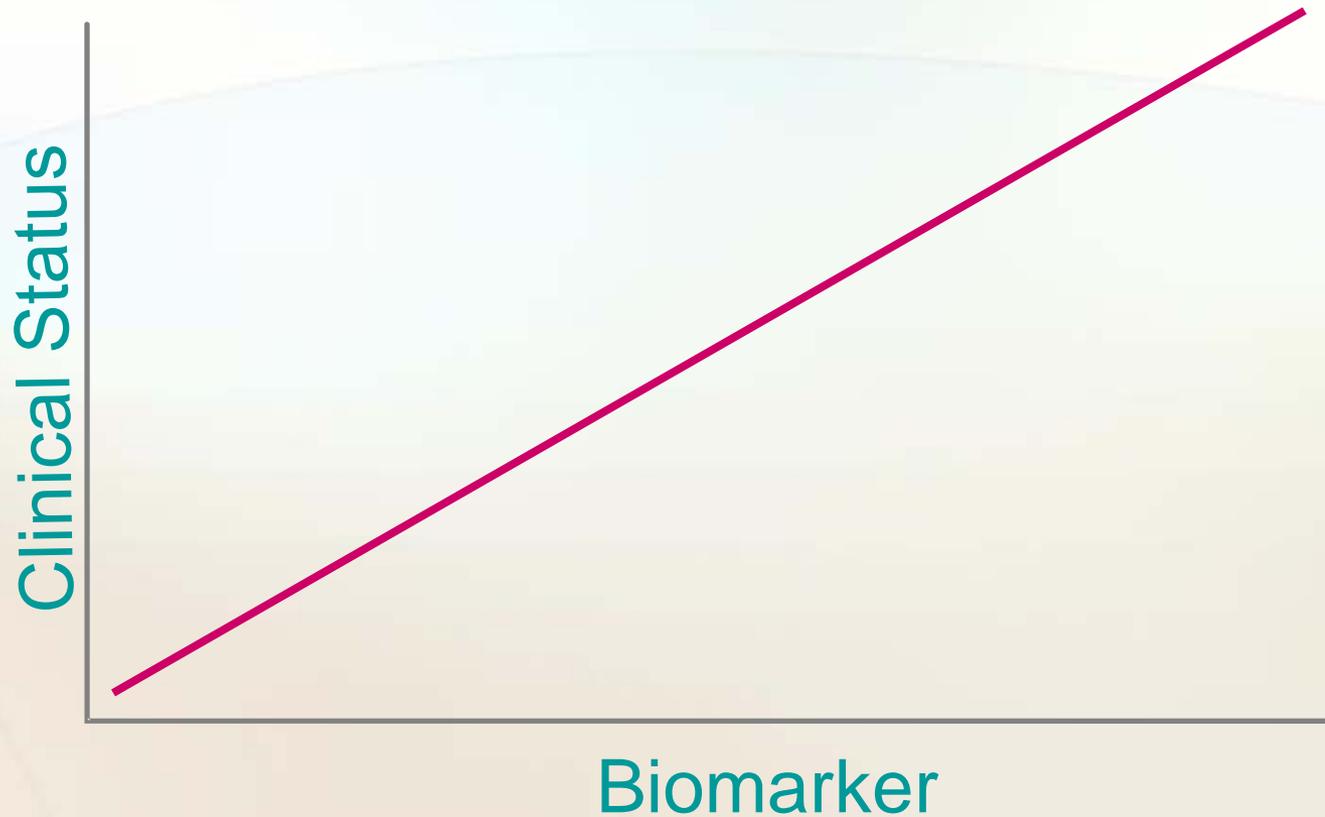
Understanding the Surrogate: Silent Surrogate



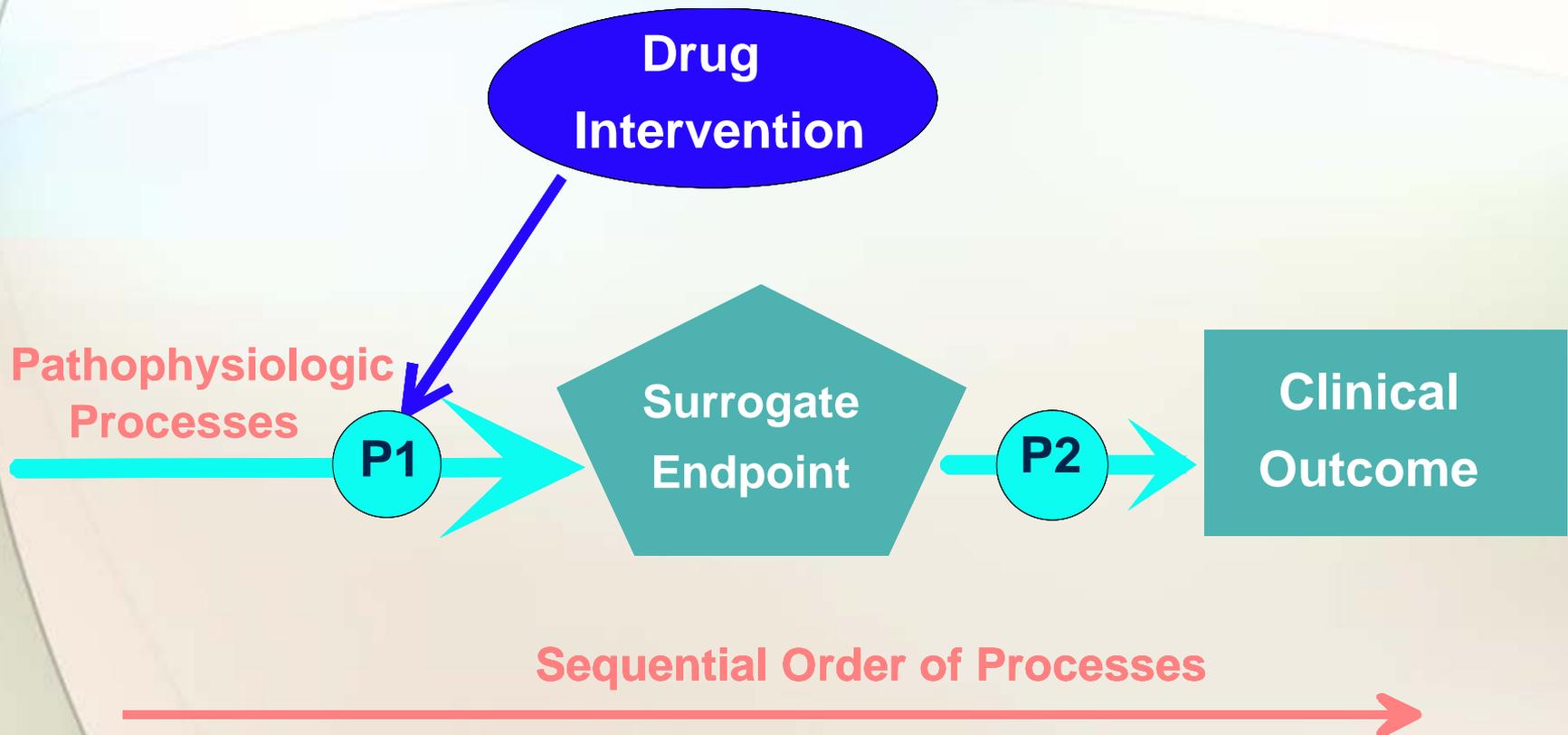
Understanding the Surrogate: Complexity



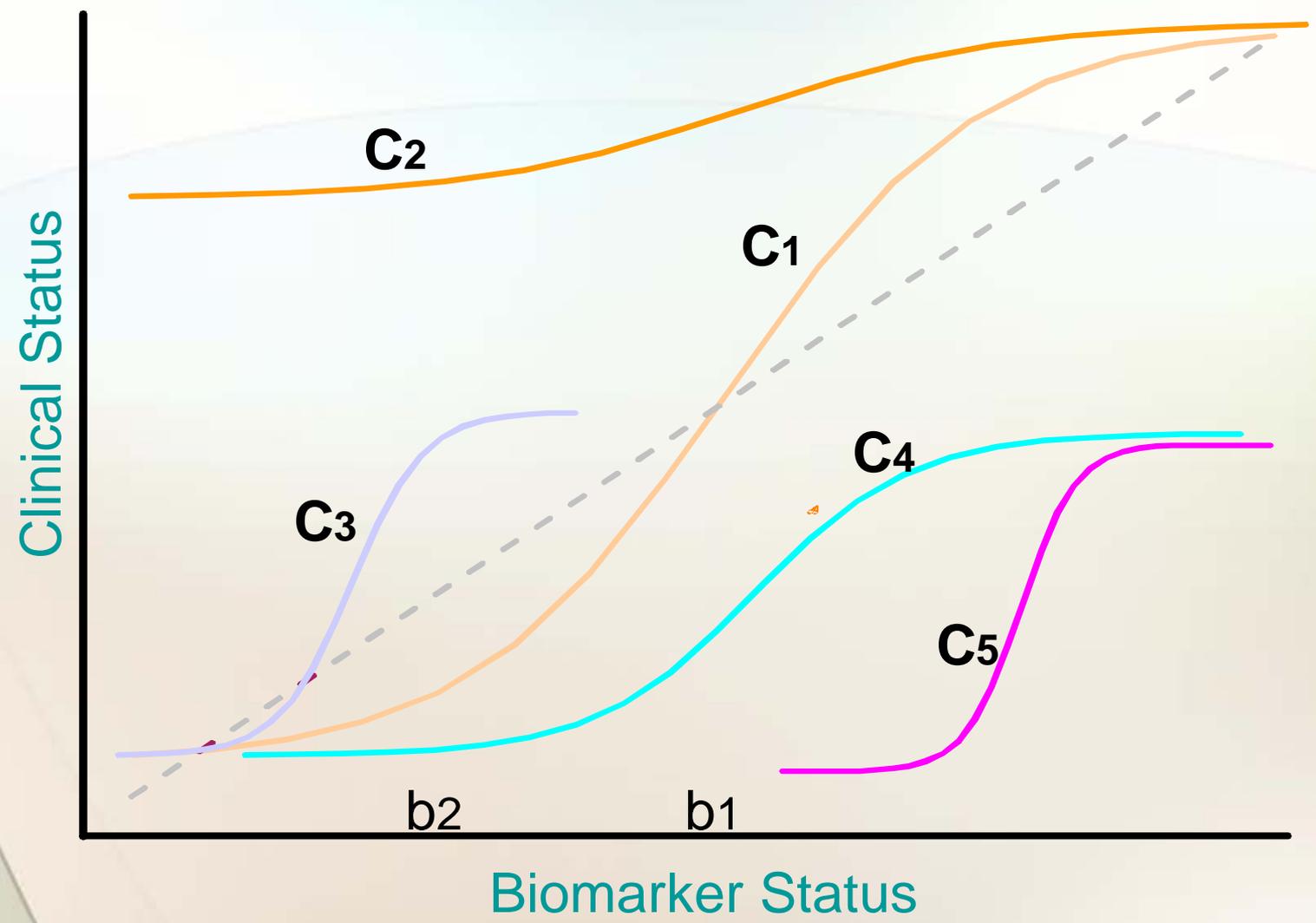
Understanding the Surrogate Measure



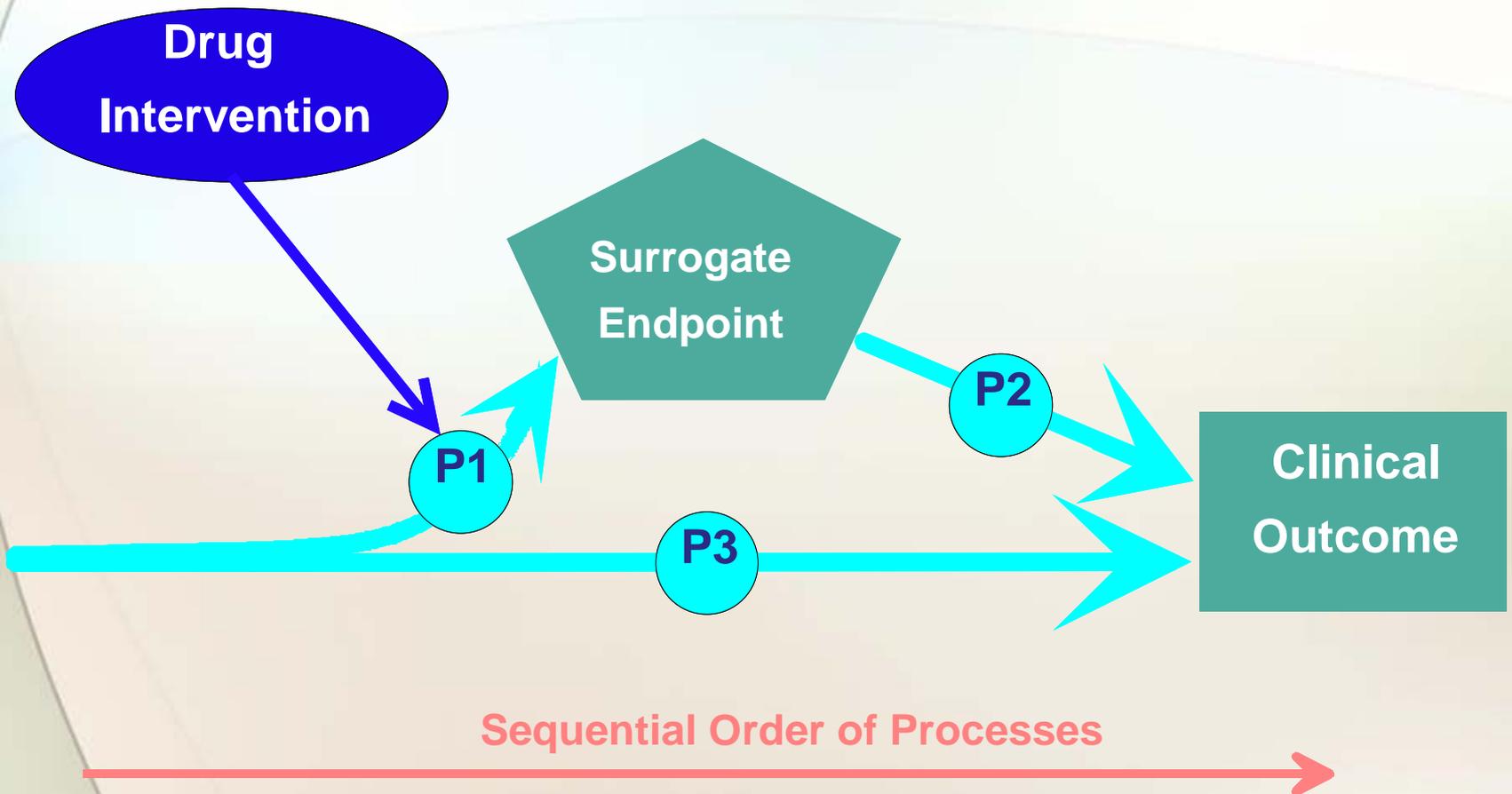
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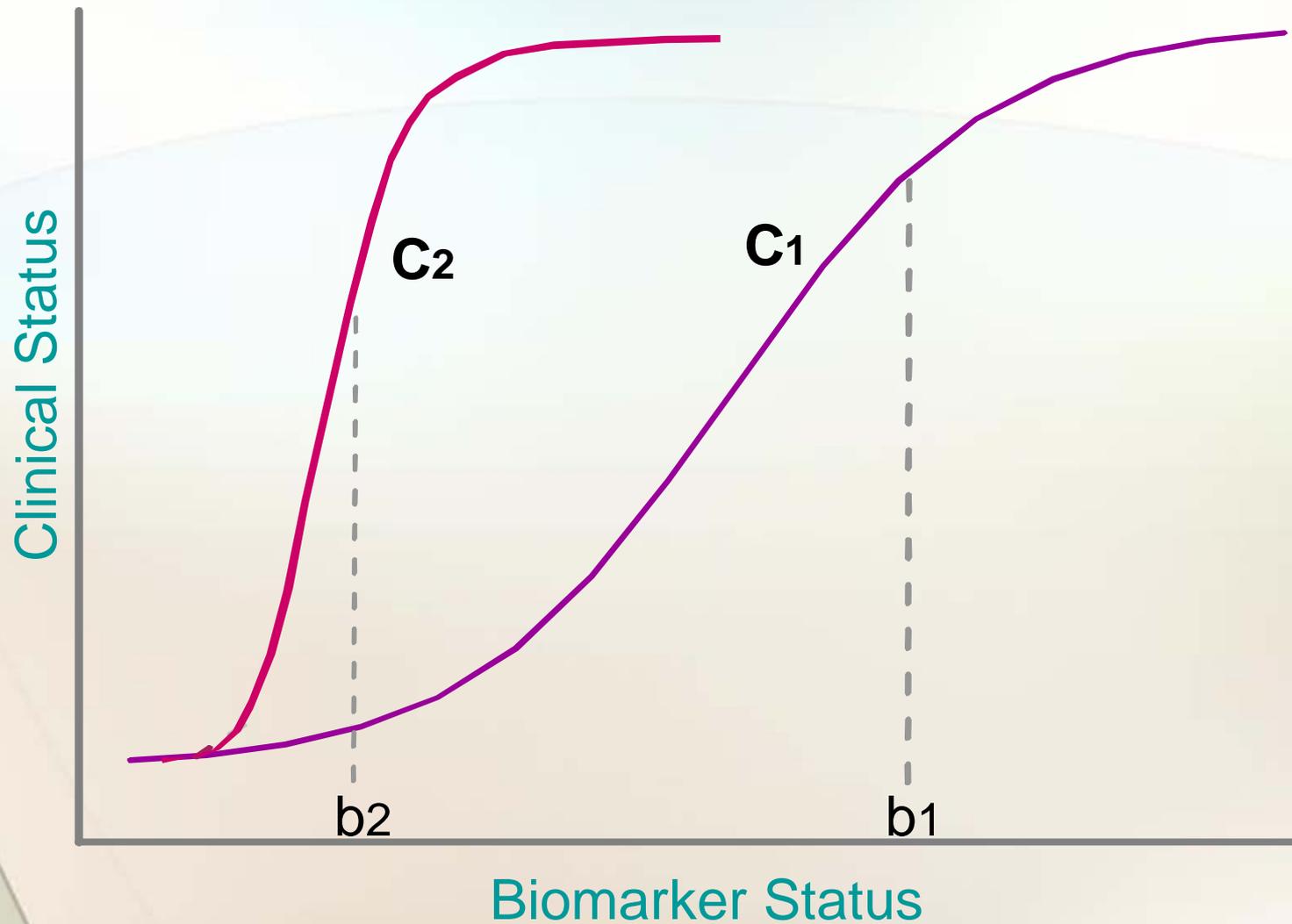
Understanding the Surrogate Measure



Understanding the Surrogate: Complexity



Potential Consequence of Complexity



How have Biomarkers become accepted?

- Case by case
 - Within a specific IND/NDA/BLA/Labeling Update
 - For a specific drug
 - Driven by a specific drug developer's needs
- General use accepted over extended period
 - Scientific experience accumulates in varied uses
 - Usually very extended time-frame
 - Evidence collection not cohesively directed

How can biomarkers become accepted?

- Co-development of drug and test
 - Companion diagnostics
 - Guidance in development
- Biomarker Qualification Process
 - Developing program within CDER
 - Guidance on process to publish soon

Biomarker Qualification at CDER

- Qualification vs Validation
 - Emphasizes context of use
 - Change in term aids awareness of need for specificity of intended use
- Outgrowth of Critical Path Initiative
 - Developing program
 - Particularly for biomarkers expected to have repeated application in multiple drug development programs

Biomarker Qualification

- A conclusion that within a carefully and specifically stated “context of use” the biomarker has been demonstrated to reliably support a specified manner of interpretation and application in decision-making
 - Utility in drug development, particularly regulatory decisions, is central to purpose of qualification

What becomes Qualified?

- Biomarker is a 'substance', analyte, anatomic image, or otherwise a describable characteristic
 - Assay methods are needed to measure the biomarker
 - Assay method is not the biomarker
- One biomarker can have multiple assays that are capable of measuring the biomarker
 - Assay method performance characteristics are important
- CDRH clears or approves commercial testing devices for clinical measurements
- CDRH clearance does not equal CDER qualification
 - Different purposes

Qualification Process within CDER

- 'Submitter' proposes project to FDA
- Interdisciplinary working team assembled within CDER & FDA
- Information Package reviewed
- Advice given as needed on how to advance development for intended use
 - Additional evidence developed
 - Ultimately development is thought complete
- Submission of full data package
- Full review and decision on qualification
- Formal qualification granted if appropriate