

SMA Summit on Drug Development

Session 6

Regulatory Requirements for Orphan and Pediatric Drug Development





Orphan designation and Paediatric Initiative

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www.emea.europa.eu



Presentation

- Orphan Designation
- Paediatric initiative



The Role of EMEA

A decentralised Agency of the European Union in charge of medicinal products (public health)

Hosting Scientific Committees (marketing authorisation, orphan drugs, paediatrics, veterinary, herbal medicines)

Providing scientific and technical support, and scientific advice

Co-ordinating the network of National medicines Agencies (27 Member States + Norway, Iceland)



EU Orphan Regulation

Regulation (EC) No 141/2000 of the European Parliament and of the Council on Orphan Medicinal Products of 16 December 1999

Commission Regulation (EC) No 847/2000 of 27 April 2000 (*implementation*)

Orphan Regulation creates necessary incentives and establishes a Scientific Committee to deliver scientific opinions on designation



Committee for Orphan Medicinal Products (COMP)

Scientific Committee: 1 Chairperson

- 27 Members (1 per Member State)
- 3 representatives from patients groups
- 3 additional members with a view to complement expertise

COMP Responsible for:

- Scientific opinions on orphan designation
- Advising Commission on orphan EU policy
- International co-operation



Orphan Medicinal Products

Main Incentives at EU level

- Ten years of market exclusivity once approved
- Free Scientific Advice from the EMA
- Fee reductions for EMA applications
- EU centralised Approval only (no more national procedures)
- Access to EU research programs (Framework Programme)

Restricted to (human) medicines, not devices

'Sponsor' can be individual, patient organisation, consultant, industry, etc.

+ National Incentives (tax, etc.)



EU Criteria for Orphan Designation

Medicinal product intended for Diagnosis, Treatment or Prevention:

1. FOR A RARE DISEASE

- Affecting less than 5 in 10,000 patients in EU

OR Lack of Return on Investment

- Development costs higher than expected revenues

2. SERIOUSNESS

- Life-threatening or disabling

3. LACK OF 'SATISFACTORY' METHODS

OR BRINGING ABOUT 'SIGNIFICANT BENEFIT'

- i.e. a clinically relevant advantage for the patient



Orphan Designations

2 for SMA

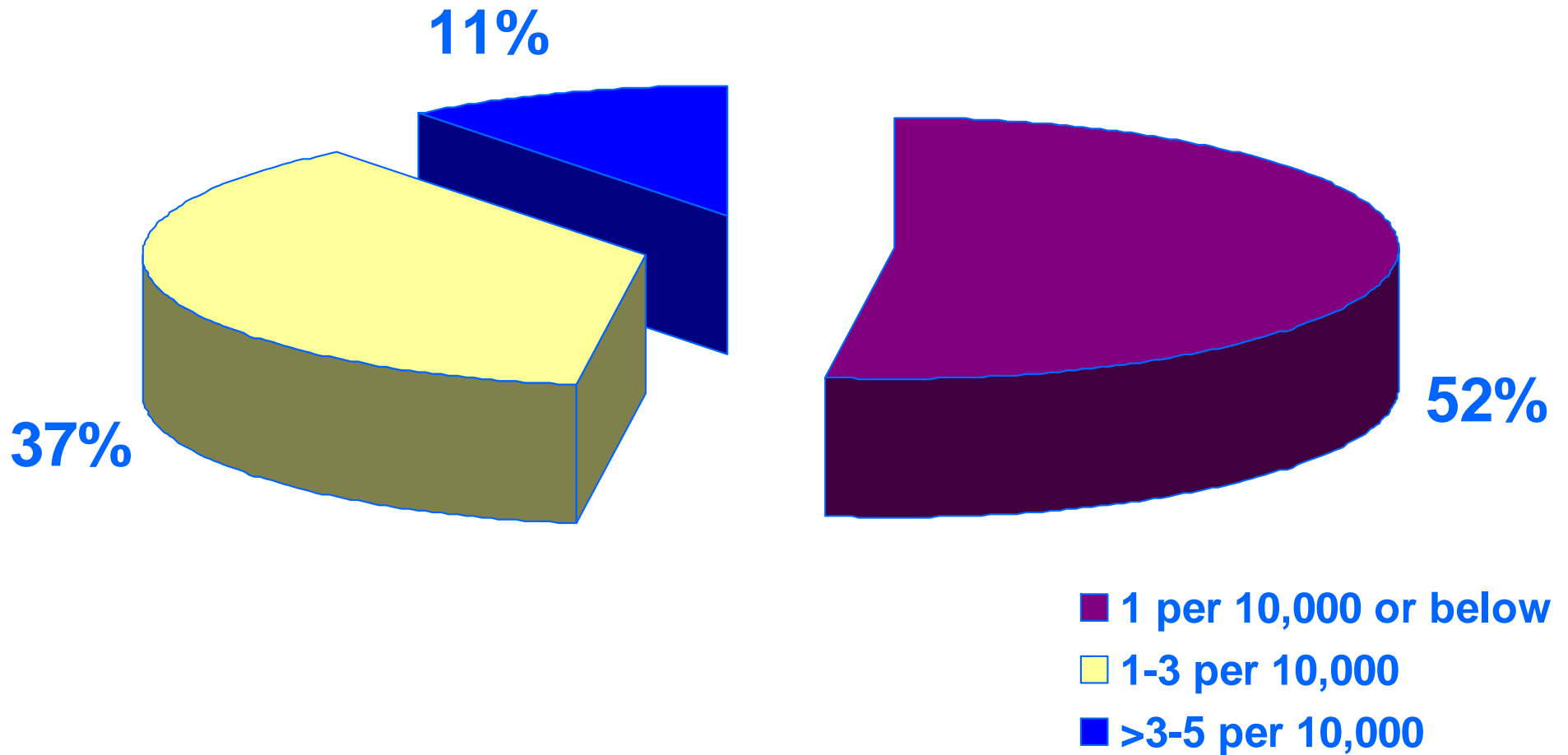
Update August 2007

	2000	2001	2002	2003	2004	2005	2006	2007	Total
No. of applications submitted	72	83	80	87	108	118	104	77	729
Positive COMP Opinions	26	64	43	54	75	88	81	51	482
Commission Decisions	14	64	49	55	72	88	80	35	457
Final Negative COMP Opinions	0	1	3	1	4	0	2	0	11
Withdrawals	6	27	30	41	22	30	20	26	202

70%

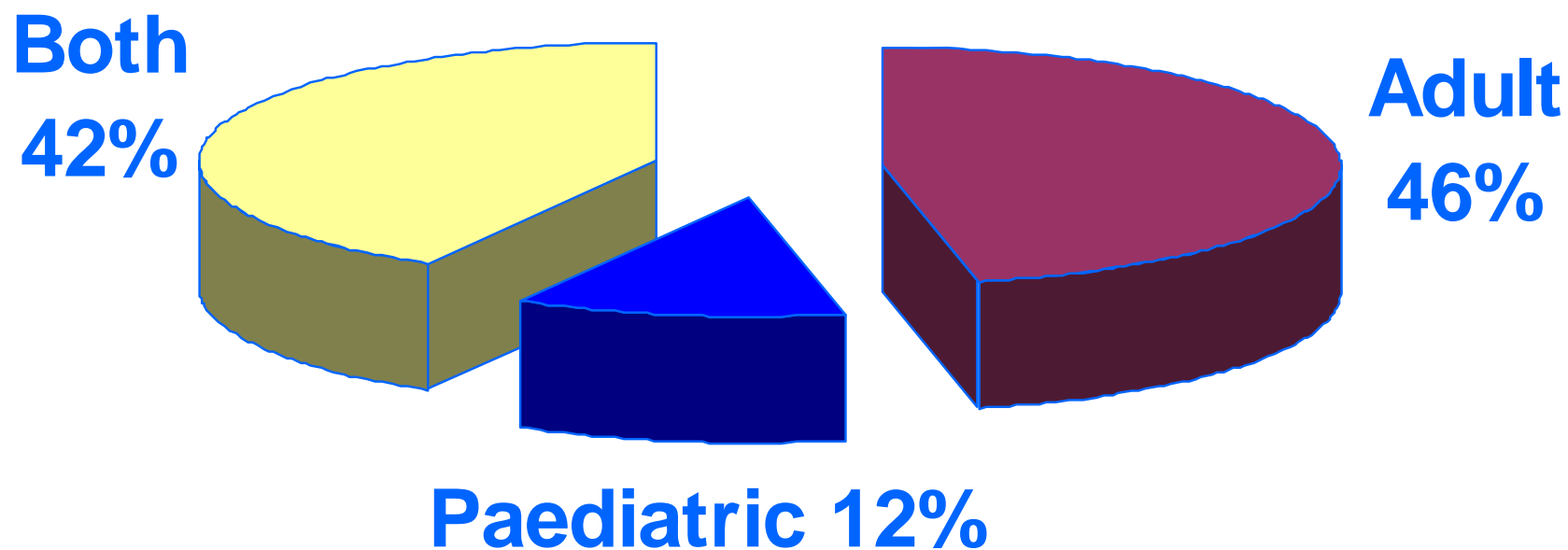


Prevalence of Designated Conditions





Adult / Paediatric Use



Update 12 January 2007



EU Paediatric Regulation

Regulation (EC) No 1901/2006 of the European Parliament and of the Council on Medicinal Products for Paediatric Use

Amending Regulation (EC) No 1902/2006

The Paediatric Regulation creates the obligations and incentives to ensure that medicines intended for children are developed, if and when they need to be developed.



Objectives of the Paediatric Regulation

- Improve the health of children
 - Increase high quality, ethical **research** into medicines for children
 - Increase **availability** of authorised medicines for children
 - Increase **information** on medicines
- Achieve the above
 - Without unnecessary studies in children
 - Without delaying authorisation for adults



What are the tools in the Paediatric Regulation?

- An expert Committee: the Paediatric Committee
- Paediatric Investigation Plans (**PIP**)
- Free Paediatric Scientific Advice
- Transparency of information: trials and products
- Stimulation of research:
 - EMA Network
 - Funding of off-patent medicines studies
 - Funding of other areas in relation to child's health



Paediatric Committee (PDCO)

Scientific Expert Committee: 1 Chairperson

- 27 Members [1 per Member State, including 5 from approval Committee (CHMP)]
- 3 representatives from patients groups
- 3 health professionals with a view to complement expertise

PDCO Responsible for:

- Scientific opinions on paediatric development
- Additional advice on approval of paediatric medicines
- Advice on other projects (network, transparency, etc.)



Obligations and Incentives

- **New products, and New routes, formulations, indications**

Obligation to submit results complying with the PIP, or Waiver, at time of application for authorisation



6 months of extension of patent

- **Off-patent products (paediatric use only)**

Optional procedure, with a PIP



10 years of data protection

- **Orphan drugs (with a PIP)**



2 years of exclusivity (added to 10 years)



Paediatric Investigation Plans (PIP)

- The PIP is a ‘research and development plan’ including timelines
- Must be submitted to the Paediatric Committee
- To be agreed and/or modified (or refused)
- Consideration for unmet paediatric needs and significant therapeutic benefit (public health needs)
- **A dialogue with companies developing medicines, but PIP is binding!**
- If no need for development, Waiver granted



Avoiding unnecessary trials?

- **Database of Paediatric Trials (EudraCT)**
 - Public access to both Protocols and Results of all trials in EU or worldwide if part of Paediatric Investigation Plan
 - Including older studies
- **Database of all authorised Products in EU**
 - Pilot phase, under development
- **Product information:**
Trials results, waivers & deferrals, compliance with PIP



Global Development

- Need for global development for children for ethical (and efficiency) reasons

NB: No requirement for studies to be in EU

Under the confidentiality arrangements EU-FDA:

- Preparation for systematic and regular exchange of information on Written Requests and Paediatric Investigation Plans/Waivers
- Monthly FDA-EMEA teleconferences in place



A European Network

A network of existing paediatric research networks

- Proposal for Strategy in 2007
- Advice from Paediatric Committee
- Consultation with the European Commission
- Adoption by EMEA Management Board in December 2007

Implementation from 2008 on...



Funding of paediatric research

- EU-Community funding for studies into off-patent medicinal products
 - 7th Framework Programme ongoing
 - Call: € 6 million max. per project, (deadline for bids: 18 Sept 2007)
 - Link with identified Priorities for research into off-patent medicines (List on EMEA website)



Conclusions

- Many opportunities for medicines intended to treat SMA
- Openness to dialogue with academics and patients organisations
- Global development
- Dialogue between FDA and EMEA with exchange of information and administrative simplification (ongoing)

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Regulatory Issues in SMA Clinical Trials

SMA Summit on Drug Development

Bethesda, Maryland

September 29, 2007

Wilson W. Bryan

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Regulatory Issues

- Phases of Drug Development
- Endpoint Selection
- Surrogate Endpoints
- Evidence of Effectiveness
- Accelerated Approval

Phases of Drug Development

- In-vitro studies
- Nonclinical animal studies
- Clinical Trials
 - Phase 1
 - Phase 2
 - Phase 3
- Marketing Approval
- Phase 4 Clinical Trials

Drug development objectives

- Nonclinical – predict clinical toxicity - guide clinical trial design; proof-of-concept
- Phase 1 – safety, tolerability, pharmacokinetics, preliminary assessment of activity
- Phase 2 – safety, preliminary efficacy; define population, endpoints, regimen, design for Phase 3
- Phase 3 – confirmatory efficacy and safety

Regulatory Issues

- Phases of Drug Development
- Endpoint Selection
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Endpoint – Definition

- Measure or event that occurs during the course of a clinical trial
- A specific outcome, at a specific timepoint, using a specific analysis plan

Endpoint Selection

- Types: Measures vs. Events
- Qualifications: Valid vs. Ideal
- Consider trial objectives
- Roles: Primary vs. Secondary

Measurements vs. Events

- Often continuous
 - Examples:
FVC, MVIC
 - Many potential values over time
 - Relatively high sensitivity to detect an effect
 - May detect unimportant changes
- Binary - yes / no
 - Examples: death, progression to a specified landmark
 - Occur at specific time
 - Relatively low sensitivity to detect an effect
 - may be more clinically meaningful and interpretable than measurements

Endpoint – Qualifications

Valid vs. Ideal

- Ideal Endpoint
- Valid Endpoint
 - Required for the primary efficacy endpoint in a Phase 3 trial

Endpoint - Qualifications

- Ideal Endpoint
 - Reliable
 - Clinically Meaningful
 - Feasible
 - Objective (resistant to bias)
 - Sensitive
 - Clinically Interpretable (translatable)
- Valid Endpoint
 - Requirements vary by study objective
 - Phase 3 – reliable and clinically meaningful

Drug development objectives

- Nonclinical – predict clinical toxicity - guide clinical trial design; proof-of-concept
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Relationships of Clinical Trial Phases to Endpoints

No single endpoint is
ideal for all phases
of all clinical trials in
SMA

Relationships of Clinical Trial Phases to Endpoints

- Choice of endpoint(s) should reflect the trial objectives
- Different endpoints will be appropriate for different phases of drug development
- Primary and secondary endpoints should be complementary

Primary vs. Secondary Endpoints

- Primary endpoint
 - the endpoint which is the single best indicator for the study objective
- Secondary endpoint(s)
 - Supportive of primary endpoint
 - Especially important when primary endpoint is subjective
 - Multiple endpoints may improve confidence

Regulatory Issues

- Stages of Drug Development
- Endpoint Selection
- Surrogate Endpoints
- Evidence of Effectiveness
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Surrogate Endpoint - Definition

A surrogate endpoint of a clinical trial is a laboratory measurement or a physical sign used as a substitute for a clinically meaningful endpoint that directly measures how a patient feels, functions, or survives. Changes induced by a therapy on a surrogate endpoint are expected to reflect changes in a clinically meaningful endpoint.

R. Temple

Potential Advantages of Surrogates

- May be more rapidly observed than clinical outcome
 - Shorter clinical trial
- May be easier to measure
 - Greater compliance in obtaining accurate measure
- Less expensive to measure
 - Less costly clinical program
- Lesser intrinsic variability than a clinical measure
 - Smaller sample size
- More objective measure
 - Accurate results (unbiased)

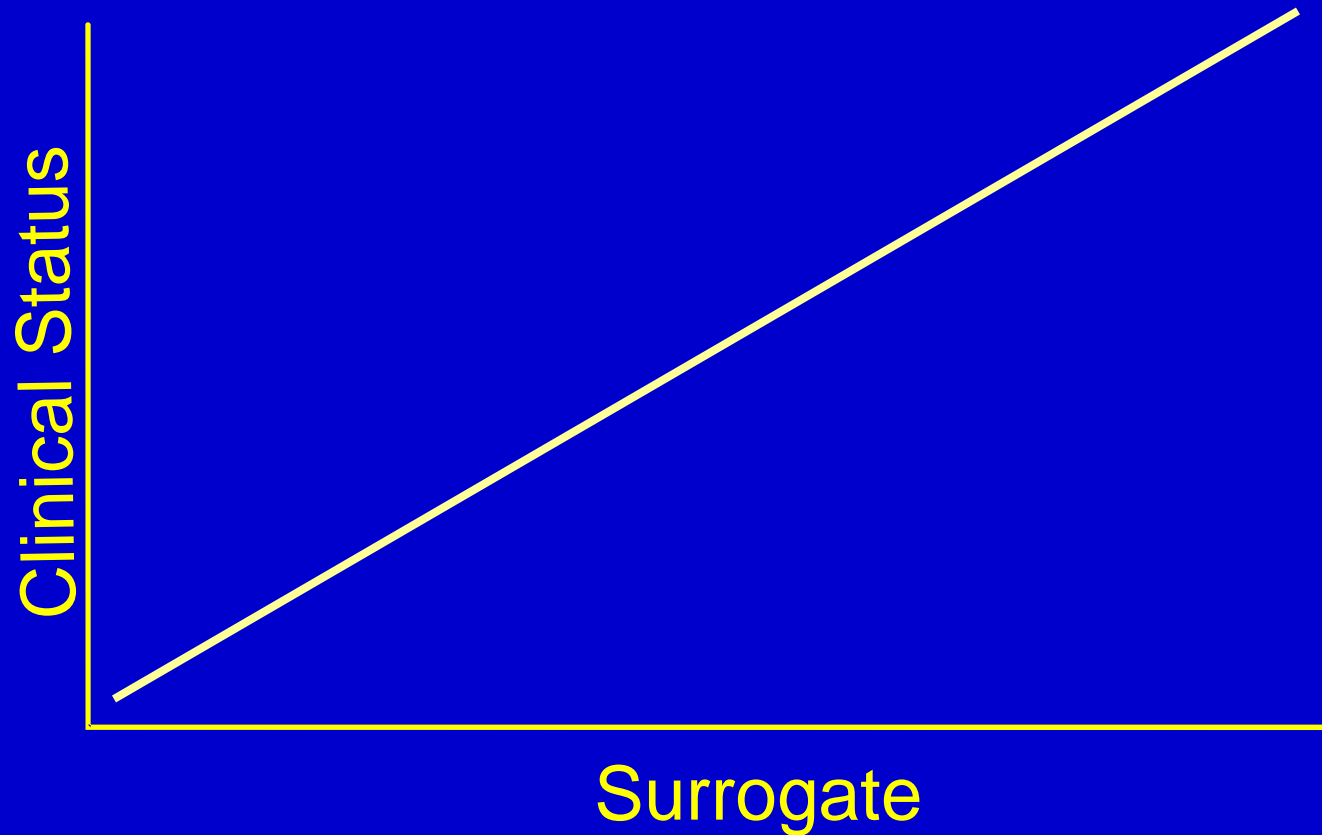
Potential Hazards of Surrogates

- May Mislead – Disparity with clinical outcome
- May result in failed trial for an effective drug
- Nature of risk from being misled depends on how critical are resulting decisions

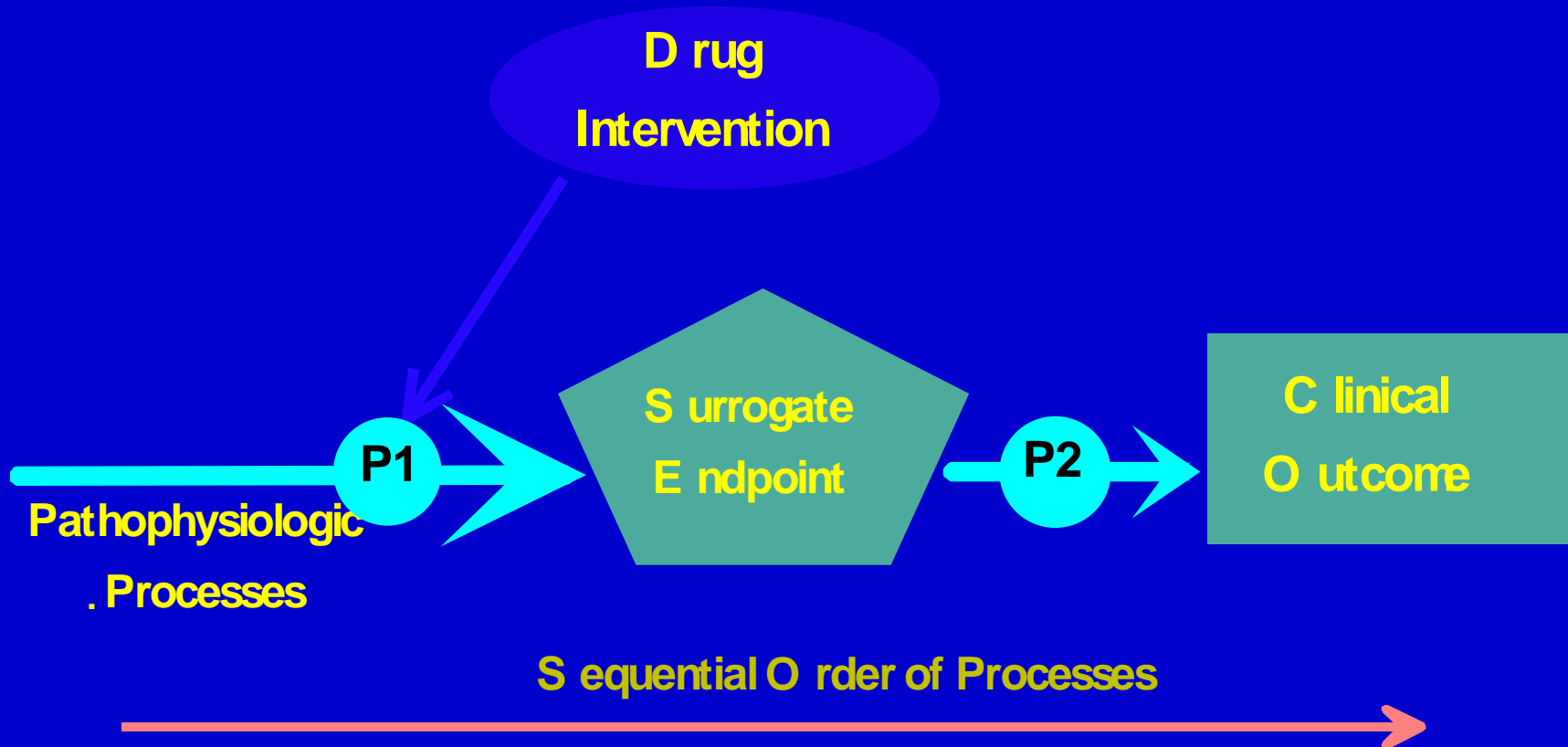
Surrogate Endpoint Characteristics

- Good Surrogate Endpoints:
 - All effects of the intervention on the true clinical endpoint are reflected in the surrogate
 - i.e.: Surrogate should be sensitive to treatment effect
 - The intervention does not have effects on the surrogate without also having clinical effects
 - i.e.: Surrogate should not be oversensitive
- Cause of divergence (i.e., when surrogates fail)
 - Alternate mechanisms of action of the intervention
 - Shape of the surrogate-clinical relationship

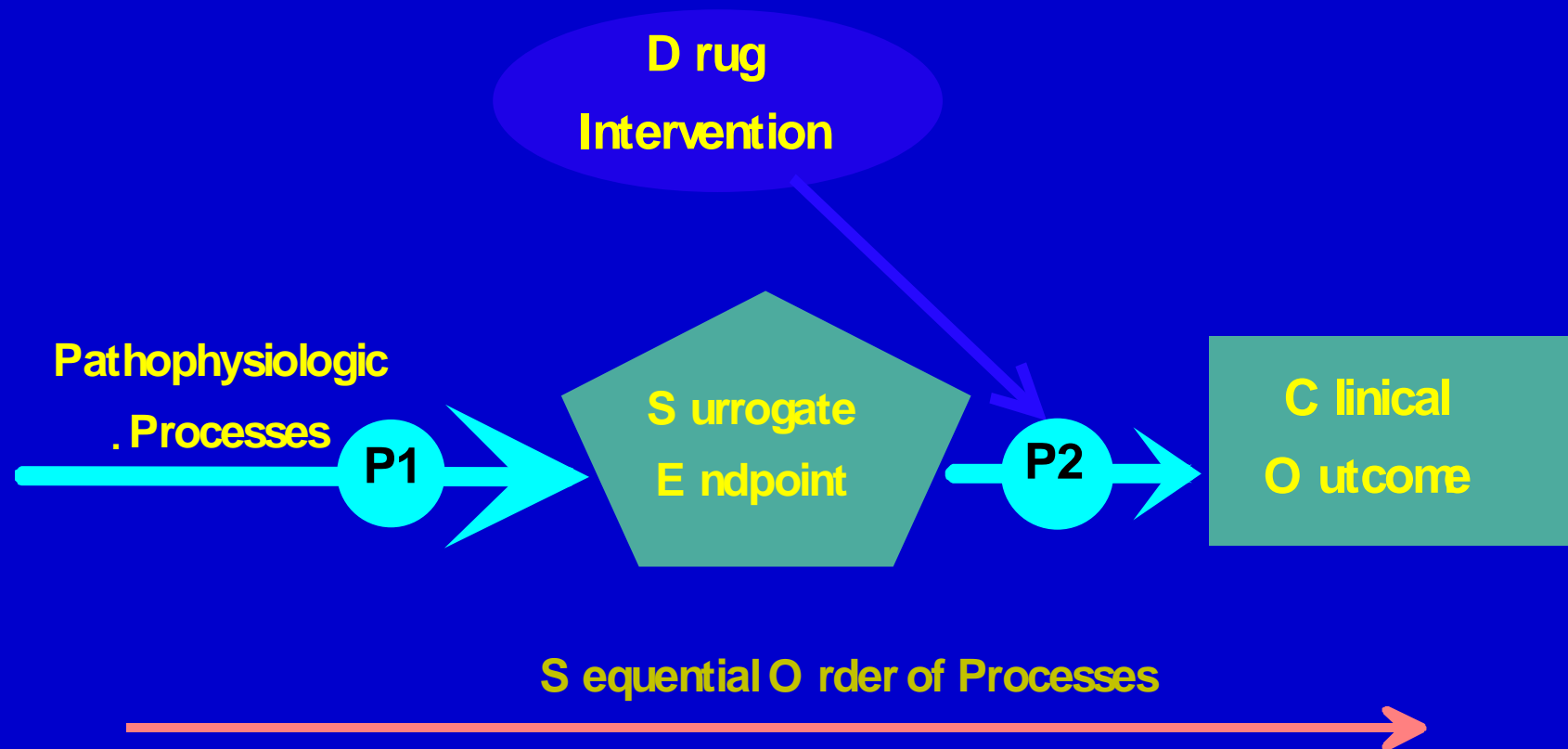
Understanding the Surrogate Measure



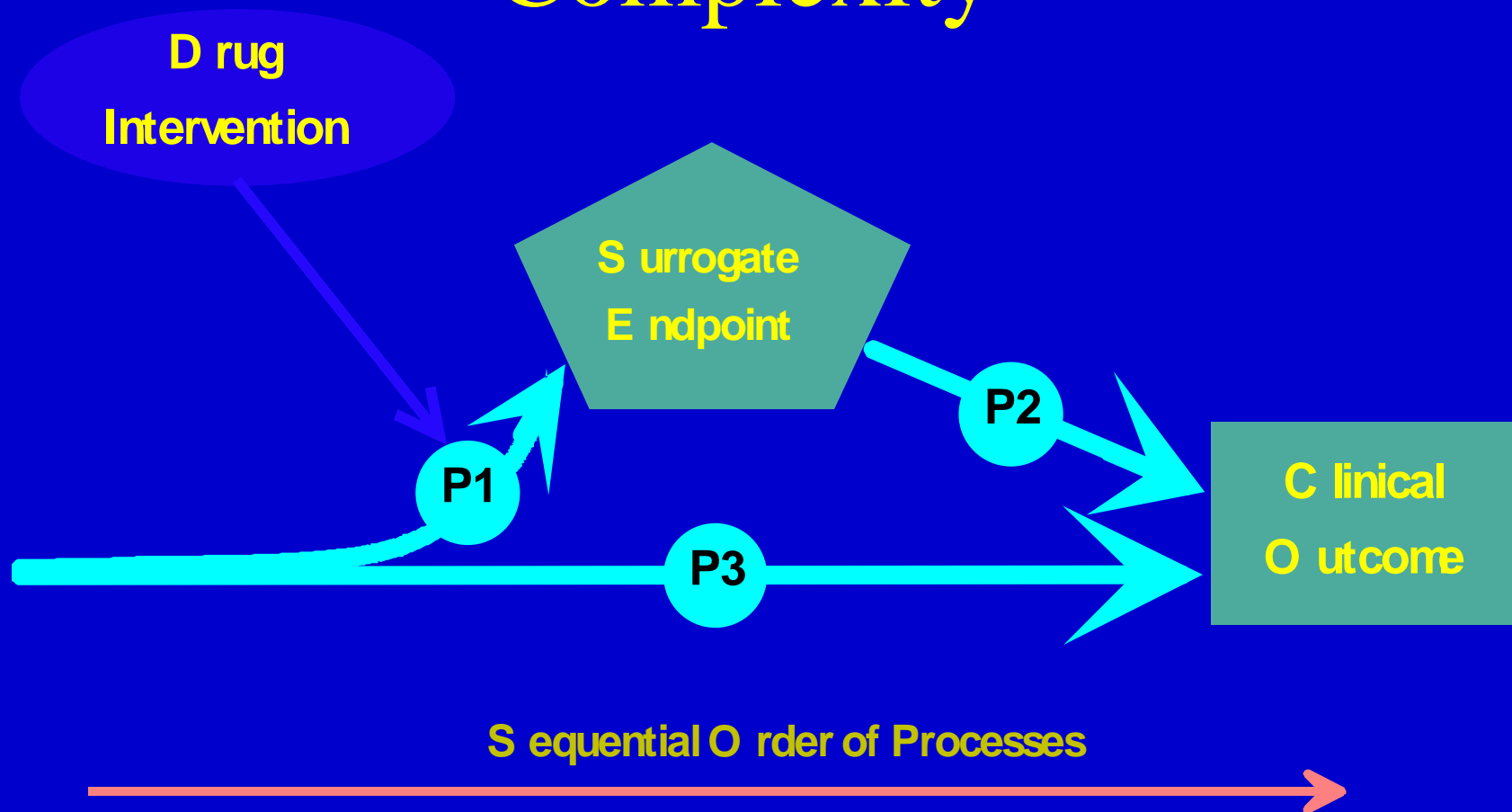
Understanding the Surrogate Measure: Idealized



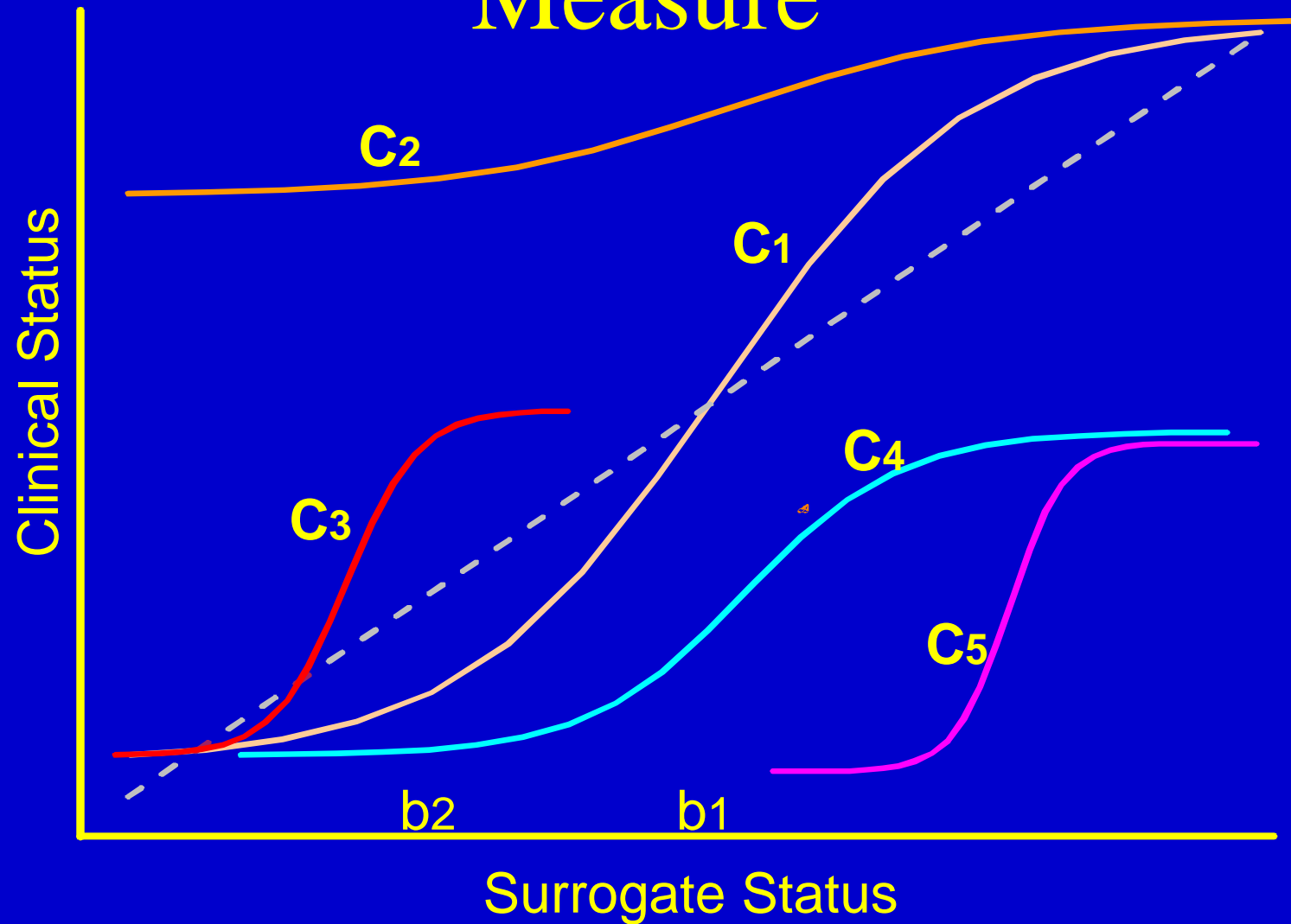
Understanding the Surrogate: Silent Surrogate



Understanding the Surrogate: Complexity



Understanding the Surrogate Measure



Surrogate Endpoints in SMA Trials

- Phase 1
 - Initial evidence of activity or safety
- Phase 2
 - Select dose / regimen/ population
- Phase 3?
 - Secondary endpoint
 - Primary endpoint?
 - » Validity depends on experience
 - » Validity depends on the intervention
 - » Validity may depend on clinical meaningfulness

Regulatory Issues

- Stages of Drug Development
- Endpoint Selection
- Surrogate Endpoints
- Evidence of Effectiveness
- Accelerated Approval

Protocol Design Issues – Phase 3

Evidence of Effectiveness
– 2 Trials vs. 1 Trial

Effectiveness

- FDA usually requires two well-designed clinical trials, each one positive, to establish that a drug is effective.
- A single positive study, especially if there are multiple centers, consistency across centers, a large sample, consistency across study subsets, good rationale, multiple endpoints, and a statistically persuasive result, may be sufficient for marketing approval.

Protocol Design Issues – Phase 3

Evidence of Effectiveness

“... reliance on only a single study will generally be limited to situations in which a trial has demonstrated a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a disease ... and ... a second trial would be practically or ethically impossible.”

(from FDA Guidance on “Providing Clinical Evidence of Effectiveness”)

Regulatory Issues

- Stages of Drug Development
- Endpoint Selection
- Surrogate endpoints
- Evidence of Effectiveness
- Accelerated Approval

Accelerated Approval

- For serious or life-threatening diseases
- May use surrogate endpoint which is reasonably likely to predict clinical benefit
- Requires adequate well-designed trials
- Requires meaningful therapeutic benefit over existing treatments
- Marketing approval includes a requirement of further studies to determine the true clinical benefit

FDA/CBER Contributors

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References

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