Ιδιαιτερότητες στην ανάπτυξη και κλινική μελέτη των ορφανών φαρμάκων

11ο Συνέδριο ΕΕΦ
Αλεξανδρούπολη, 4 Οκτ 2020

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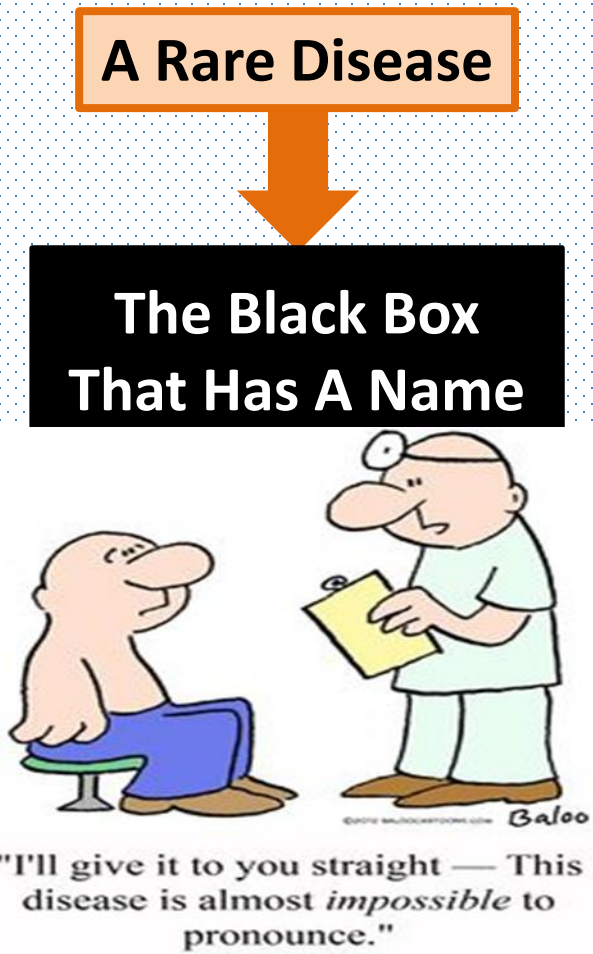
Μερικά στοιχεία για τις σπάνιες νόσους

- Στην Ευρώπη, μία νόσος χαρακτηρίζεται σπάνια όταν εμφανίζεται σε λιγότερο από 1 στους 2.000 ανθρώπους
- Στις ΗΠΑ, όταν προσβάλλει λιγότερα από 200.000 άτομα
- οι περισσότερες από αυτές είναι τόσο σπάνιες, που μπορεί να προσβάλλουν μόλις 1 ή και λιγότερα στα 100.000 άτομα
- τα σπάνια νοσήματα είναι χρόνια, εκφυλιστικά, συχνά απειλητικά για τη ζωή, ενώ κάποιες φορές επιφέρουν χρόνια αναπηρία, επηρεάζοντας έτσι την ποιότητα ζωής των ασθενών
- Σήμερα υπολογίζεται πως υπάρχουν 6-8.000 σπάνιες παθήσεις, με το 70% εξ αυτών προσβάλουν παιδιά
- Στη χώρα μας, σύμφωνα με τα τελευταία διαθέσιμα στατιστικά στοιχεία, ο αριθμός των ασθενών πλησιάζει το 1 εκ
- στην Ευρώπη σχεδόν 30 εκατομμύρια
- Παγκόσμια οι ασθενείς με σπάνιες νόσους προσεγγίζουν τα 300 εκατομμύρια

Lack of Thorough Understanding of Rare Diseases

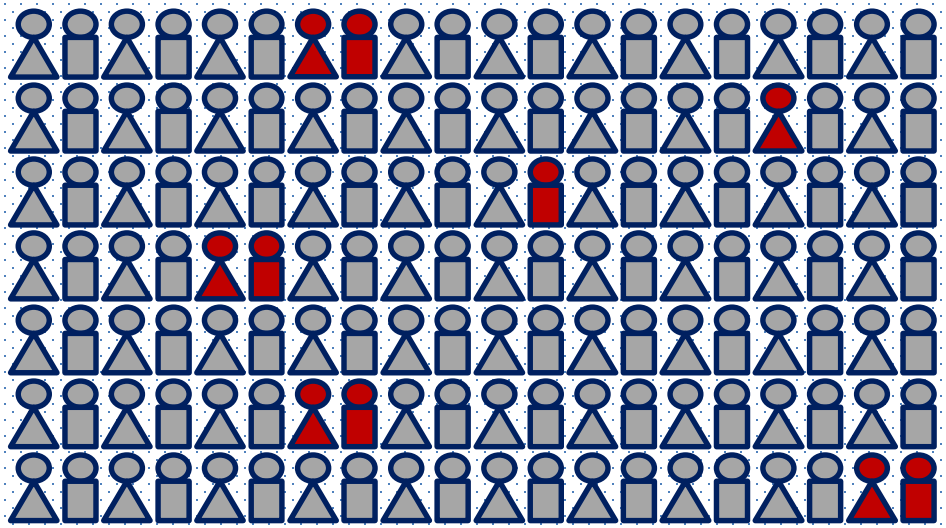
- **Vast majority of rare** diseases
  - **Have**
    - **A name**
    - **Rough description of clinical manifestations**
  - **Don't have**
    - **Thorough understanding of the natural history of the disease**
    - **Understanding of pathogenesis**
    - **Targeted treatments**



The orphan drug discovery ladder

A thorough understanding of the natural history of a disease is the foundation of any treatment development program, *especially for rare diseases!*

Rare Diseases and Challenges

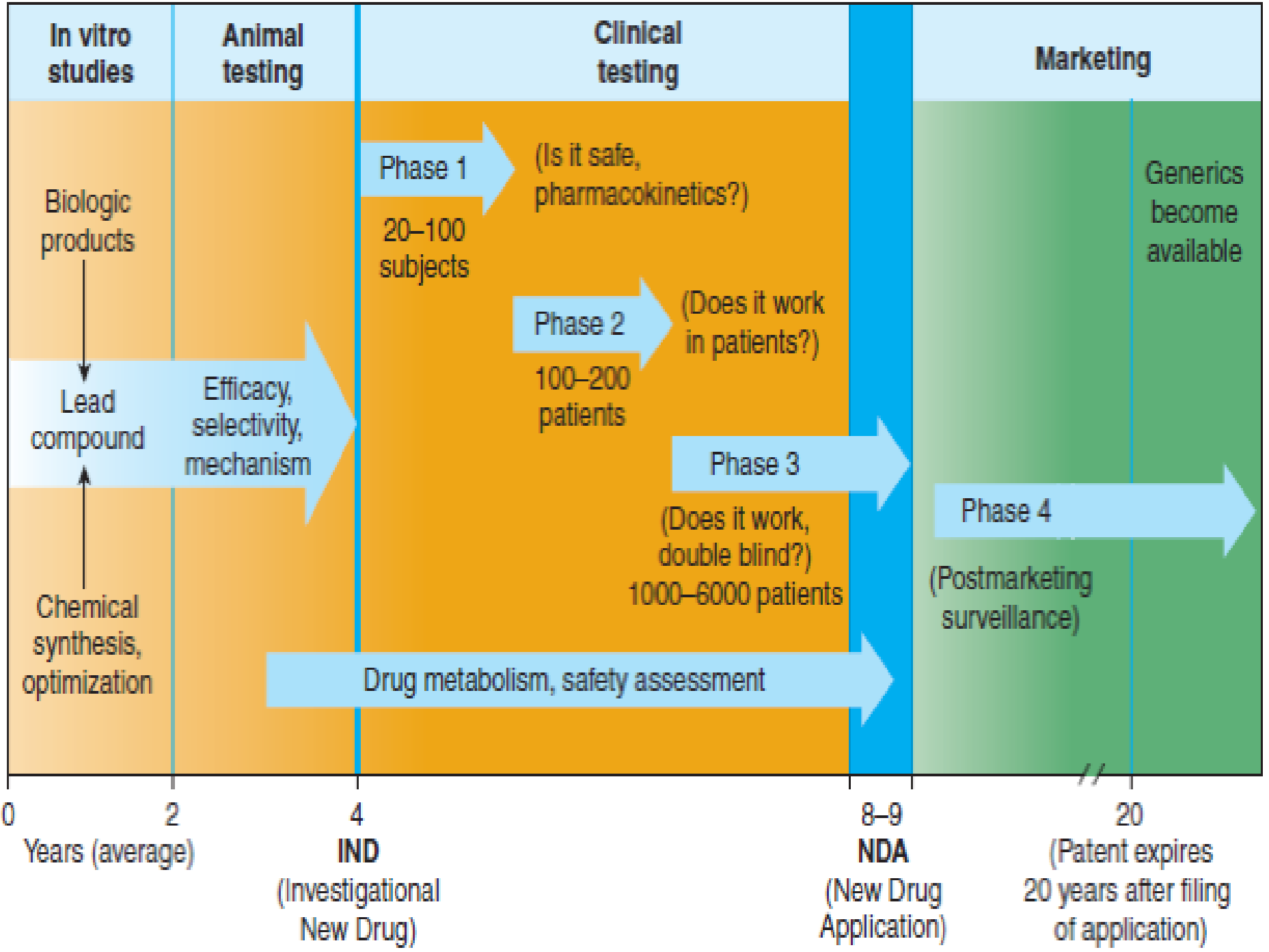


- ~7,000 known rare diseases
- Only a small portion have approved treatments
  - 518 orphan drug approvals (drugs & biologics)*
  - 69 Humanitarian Use Device approvals*

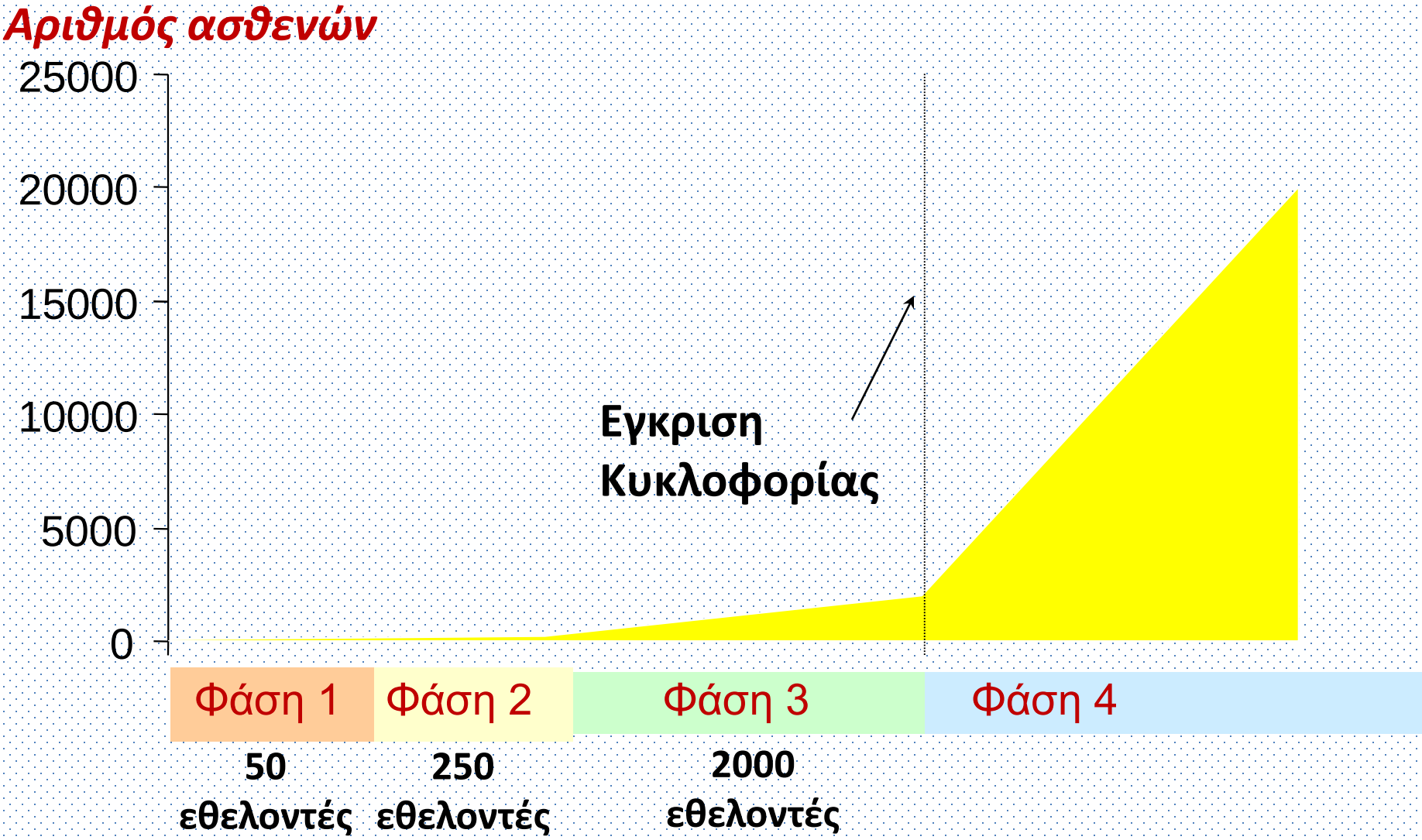
*as of 01/29/2016

ΟΡΦΑΝΑ ΦΑΡΜΑΚΑ (ORPHAN DRUGS)

- **Ορφανό φάρμακο καλείται ένα φάρμακο που προορίζεται για την αντιμετώπιση μιας σπάνιας νόσου**
- **Η έρευνα για τα φάρμακα αυτά συχνά δεν τυγχάνει του απαιτούμενου ενδιαφέροντος από τις φαρμακευτικές εταιρείες, καθώς τα κέρδη από την πώληση ενός ορφανού φαρμάκου μπορεί να μην αντισταθμίσουν τα έξοδα που απαιτούνται για την ανάπτυξη του φαρμάκου αυτού.**
- **Για το λόγο αυτό, στις ΗΠΑ και σε άλλες χώρες έχουν θεσπιστεί ειδικές νομοθετικές ρυθμίσεις που παρέχουν φοροελαφρύνσεις και άλλα κίνητρα στις φαρμακοβιομηχανίες που ασχολούνται με την ανάπτυξη ορφανών φαρμάκων.**


In vitro studies
Animal testing
Clinical testing
Marketing
Biologic products
Lead compound
Chemical synthesis, optimization
Efficacy, selectivity, mechanism
Phase 1
20–100 subjects
(Is it safe, pharmacokinetics?)
Phase 2
100–200 patients
(Does it work in patients?)
Phase 3
(Does it work, double blind?)
1000–6000 patients
Drug metabolism, safety assessment
Generics become available
Phase 4
(Postmarketing surveillance)
0
2
4
8–9
20
Years (average)
IND
(Investigational New Drug)
NDA
(New Drug Application)
(Patent expires 20 years after filing of application)

ΦΑΣΕΙΣ ΚΛΙΝΙΚΩΝ ΜΕΛΕΤΩΝ



The 1983 Orphan Drug Act (ODA)

- Enacted to stimulate product development for rare disease/condition diagnosis, prevention or treatment

- Pre ODA less than 1 drug a year approved for rare diseases in the US

What does Orphan Designation provide?

- **Financial incentives**
  - ✓ tax credits up to 50% of qualified clinical trial costs
  - ✓ waiver of FDA User Fees

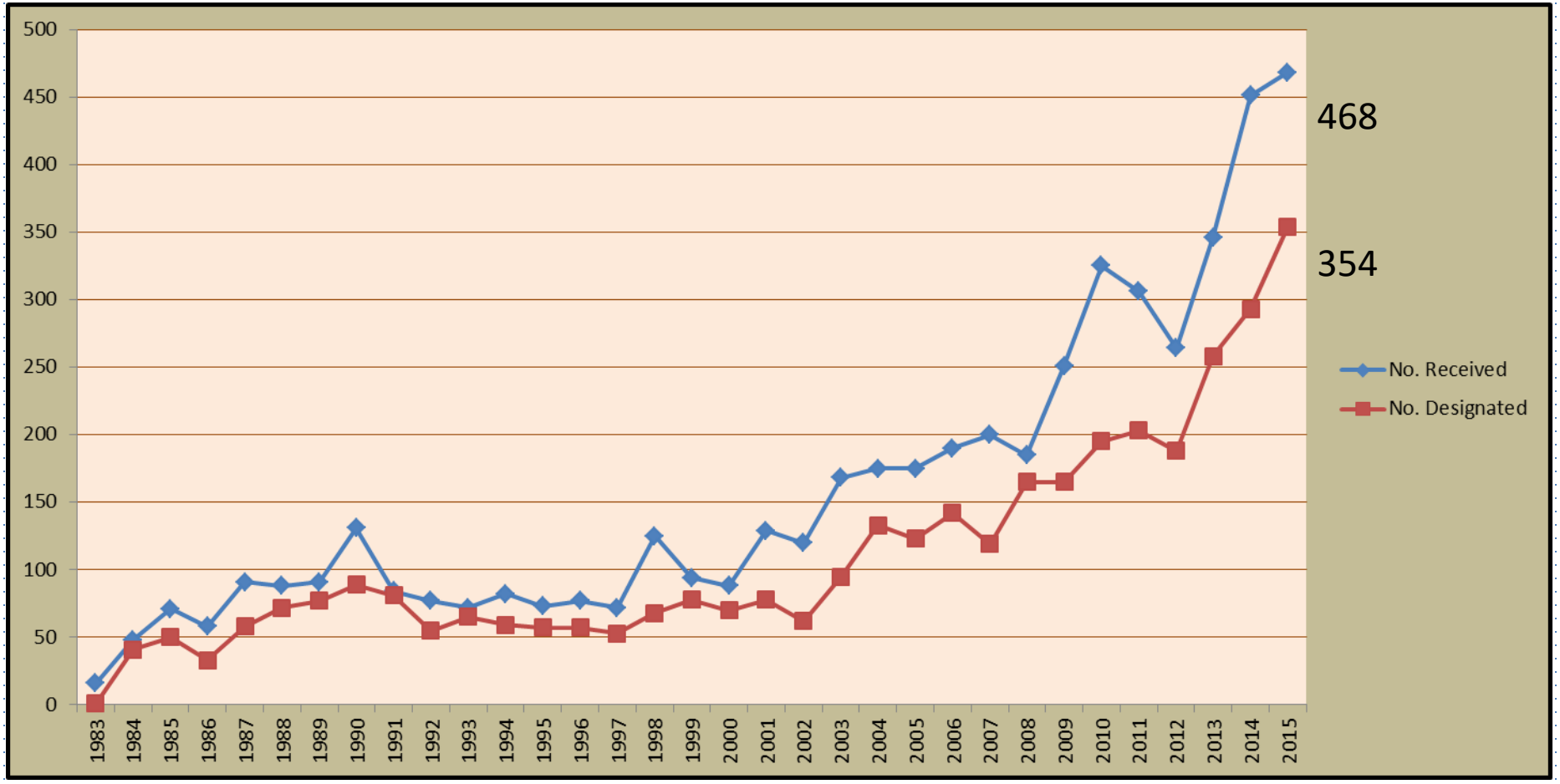
    note: the fee *is* applied if application includes an indication other than the rare disease for which the drug was designated
  - ✓ seven years of marketing exclusivity
- **PREA exemption**

  products with orphan drug designation are exempted from Pediatric Research Equity Act (21 U.S.C. 355c) requirements

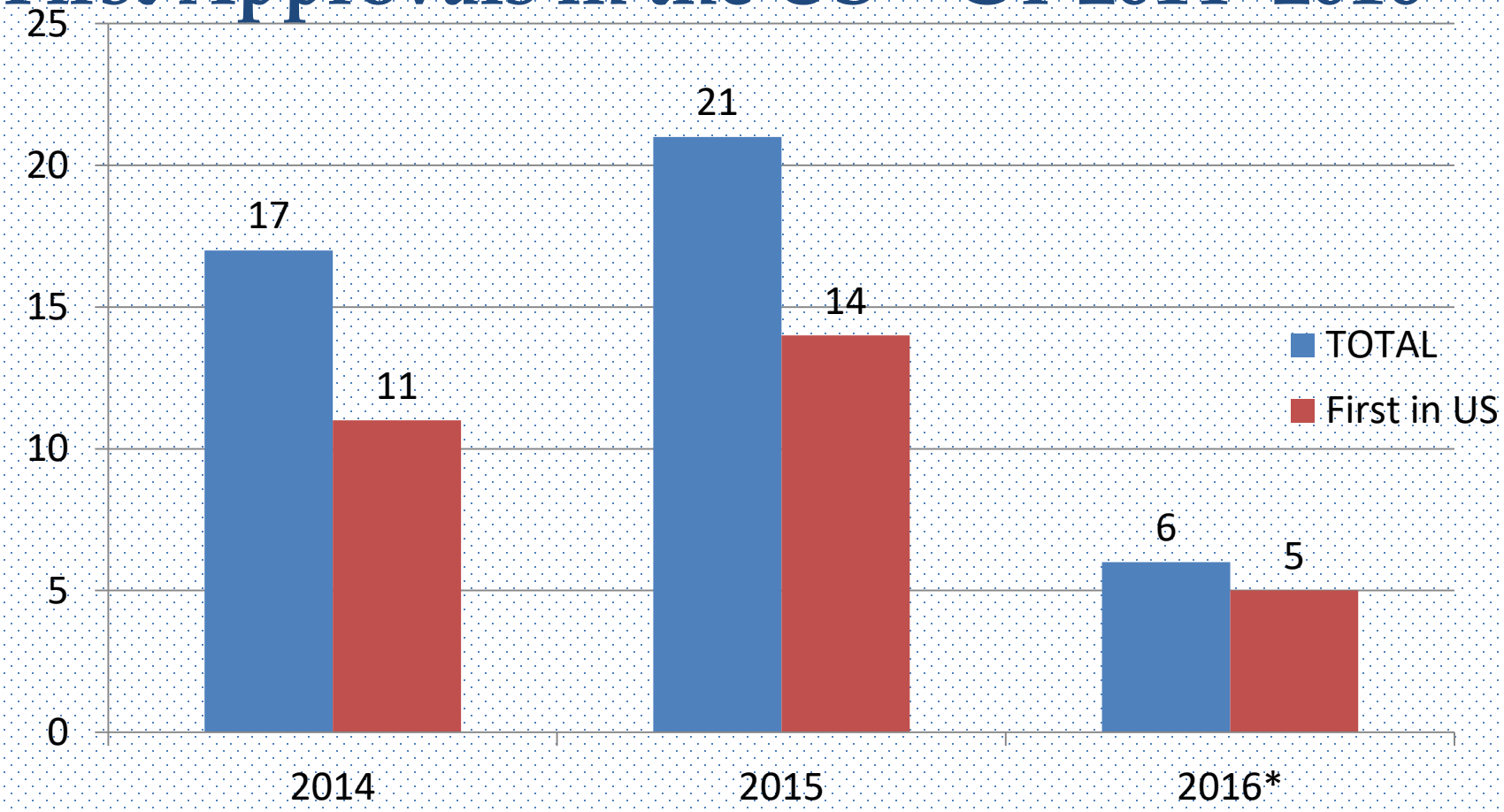
The ODA *does not* alter the statutory standard for drug approval

Patients affected by rare diseases deserve the same level of quality, safety and efficacy

Orphan Drug Designations



CDER Novel *Orphan* New Drug Approvals
First Approvals in the US – CY 2014 -2016*



* as of September 19, 2016

For Rare or Prevalent Disease Approval There Must Be:

- Substantial evidence of effectiveness for treatment of the proposed indication
- Demonstration that the benefits of the drug must outweigh its risks for the patient population for which the drug is indicated
- Adequate manufacturing methods to ensure product identity, strength, quality (and purity)
- Evidence-based drug labeling that adequately guides providers and patients on how to use the drug safely and effectively

Challenges in Rare Disease Drug Development and Regulation (I)

- Populations are small. This may restrict study design and replication
- Phenotypic (disease presentation) diversity adds to complexity, as do genetic subsets
- Natural history often incompletely understood
- Robust endpoints, outcome measures and biomarkers usually lacking

Challenges in Rare Disease Drug Development and Regulation (II)

- Diseases tend to be progressive, serious, life-limiting and life-threatening and lack approved therapy
- Large pediatric representation/ethical considerations
- Lack of precedents for drug development
- Logistical trial issues due to rarity and disease burden

US Regulatory Requirements for Drug Approval

- Demonstration of substantial evidence of effectiveness
  - Substantial evidence of effectiveness requires studies designed well enough "to distinguish the effect of a drug from other influences, such as spontaneous change…, placebo effect, or biased observation"
- "The benefits exceed the risks under the conditions stated in the labeling."
- Usual approval standard is two adequate and well-controlled studies

CHALLENGE

How can drug development programs for low prevalence diseases be expected to meet the same standards as for common diseases?

NDA Regulations 21 CFR 314.105

- While the statutory standards apply to all drugs…the wide range of uses demand **flexibility** in applying the standards

- Thus FDA is **required** to exercise its **scientific judgment** to determine the **kind and quantity of data** and information an applicant is required to provide for a particular drug to meet the statutory standards

FDA Modernization Act 1997 (FDAMA)

- Section 505(d) of the Act was amended to make it clear that the Agency may consider **"data from one adequate and well-controlled clinical investigation and confirmatory evidence"** to constitute substantial evidence **if** FDA determines that such data and evidence are sufficient to establish effectiveness

Application of Flexible Clinical Development Programs

CDER NME approvals 1/1/2008 – 9/25/2015

Flexible Development Programs	Rare Approvals	Non-Rare Approvals
Use of ≥ 1 flexible development approaches*	81% (n=73)	36% (n=64)
Traditional development program**	19% (n=17)	64% (n=113)

*Flexible Development approaches are defined as approval supported by other than 2 AWC Studies and/or use of a novel end point

**Traditional Development defined as ≥2 AWC studies using endpoints with prior precedents

Expediting Rare Diseases Drug Development

- Programs have been developed to target serious diseases with unmet medical needs when a new treatment could provide meaningful clinical benefit

Guidance for Industry Expedited Programs for Serious Conditions – Drugs and Biologics, May 2014

Expediting Rare Diseases Drug Development

- **Fast Track**
  - FDAMA 1997/FDASIA 2012
- **Breakthrough Designation**
  - FD&C Act/FDASIA 2012
- **Priority Review**
  - PDUFA 1992
- **Accelerated Approval**
  - 21CFR314 subpart H, 601 subpart E/FDASIA 2012

Guidance for Industry Expedited Programs for Serious Conditions – Drugs and Biologics, May 2014

Fast Track

Fast track is a *process* to expedite development and review, such as frequent interactions with the review team, ‘rolling review ‘ of a marketing application

- Non-clinical or clinical data may be submitted to qualify
- Ideally apply early in IND phase to get maximum benefit of FDA interactions

Breakthrough Therapy Designation

Breakthrough is a *process to:*

> "…expedite the development and review of such drug …to treat a **serious or life-threatening disease** or condition and **preliminary clinical evidence** indicates that the drug may **demonstrate substantial improvement over existing therapies** on one or more **clinically significant endpoints…**"

FDAISA Section 902, available at: http://www.gpo.gov/fdsys/pkg/BILLS-112s3187enr/pdf/BILLS-112s3187enr.pdf

Priority Review

Priority review is a *process* for review with a User Fee Goal Date of 6 months vs. 10 months

- FDA determines whether the application qualifies
- Applicant may request priority review with an original BLA, NDA, or efficacy supplement; the decision is communicated at filing

Approval Pathways

- Traditional
- Accelerated

Approval Pathways

- **Both** pathways must meet the statutory standards: substantial evidence of effectiveness based on adequate and well-controlled clinical study(ies) and demonstration that the benefits exceed the risks under the labeled conditions
- Accelerated approval expedites new drug availability for *serious unmet need* by relying on a more readily measured **surrogate** or **intermediate clinical endpoint**
- Consider accelerated approval when a lengthy trial would be needed to measure intended clinical benefit of a drug for a serious unmet need

Approval Pathway: The Importance of the Endpoint

- Accelerated Approval Pathway depends on strength of evidence about **ability of the endpoint to predict** effect on irreversible morbidity or mortality (clinical benefit)
- A surrogate or intermediate clinical endpoint is a marker thought to predict clinical benefit, not itself a measure of benefit: lab value, radiographic image, physical sign, etc.

Expedited Clinical Development Programs

CDER NME approvals 2008-2016*

Expedited Programs	Number Rare (n = 109)	Number Non-Rare (n = 193)
Fast Track	54%	22%
Breakthrough Therapy	18%	4%
Priority Review	75%	30%
Accelerated Approval	26%	2%
Used any Expedited Program	86%	35%

*as of September 7, 2016

Developing Drugs for Rare Diseases: Examples

glucarpidase

http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/125327Orig1s000TOC.cfm

rilonacept

http://www.accessdata.fda.gov/drugsatfda_docs/nda/2008/125249s000TOC.cfm

The presented information is derived from FDA reviews posted on Drugs@FDA; consult these links for complete information about the basis for approval

Example 1: Glucarpidase

A carboxypeptidase enzyme indicated for the treatment of toxic plasma methotrexate concentrations (>1 micromole per liter) in patients with delayed methotrexate clearance due to impaired renal function

Glucarpidase: Design Features

- Single-arm, open-label, historically-controlled trial in patients

- Validated pharmacodynamic endpoint in 22 patients: proportion who had rapid and sustained clinically important MTX reduction (to $\leq$1 µmol/L)

Scientific Rationale for Flexible Glucarpidase Design

- Methotrexate in extensive clinical use since 1948; effects, mechanism of action, toxicity, excretion and metabolism well understood
- Well established that 1 µmol/L plasma concentration at 48 hours → severe toxicity not treatable with leucovorin or hemodialysis rescue

Glucarpidase Evidence

From medical officer review BLA 123327 Drugs@FDA

- All patients showed large pharmacodynamic effect: ≥ 97% reduction within 15 minutes
- All patients had > 95% reduction in MTX concentration maintained for up to 8 days
- Efficacy endpoint success dependent on pre-treatment MTX concentration

VORAXAZE
(glucarpidase)
1000 units/vial for intravenous injection

Example 2: Rilonacept

An interleukin-1 inhibitor (IL-1 Trap) indicated for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS), including Familial Cold Autoinflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS) in adults and children 12 and older

Rilonacept: Design Features

- 47 patients in one trial with two parts
  - Part A: 6 week randomized, double-blind, placebo-controlled trial
  - Part B: All participants (blinded) received rilonacept for 9 weeks followed by a 9 week double blind, withdrawal period with randomization to rilonacept or to placebo
- Primary efficacy endpoint: change in disease symptom composite score 0-10 (daily record of fever/chills, rash, eye redness/pain, fatigue, joint pain)

Rilonacept Evidence

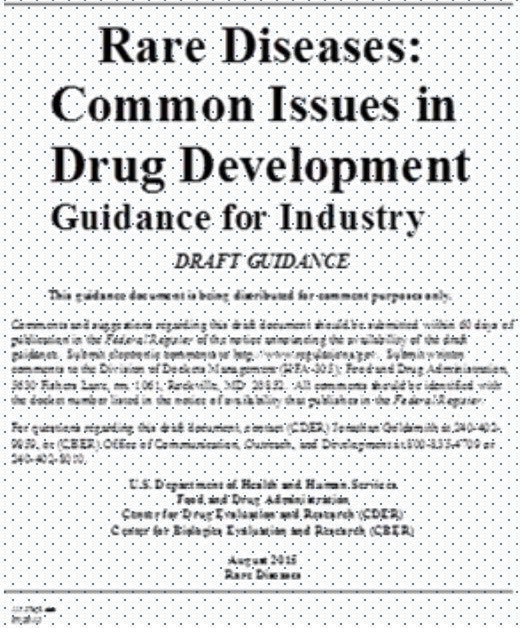
From medical officer review BLA 125249 Drugs@FDA

- Trial Part A: Change in disease activity with rilonacept -2.6 compared to -0.3 for placebo ($p<0.0001$)
- Part B: No change in patients remaining on rilonacept compared to increase from 0.2 to 1.2 for placebo ($p=0.0002$)
- Effect seen within a few days after a single injection
- Consistent results for multiple pre-specified secondary endpoints and serum acute phase reactant levels

Arcalyst® (rilonacept) Injection for Subcutaneous Use

Rare Diseases: Common Issues in Drug Development August 2015 (Draft Guidance)

- To assist sponsors of drug and biological products intended to treat or prevent rare diseases
- To help sponsors conduct more efficient and successful development programs



Rare Diseases: Common Issues in Drug Development

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Jonathan Goldsmith at 240-402-8630, or (CBER) Office of Communication, Outreach, and Development at 800-835-4709 or 240-402-8010.

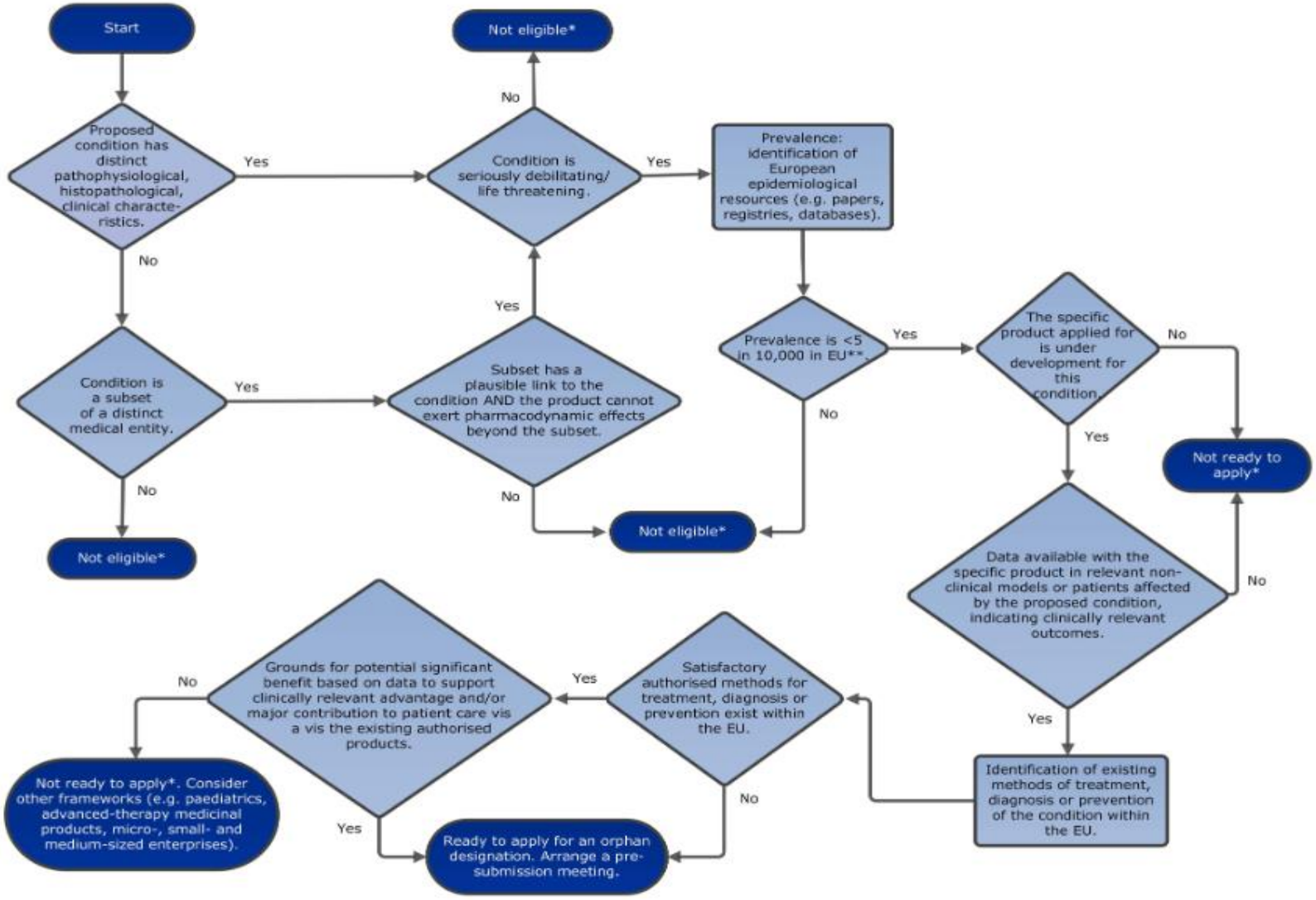
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

August 2015
Rare Diseases

EMA's role in orphan designation

- The Agency is responsible for reviewing applications from sponsors for orphan designation.
- Applications for orphan designation are examined by the EMA's Committee for Orphan Medicinal Products (COMP)
- To qualify for orphan designation, a medicine must meet a number of **criteria**:
  - it must be intended for the treatment, prevention or diagnosis of a disease that is **life-threatening** or **chronically debilitating**;
  - the **prevalence** of the condition in the EU must not be more than 5 in 10,000 or it must be unlikely that marketing of the medicine would generate sufficient returns to justify the investment needed for its development;
  - no satisfactory method of diagnosis, prevention or treatment of the condition concerned can be authorised, or, if such a method exists, the medicine must be of **significant benefit** to those affected by the condition.

Sponsor's guide to an orphan designation



EU/EMA Orphan Drug Incentives

- **A range of incentives is offered in the European Union (EU) to develop medicines that have been granted an orphan designation by the European Commission.**

1.Protocol Assistance

- The Agency provides a form of scientific advice specifically for orphan medicines called **protocol assistance**. This allows sponsors to get answers to their questions on the types of studies needed to demonstrate the medicine's quality, benefits and risks, and information on the significant benefit of the medicine.
- Update: Protocol assistance is available at a **reduced charge** for designated orphan medicines, linked to a fee-reduction scale that depends on the status of the sponsor. There is no restriction on the number of times a sponsor can request protocol assistance.

2. Access to the centralised authorisation procedure

- All designated orphan medicines are assessed for marketing authorisation **centrally** in the European Union.
- This allows companies to make a single application to the EMA, resulting in a single opinion and a single decision from the European Commission, valid in all EU Member States.
- Sponsors may also have access via orphan designation to conditional approval, which is conducted under the centralised procedure.

3. Market exclusivity

- Authorised orphan medicines benefit from 10 **years of protection** from market competition with similar medicines with similar indications once they are approved
- This period of protection is extended by two years for medicines that also have complied with an agreed paediatric investigation plan granted at the time of review of the orphan medicine designation.

4. Fee reductions

- Companies applying for designated orphan medicines pay **reduced fees** for regulatory activities
- This includes reduced fees for protocol assistance, marketing-authorisation applications, inspections before authorisation, applications for changes to marketing authorisations made after approval, and reduced annual fees
- Fee reductions are revised each year in relation to the budget available

5. Additional incentives for SMEs

- Companies classified as **SMEs** benefit from further incentives when developing medicines with orphan designation. These include administrative and procedural assistance from the Agency's SME office and extra fee reductions.

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Commentary

Time for Change? The Why, What and How of Promoting Innovation to Tackle Rare Diseases – Is It Time to Update the EU's Orphan Regulation? And if so, What Should be Changed?

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What Is It about?

Rare diseases is a priority area for EU Community action within the framework for action in the field of public health. A conducive regulatory environment can further support the development of medicines to treat rare diseases. Overall there is a need for joined-up regulatory process coordination. Better integration of regulatory pathways and better integration of regulatory systems, such as scientific tools and methods to generate evidence, would be helpful. This paper explores the successes – and imperfections – of the regulation, and sets out some options for reflection on remedying imperfections within the broader framework of improving patient access.


THANK YOU
GRACIAS
ARIGATO
SHUKURIA
DANKSCHEEN
JUSPAXAR
GOZAIMASHITA
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KOMAPSUMNIDA
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SUKSAMA
EKHMET
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YAQHANYELAY
TINGKI
BÏYAN
SHUKRIA
BOLZÏN
MERCI

Ευχαριστώ...!