

Biomarkers and Qualification

A focus on drug development

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

What is a 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 clinical assessment of the patient
- Clinical measures are those measures that intrinsically are not fully objective
 - The 'mind' of the evaluator or patient is involved

What is a Biomarker?

- Clinical measures are, or are intended to be interpreted as, an assessment of how the patient feels or functions
- Biomarkers are not direct, but may be intended to be interpreted as, assessments of how the patient feels or functions
- Biomarkers may also be intended for other interpretations

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 standard care Tx, recorded
 - No relationship to any particular new Tx
 - Applying a new Tx may invalidate the preTx inference
 - ❖ Marker-clinical relationship can change with a 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 (PD)
 - 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

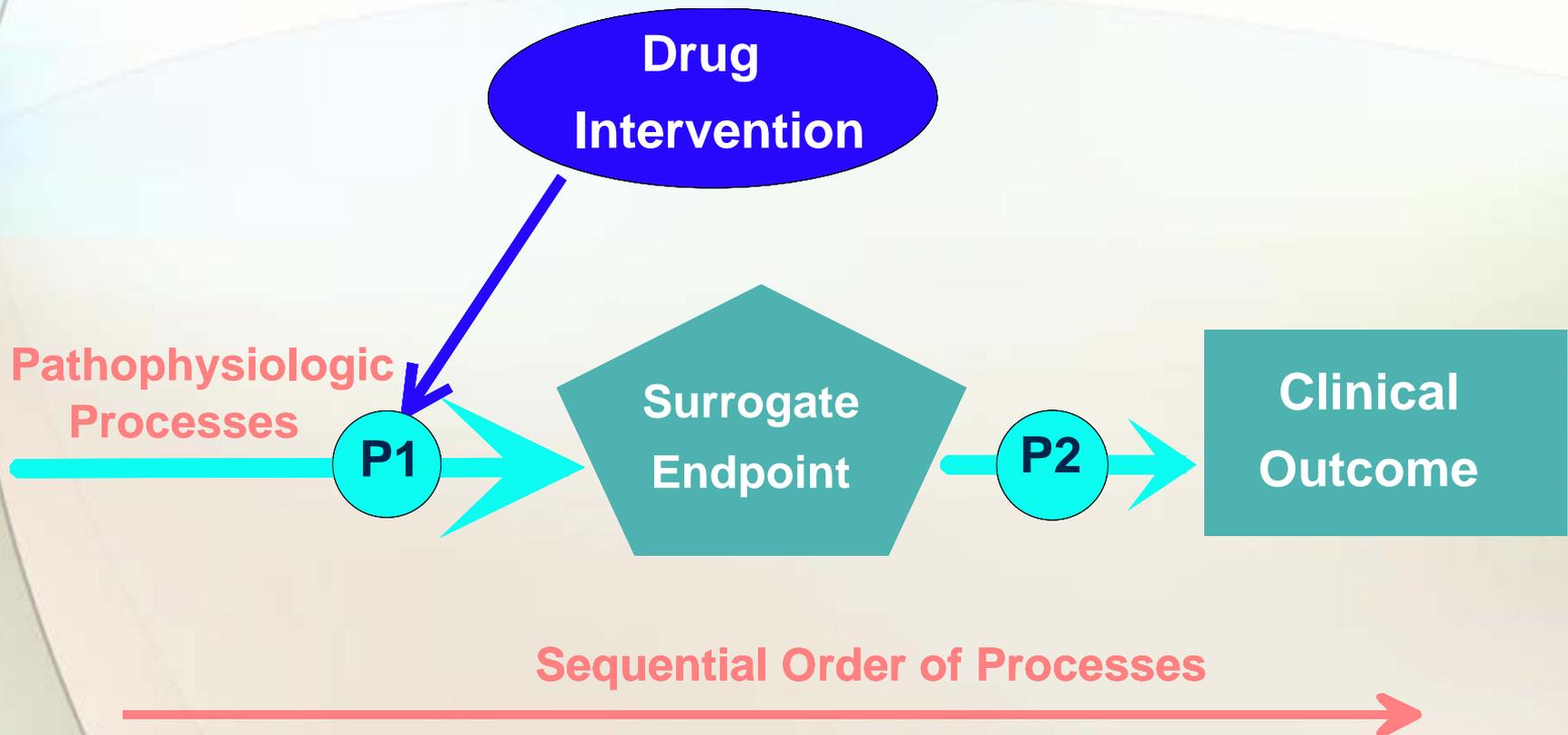
Types of Biomarkers (4)

- Efficacy-response biomarker
 - ❖ Efficacy-surrogate biomarker, Surrogate endpoint
 - Small 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

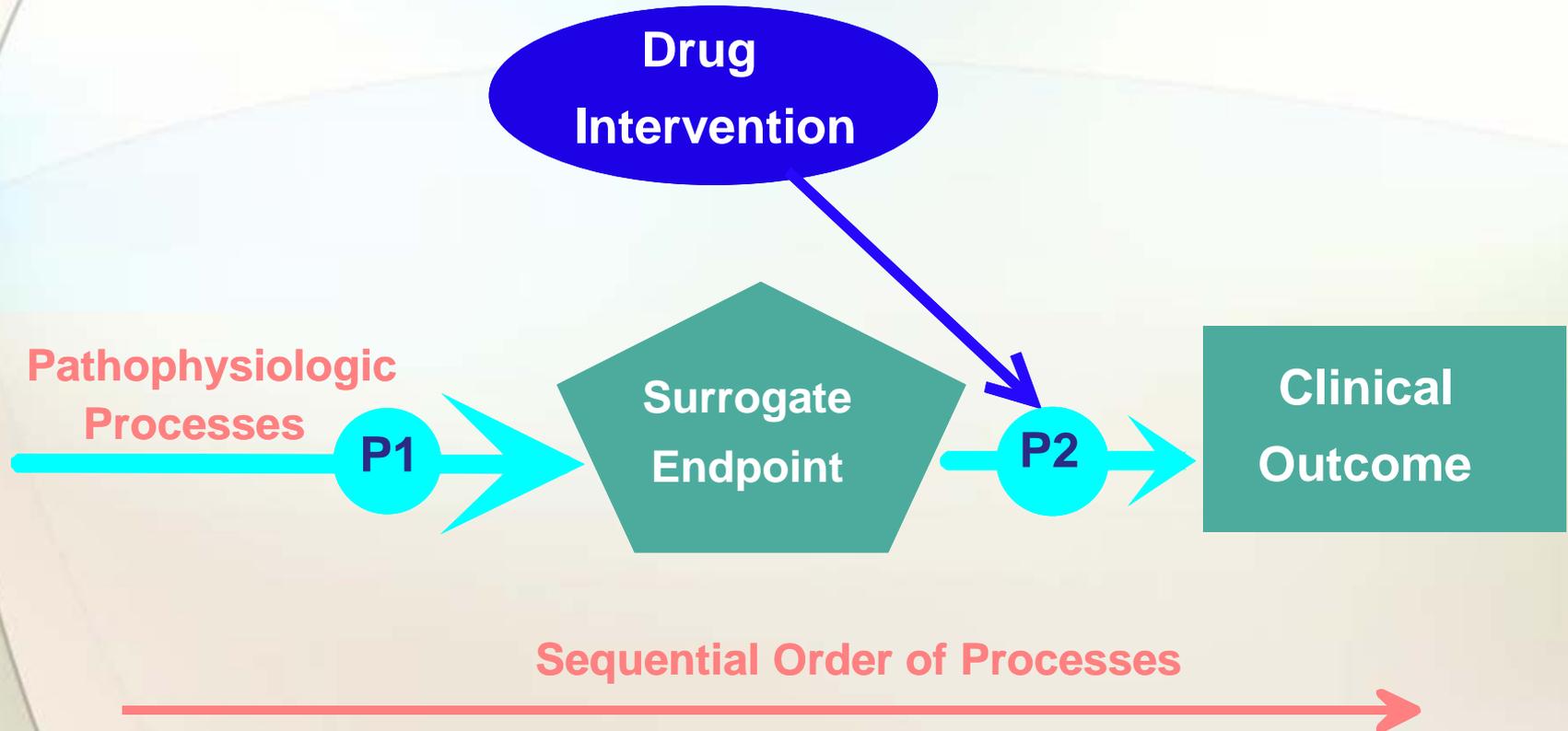
Biomarker Characteristics

- Biomarkers can have utility in more than one category
 - Depends on the specific characteristics of the specific biomarker
- Biomarker is applied differently for utilizing the different characteristics

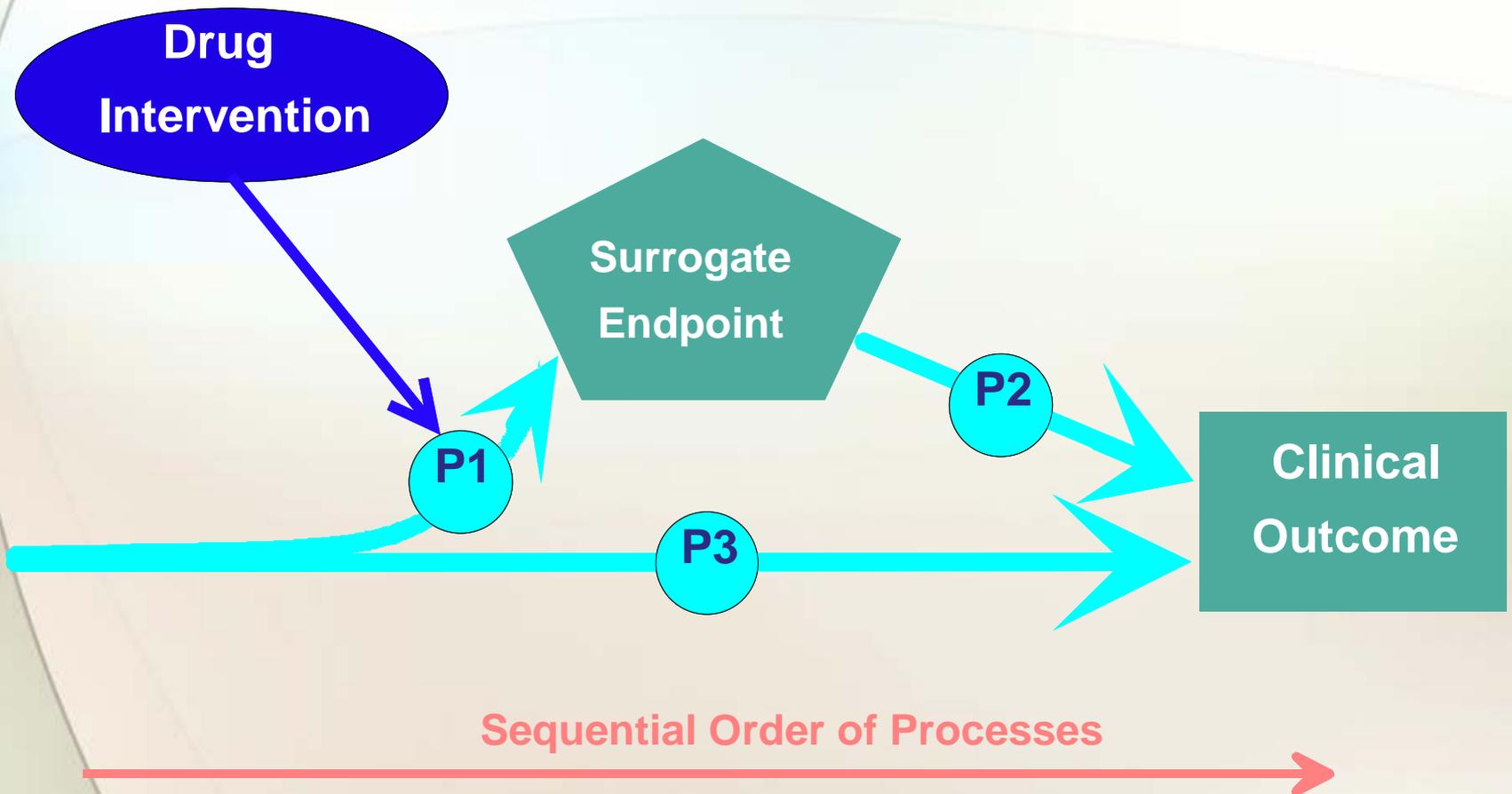
Understanding the Surrogate Measure: Idealized



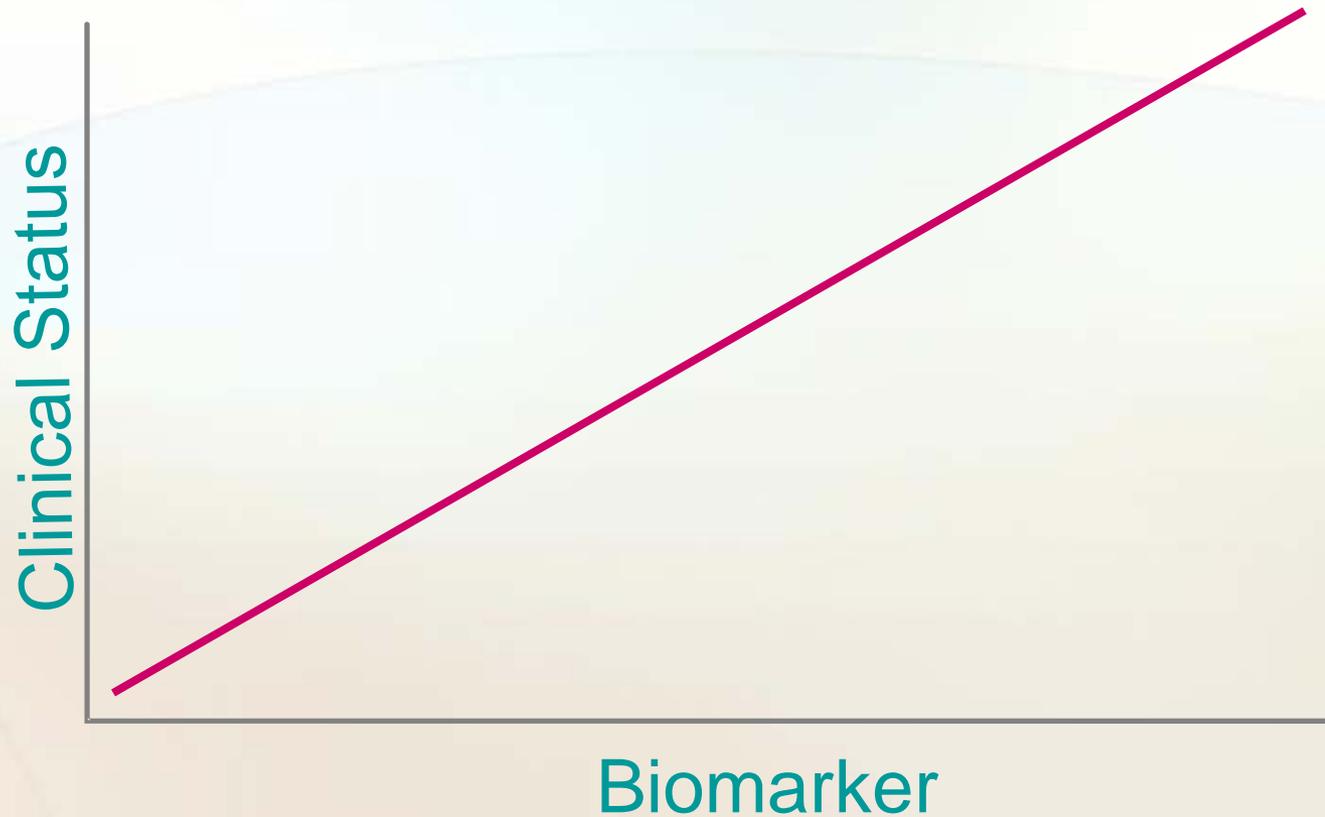
Understanding the Surrogate: Silent Surrogate



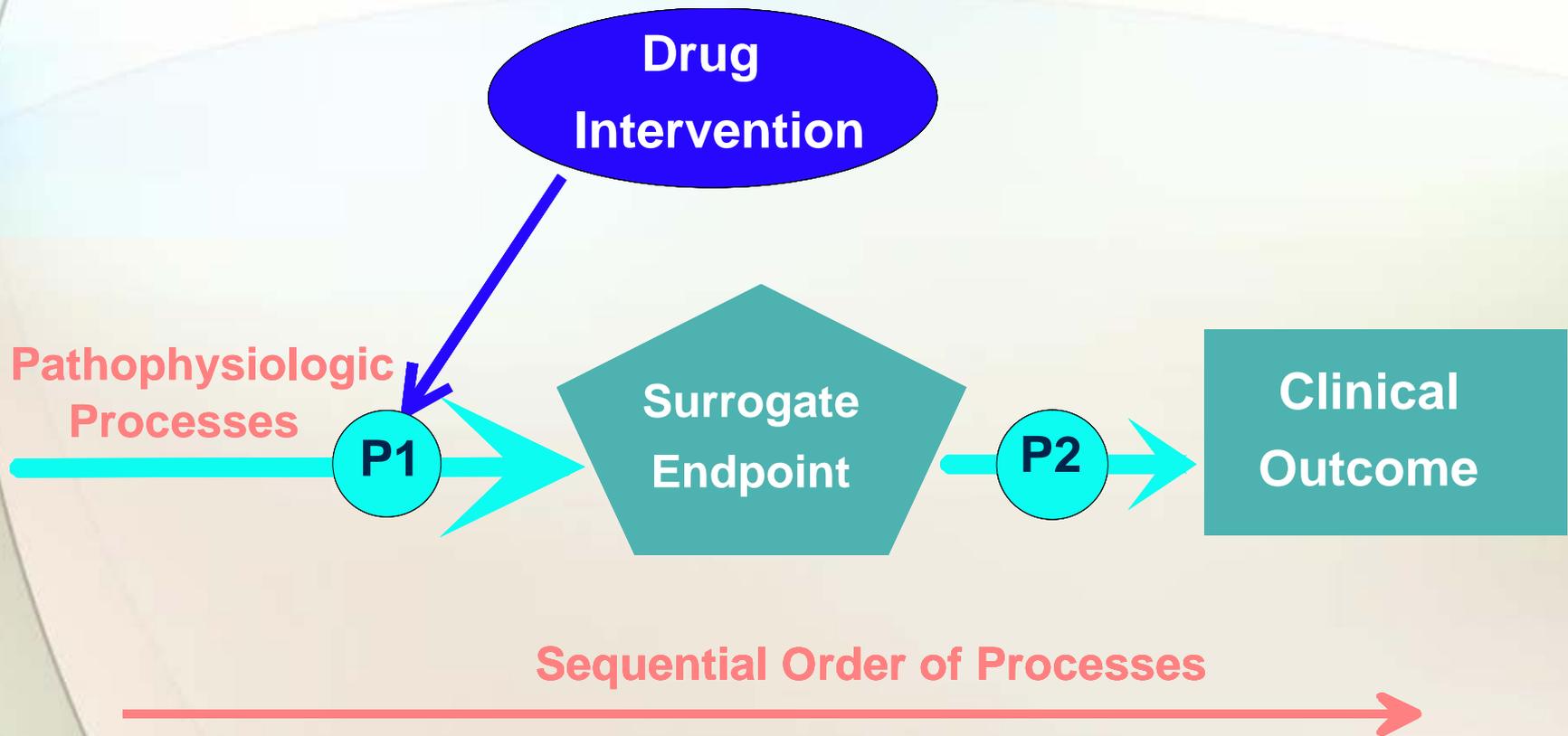
Understanding the Surrogate: Complexity



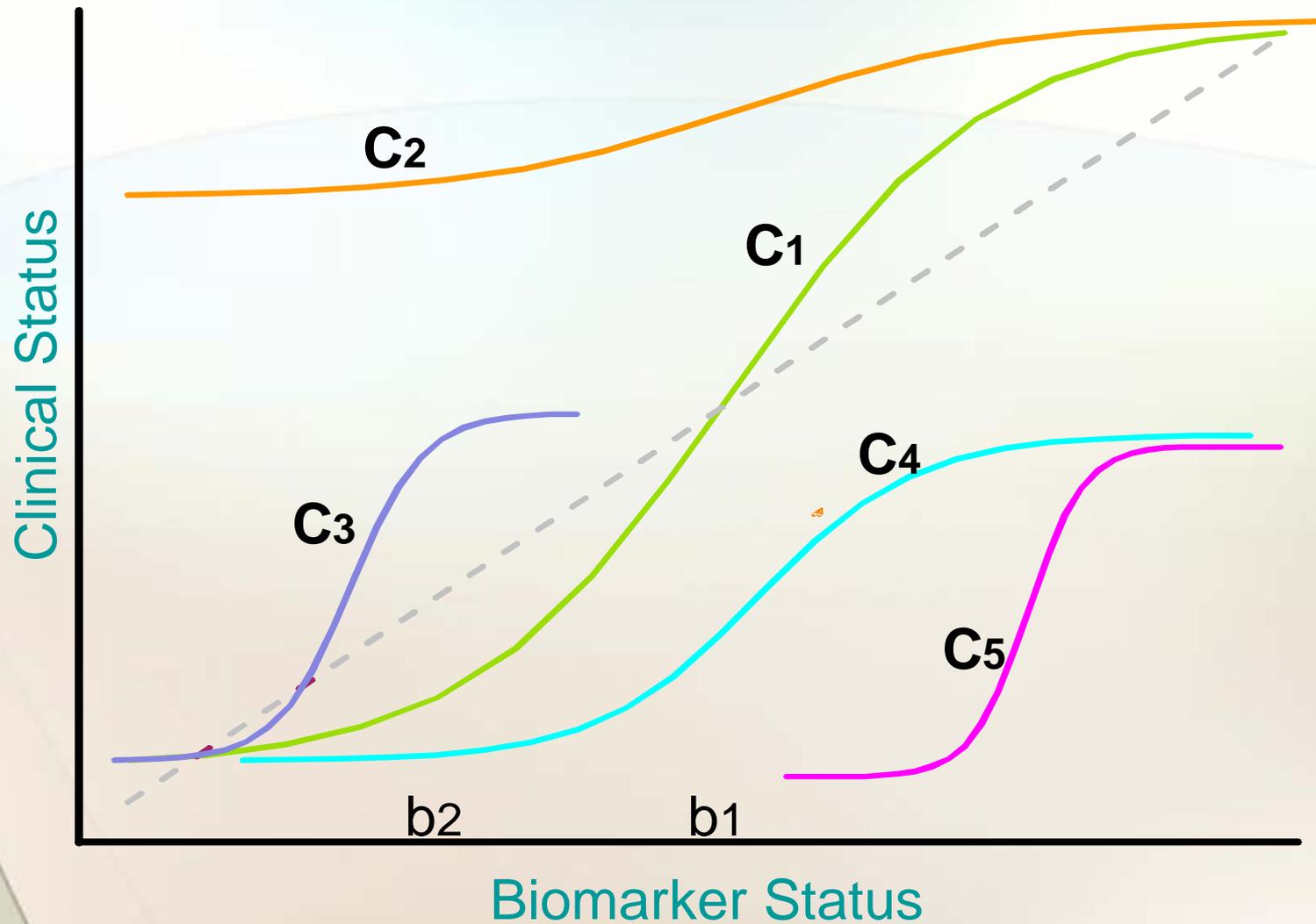
Understanding the Surrogate Measure



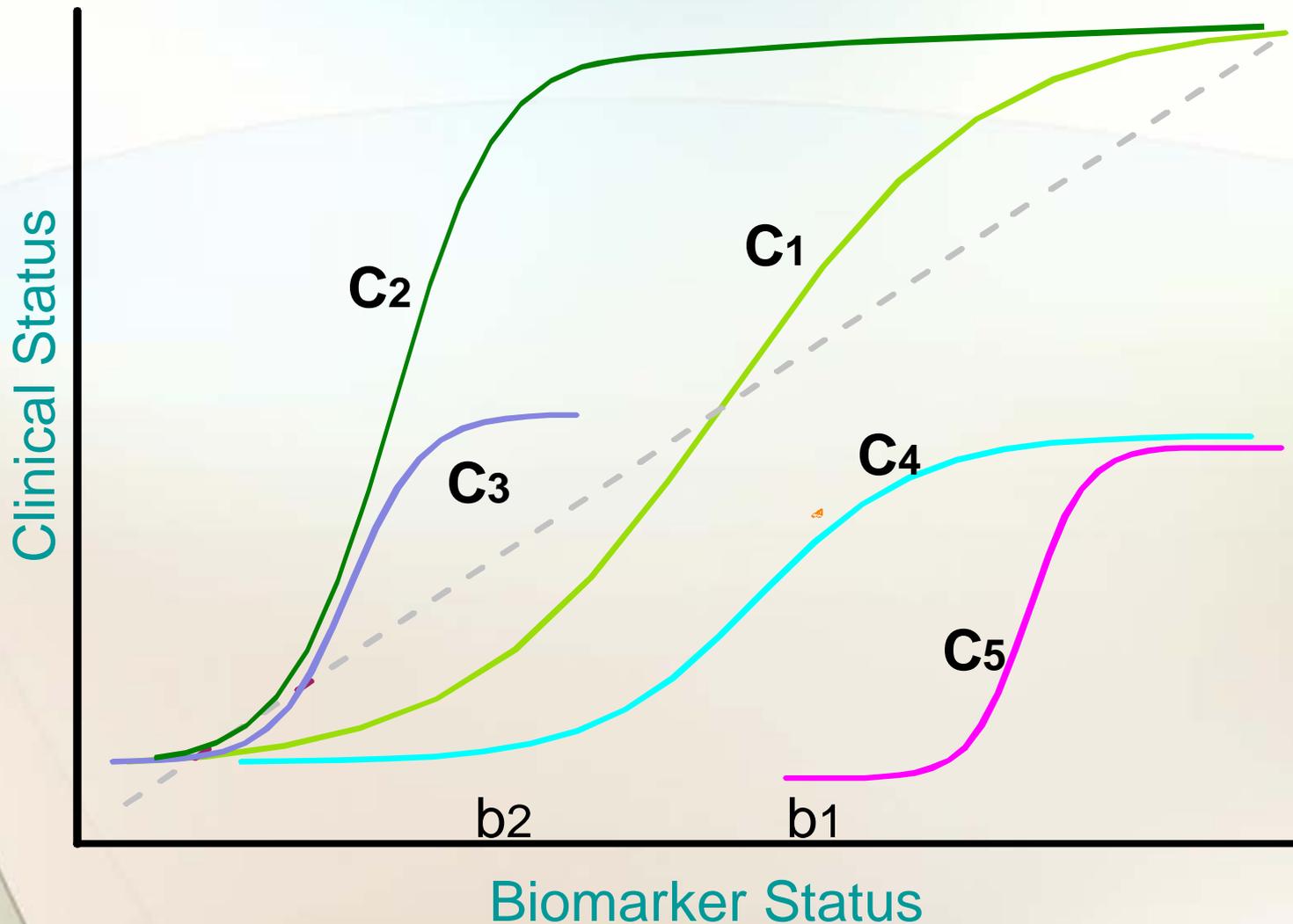
Understanding the Surrogate Measure: Idealized



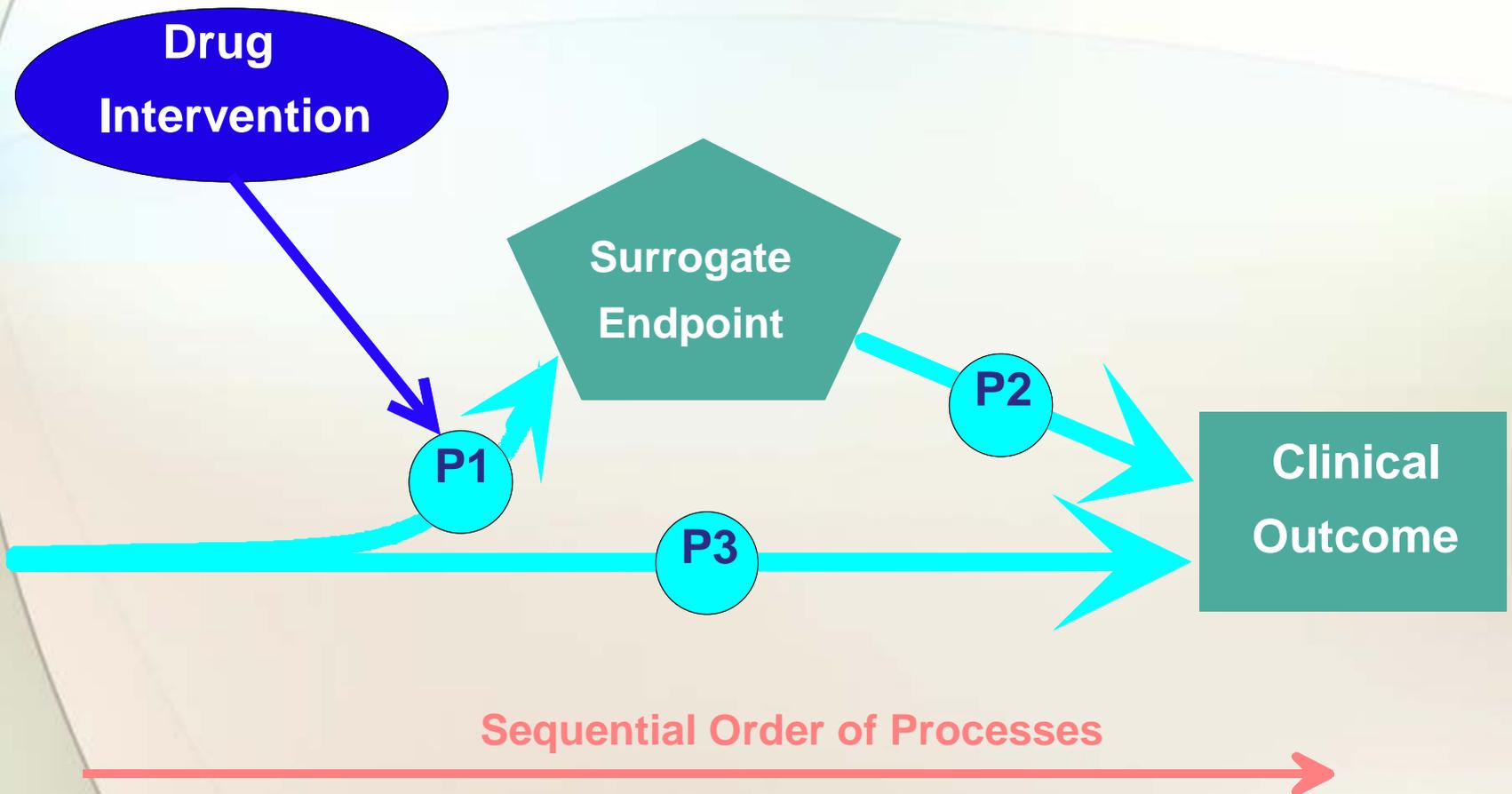
Understanding the Surrogate Measure



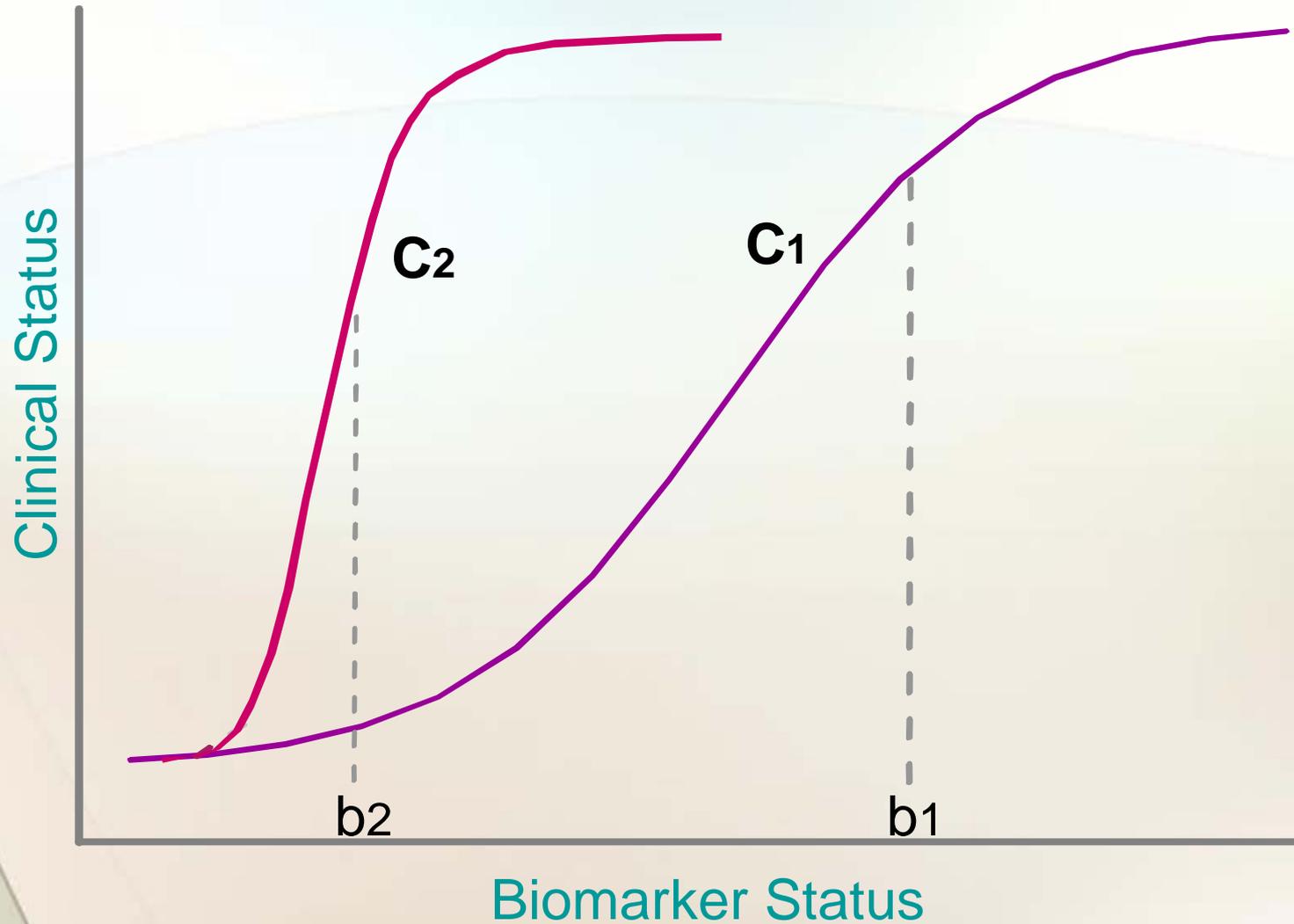
Understanding the Surrogate Measure



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 through varied uses
 - Usually very extended time-frame
 - Evidence collection not cohesively directed

How can Biomarkers Become Accepted?

- Previous routes remain available
- Co-development of drug and test
 - Companion diagnostics
 - Guidance in development
- Biomarker Qualification Process
 - Developing program within CDER
 - Outgrowth of Critical Path Initiative

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 drug development
 - Utility in drug development, particularly regulatory decisions, is central to purpose of qualification
 - Particularly for biomarkers expected to have repeated application in multiple different drug development programs
- Validation ??

What becomes Qualified?

- Biomarker is a 'substance', analyte, or otherwise a 'thing'
 - 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

Context of Use (CoU)

- Biomarkers are qualified for a specific context of use
- A CoU is a comprehensive statement of the manner and purpose of use, including how to apply results to decision making and the impact on drug development
- The CoU identifies the boundaries of known reliability as shown by evidence
 - Not all boundaries of non-reliability are known
- Biomarker may also have utility outside the currently qualified CoU
 - Accept on case by case (IND specific) basis
 - Expand qualified CoU as further data justifies

Context of Use (CoU)

- When, how the biomarker is sampled
- How the samples are analyzed
- How the data are analyzed and interpreted
- What decision is made based on the data
- What action, and how, drug development is altered by the biomarker results

Qualification's Place in Therapeutic Development

- Qualification is not required
 - Case by case approach for accepting use in a single IND/NDA/BLA program remains valuable
- Qualification is voluntary
 - Holder of biomarker data can choose to pursue or not pursue qualification
- Qualification is intended for biomarkers that will be used in multiple drug development programs
 - Public knowledge and availability essential
 - Consortia or collaborative groups likely to be source of biomarkers for qualification

DDT Qualification Process

- Three major parts
 - Initial evaluation for agreement to collaborate
 - Interactive Consultation and Advice Stage
 - In depth Review Stage
- Initial contact - High level evaluation
 - Submitter proposes project to FDA – Letter of Intent
 - ❖ Identifies biomarker and proposed context of use
 - ❖ Information on current state of development
 - FDA decides to collaborate based on whether potential is sufficient to justify Agency resources
- Interdisciplinary working team assembled
 - Working team will guide submitter, and ultimately review the complete evidence

Qualification Process within CDER

- Advice & Consultation stage begins
- Summaries of available information reviewed
 - Advice to submitter on how to advance development for intended use
 - Additional studies conducted as needed
- Summary results discussed with submitter as developed
 - Advice on next steps for development
 - Cycles of Briefing Document / Meeting / Conducting next steps as needed
 - Ultimately development is thought complete

Qualification Process within CDER

- Biomarker Review stage begins
- Submission of full data package
- Full review and CDER decision on qualification
- Formal qualification granted if appropriate
- Qualification statements made public on FDA website as appendix to Guidance on process for development of Drug Development Tools
 - Initially as “draft” guidance statement; subsequently finalized

How do Biomarkers Become Developed?

- Disease biochemistry, pathophysiology, natural history as guide to selecting assessments to develop
 - Collection of scientific data related to a particular context of use justifies relying on the biomarker
- Substantial amount of effort may be required
 - Collaborative model for this work
 - ❖ Including pharmaceutical industry as “pre-competitive” space
 - Reduced resources per participant
 - ❖ Development resources needed well in advance of applying biomarker in drug development