Targeted Product Development: Personalized Medicine and Orphan Product Development

David Shoemaker, SVP, R&D
Rho

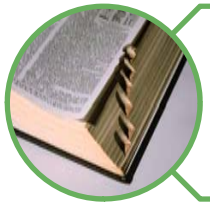
Rho®
Giving flight to research.

Introduction

- Personalized Medicine
- US Orphan Product Development
- EU Orphan Product Development

Rho®
Giving flight to research.

Personalized Medicine



What Does it Mean?

What is the Current Status?

What are the Future Goals?

Personalized Medicines as Orphan Products

Rho®
Giving flight to research.

Personalized Medicine: What Does It Mean?

Tailoring medicines to an individual

A priori identification of therapeutic targets

Companion diagnostic products

FDA Safety and Innovation Act vs. Comparative Effectiveness Research

Personalized Medicine Coalition (PMC)

Personalizedmedicinecoalition.org

Rho®
Giving flight to research.

Companion Diagnostic Products

Herceptin (Genentech/ Dako) - 1998	Selzentry (Pfizer/ Monogram) - 2007	Xalkori (Pfizer/Abbot) – 2011	Zelboraf (Roche/Plexxikon) – 2011
(HER2+) Breast Cancer	HIV Subtype	5 percent of lung cancer patients	50 percent of melanoma patients

> 70 Diagnostic Tests Currently

FDA Guidance 7/2011

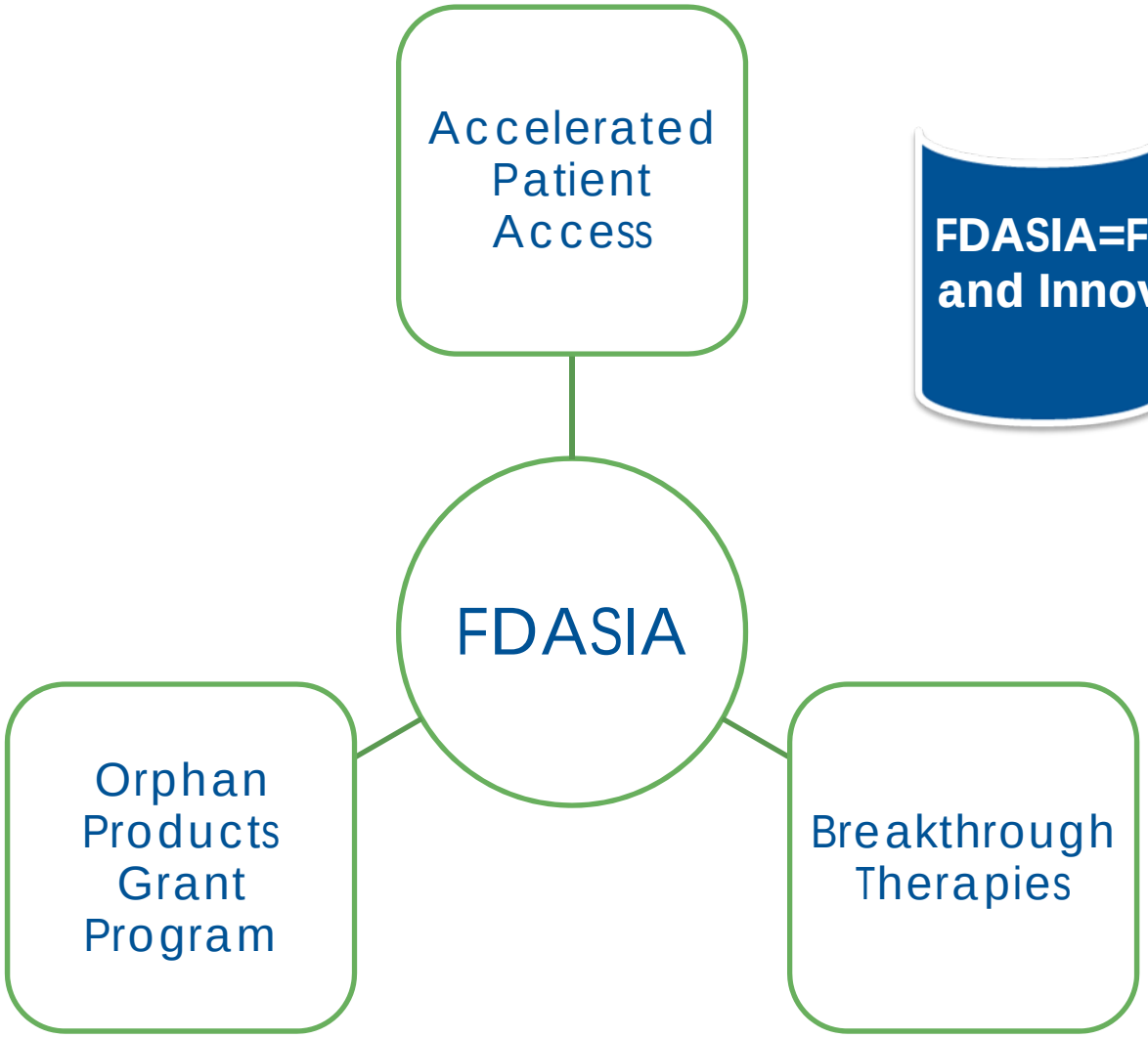
Rho®
Giving flight to research.

Companion Diagnostic Development Problems

- Large Pharma/Small Device Company
- Limiting to Pharma Profits
- Sufficient Understanding of Mechanism of Action
- Drug May Never Reach Market
- How to Divide the Profits?
- Diagnostics Have No Exclusivity

Rho®
Giving flight to research.

Personalized Medicine – Current Status



FDASIA=FDA Safety and Innovation Act

Rho
Giving flight to research.

Comparative Effectiveness Research (CER)

"One size fits all"

Patient Centered Outcomes Research Institute (PCORI)

Objections voiced by PMC and National Organization of Rare Diseases (NORD) is probably not happy

Cost of CER clinical studies more practical with personalized medicines

Rho®
Giving flight to research.

Personalized Medicine: Future Goals

Biomarker Identification

- Surrogate marker validation
- Accelerated approval utilization

Electronic Health Data Systems

- Greater collaboration
- Proteomic and genomic databases

Better Patient Care Through Advanced Science

- Greater chance of successful therapy
- Fewer failed treatment regimens
- Fewer adverse events

Rho®
Giving flight to research.

Personalized Medicines: Orphan Products

An Understanding of Orphan Product Development is More Important that Ever!

Rho®
Giving flight to research.

US Orphan Product Development

Rho
Giving flight to research.

Overview

- US Orphan Drug Act (ODA)
- Recent experience with Orphan Products
- Application Process

Rho
Giving flight to research.

US Orphan Drug Act

Orphan Drug Act (ODA) was signed into law on 4 January 1983

Amended the Federal Food Drug and Cosmetic Act (FD&C Act)

Provides Product Sponsors incentives to develop drugs for rare diseases

Proposed Rule Amending Act

Rho
Giving flight to research.

Orphan Drug Act

Product that treats a rare disease affecting fewer than 200,000 Americans (prevalence of less than 200,000)

Product may treat more than 200,000 persons in the US, but there is no reasonable expectation that the cost of developing and making the product available in the US will be recovered from sales

Rho
Giving flight to research.

Prevalence Versus Incidence

Prevalence: Total number of cases of a disease in a given population at a specific time

Incidence: Number of new cases of a disease during a given interval (frequency of occurrence)

Rho®
Giving flight to research.

The US Orphan Drug Act's Incentives

- Tax incentives
- Research grants for early clinical studies
- Waiver of application user fees
- Additional market exclusivity upon approval
- Potentially faster product approvals
- FDA protocol assistance

Rho®
Giving flight to research.

Tax Credits

Internal Revenue Code Section 45C allows a 50% tax credit for clinical testing expenses after the drug has received Orphan Drug designation, but before the date the FDA approves a market application

Able to carry back 1 year and forward for 20 years

No tax credit can be allowed for testing outside the US unless there is proof of an insufficient testing population exists in the US

Rho
Giving flight to research.

Research Grants

- Administered by FDA Office of Orphan Product Development
- Orphan Designation not required
- Typically $200,000-$350,000 for up to 3 years
- Grant applications solicited through the Request for Applications (RFA) published in the Federal Register
- To date, grants have provided financial support contributing to approval of 45 orphan products

Rho®
Giving flight to research.

Exemption From Application User Fees

Fiscal 2012 PDUFA NDA user fee: $1,841,500

NDA for an orphan product is exempt from this fee unless the application includes an indication for other than a rare disease	No specific exemption from annual marketed product and establishment fees • Possible to request a waiver

Rho
Giving flight to research.

Market Exclusivity

7 Years	• Orphan Drug Act Section 527 provides market exclusivity for a designated orphan drug or biologic
Multiple	• Indications can be developed for a single product, with each covered by a separate Orphan Drug designation and potentially granted a separate market exclusivity term
Not guaranteed	• Clinically superior products will trump exclusivity agreements

Rho®
Giving flight to research.

Faster Product Approvals

Smaller patient populations

Less clinical data

Reviews require less time

Potential Priority Review

Example: Orphan drugs approved in 2004 had an average approval time of 5.6 months

Rho®
Giving flight to research.

FDA Protocol Assistance

Orphan Drug Act Section 525 provides for formal protocol assistance upon sponsor request

Review responsibility resides with the review division

Office of Orphan Product Development acts as sponsor advocates by monitoring protocol review and acting to resolve issues

Access to protocol assistance does not waive IND submission requirements

Rho
Giving flight to research.

Pediatric Drug Development and the Orphan Drug Act Incentives

- Office of Orphan Products Development (OOPD) encourages Sponsors to obtain orphan-drug designation for a drug for pediatric use
- OOPD has determined that pediatric patients constitute a “medically plausible” subset of patient population
- Number of pediatric patients affected by the disease must meet the statutory prevalence limit of 200,000

Rho®
Giving flight to research.

Orphan Product Facts

350	• Orphan products that have received US Orphan Product Designation
45	• # of products from the US Orphan Products Grant Program that have received marketing approval
6,000	• Documented rare diseases • http://rarediseases.info.nih.gov

Common EU and US Orphan Designation Application exists

Rho
Giving flight to research.

Recent Examples of Orphan Drug Approvals

Voraxaze® (Glucarpidase)

- Toxic methotrexate plasma concentrations due to impaired renal function

Jakafi® (Ruxolitinib)

- Intermediate or high-risk myelofibrosis

Erwinaze® (Asparaginase Erwinia chrysanthemi)

- Acute Lymphoblastic Leukemia in patients with hypersensitivity to E. coli-derived asparaginase

Ferriprox® (Deferiprone)

- Transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate

Rho®
Giving flight to research.

Some Challenges

Accrual of patients for studies is difficult

- Patients are few
- Generally patients are geographically dispersed

Challenges to using non-US centers

- Design and methods followed must be the same as those used in the US for the data to be acceptable to the FDA

Rho®
Giving flight to research.

How to Apply for Designation as an Orphan Product

A sponsor shall submit two copies of a completed, dated, and signed request for designation:

- Request statement, name, and address of the sponsor
- A description of the rare disease, the proposed indication(s), and the need for the therapy
- A description of the drug and the scientific rationale for using the drug for the rare disease or condition
- Explanation of clinical superiority for subsequent drugs for the same condition
- Demonstration that subset is medically plausible
- The regulatory and marketing history of the drug
- Documentation that the disease affects fewer than 200,000 people in the United States
- A statement as to whether the sponsor submitting the request is the real party in interest of the development and the intended or actual production and sales of the product

Common EMA/FDA Application Recommended

Rho®
Giving flight to research.

NO SALAMI SLICING ALLOWED!

Rho®
Giving flight to research.

EU Orphan Product Development

(Medicines for Rare Diseases)

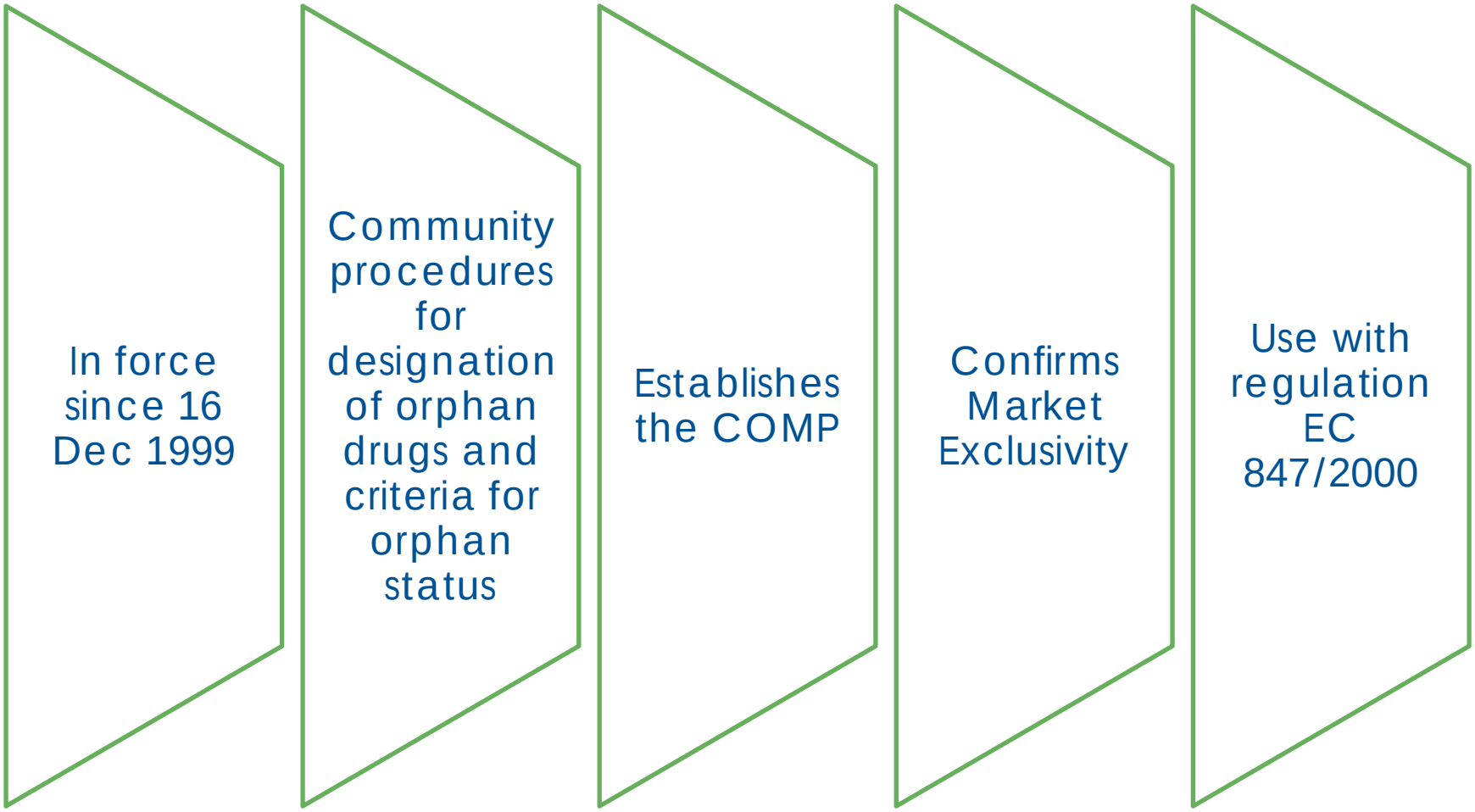
Rho®
Giving flight to research.

Overview

- Regulation EC 141/2000
- Committee for Orphan Medicinal Products (COMP)
- Pre-Submission
- Application and Process
- COMP Opinion
- Appeal?
- Annual Update Report

Rho
Giving flight to research.

Regulation EC 141/2000



Rho
Giving flight to research.

Article 3 - Criteria

A medicinal product shall be designated as an orphan medicinal product if its sponsor can establish:

(a) that it is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than 5 in 10 thousand persons or, without incentives it is unlikely that the marketing of the medicinal product would generate sufficient return to justify the necessary investment;

and

(b) that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question or, if such method exists, that the medicinal product will be of significant benefit to those affected by that condition.

Rho®
Giving flight to research.

COMP

Committee within EMA consisting of one member nominated by each member state, three nominated by the commission representing patient groups (European Organization of Rare Diseases (EURODIS) & three recommended by the EMA. Tasks:

(a) examine applications for the designation of a medicinal product as an orphan medicinal product submitted to it in accordance with Regulation 141/2000;	(b) advise the Commission on the establishment and development of a policy on orphan medicinal products for the EU;	(c) assist the Commission in liaising internationally on matters relating to orphan medicinal products, and in liaising with patient support groups;	(d) assist the Commission in drawing up detailed guidelines.

Rho®
Giving flight to research.

Marketing Exclusivity

The community and member states shall not, for a period of 10 years, accept another application for a MA, or grant a MA or accept an application to extend an existing MA for the same therapeutic indication in respect of a similar medicinal product.

The period may be reduced to six years if at the end of the 5th year the criteria in article 3 of regulation 141/2000 are no longer met

Rho
Giving flight to research.

Pre-Submission 1

- Notify EMA of intent to submit
- Request pre-submission meeting – NO FEE
- Usually via teleconference
- Follow up teleconferences are possible

Rho
Giving flight to research.

Pre-Submission 2

EMA will send invite for the meeting via email

One week before meeting must send:

- Draft of application
- List of questions
- Short power point presentation
- List of participants
- Dial in details (expenses incurred by sponsor)

Rho®
Giving flight to research.

Submission

- Format of application must be in line with guideline ENTR/6283/00 Rev 3
- Application must be signed and dated by sponsor
- Sponsor must be EU defined as “legal or natural person, established in the community”
- Paper = One original
- Electronic = Two (main sections in word format, bibliography in pdf)

Rho
Giving flight to research.

Language

Full application usually in English

If references are not in English usually require a summary in English if possible

The following should be translated in all languages of the EU plus Icelandic and Norwegian (24 languages):

- The name of the product (INN)
- The proposed orphan indication

Rho
Giving flight to research.

Content of EMA Application

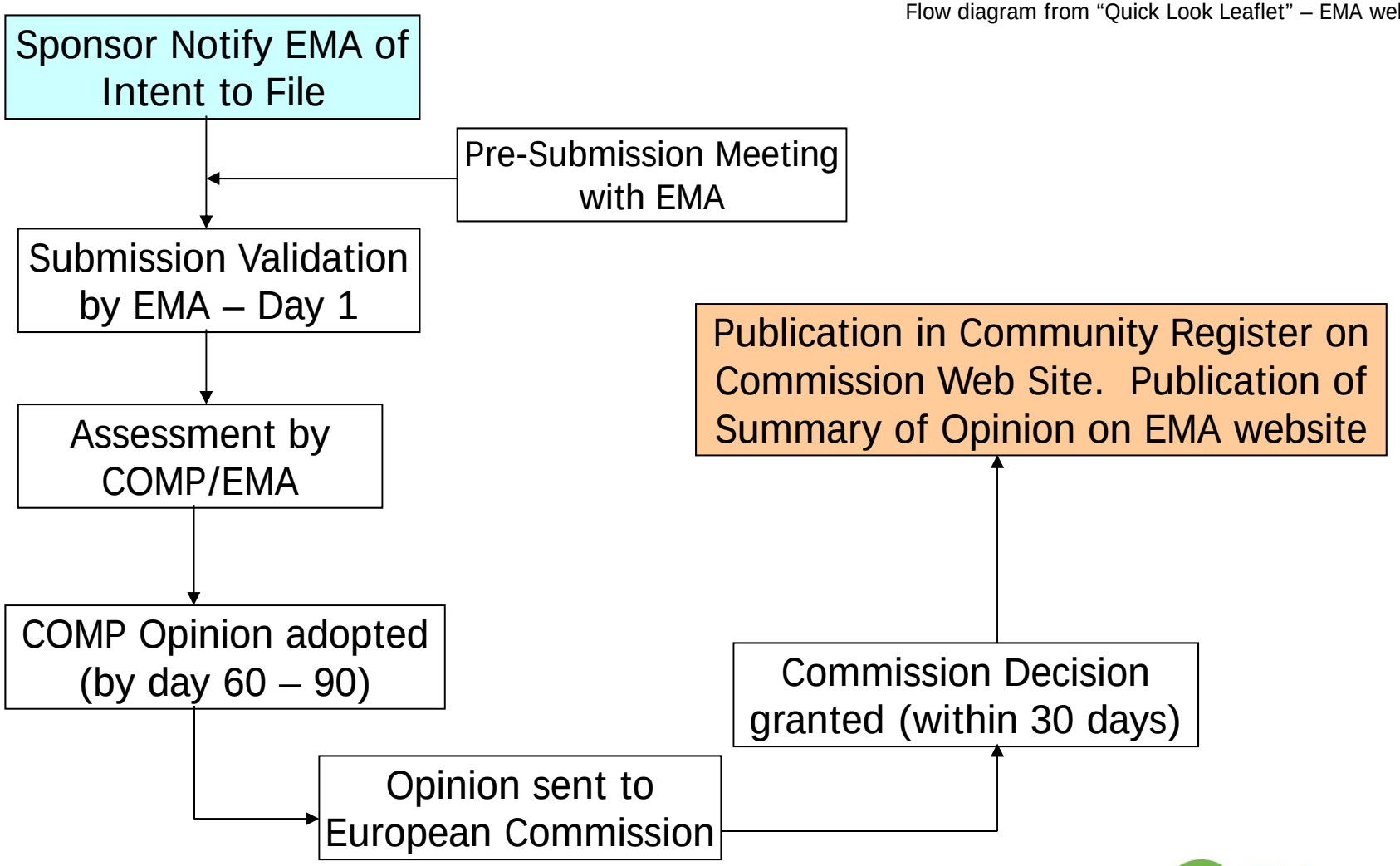
Application Divided into Six Sections:

A	• Description of Condition
B	• Prevalence of condition
C	• Potential for Return of Investment
D	• Other methods of diagnosis, prevention or treatment
E	• Description of the stage of Development
F	• Bibliography

Rho®
Giving flight to research.

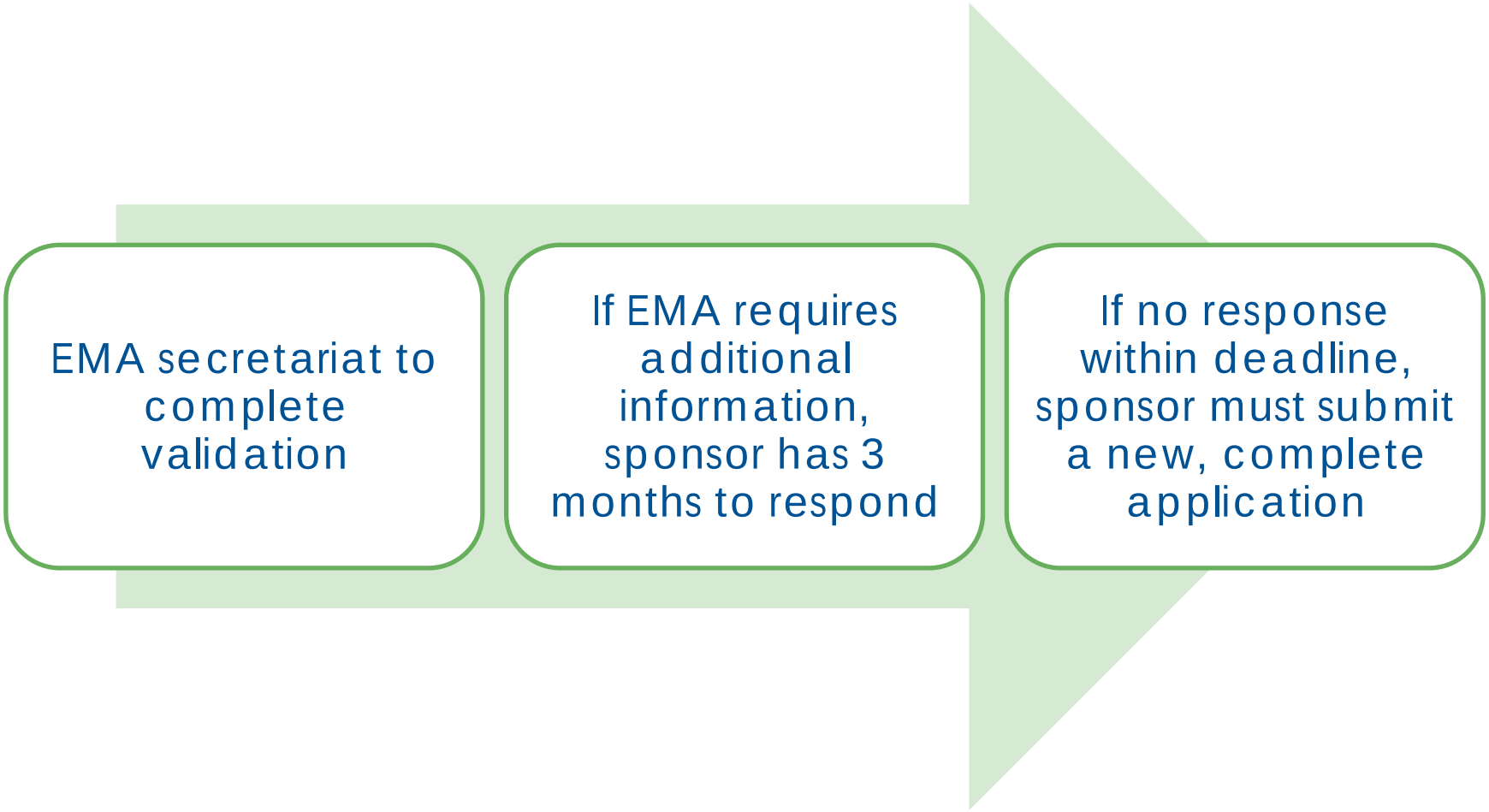
Process Overview

Flow diagram from “Quick Look Leaflet” – EMA website



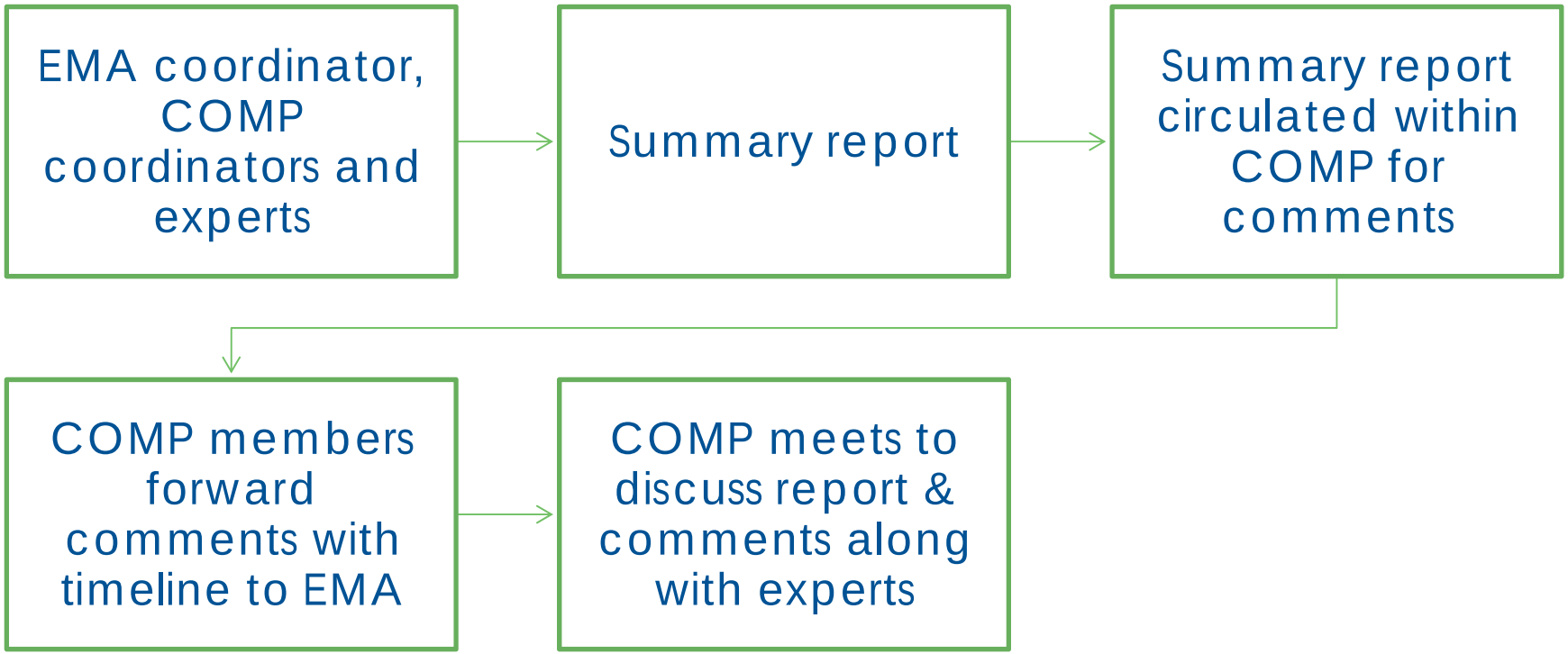
Rho
Giving flight to research.

Validation



Rho
Giving flight to research.

Evaluation



Rho
Giving flight to research.

Opinion 1

Before Day 90, COMP adopts opinion

If negative outcome, sponsor may be invited for an oral explanation

Opinion may be obtained during COMP meeting or by written procedure

If no consensus, then majority of two thirds (at least 22 members) will adopt the opinion

Rho®
Giving flight to research.

Opinion 2

EMA revise summary report taking into account COMP discussions

EMA forwards opinion to Commission and Sponsor

Decision adopted by Commission within 30 days of receipt

If favourable decision, product is entered in the community register of Orphan Medicinal Products

Rho
Giving flight to research.

Appeal

If negative opinion, sponsor can appeal

Must notify of intent to appeal without delay in writing

Must forward detailed grounds for appeal to EMA within 90 days of receipt of opinion

EMA refer grounds for appeal to COMP

Decision is re-evaluated at next available meeting

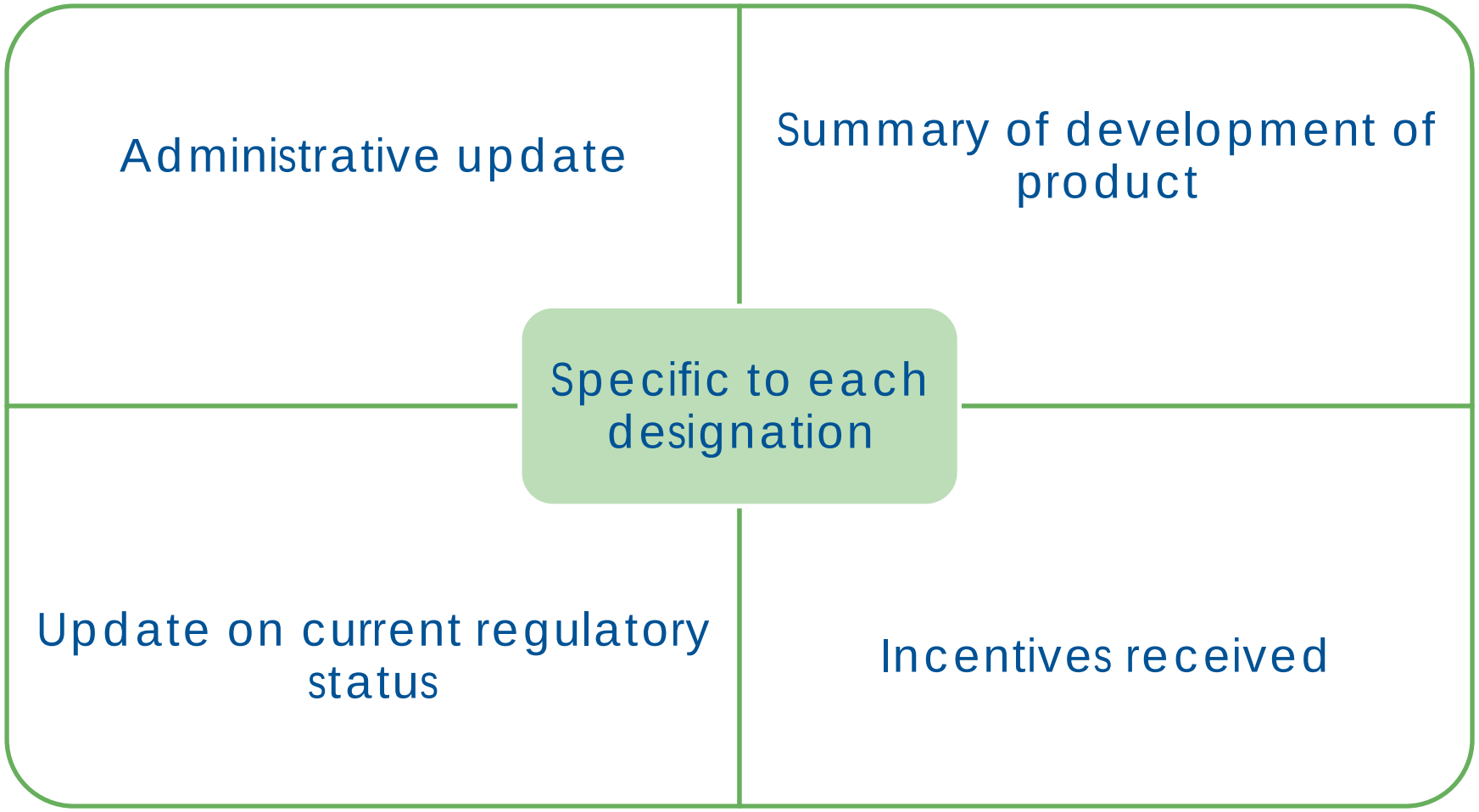
Rho®
Giving flight to research.

Incentives

- ✓Market Exclusivity
- ✓Protocol Assistance – Free
- ✓Centralised Procedure – Mandatory
- ✓Fee Reductions
- ✓EU-Funded Research
- ✓Member State Specific Measures

Rho®
Giving flight to research.

Annual Reports



Rho
Giving flight to research.

Calendar for Annual Reports

Include all information available up to one year after initial Orphan Designation

Submit within two months after anniversary

Continue to submit up until first application for MAA within scope of orphan condition; or specific request by EMA

If development is halted, inform EMA and request removal of product from EU register

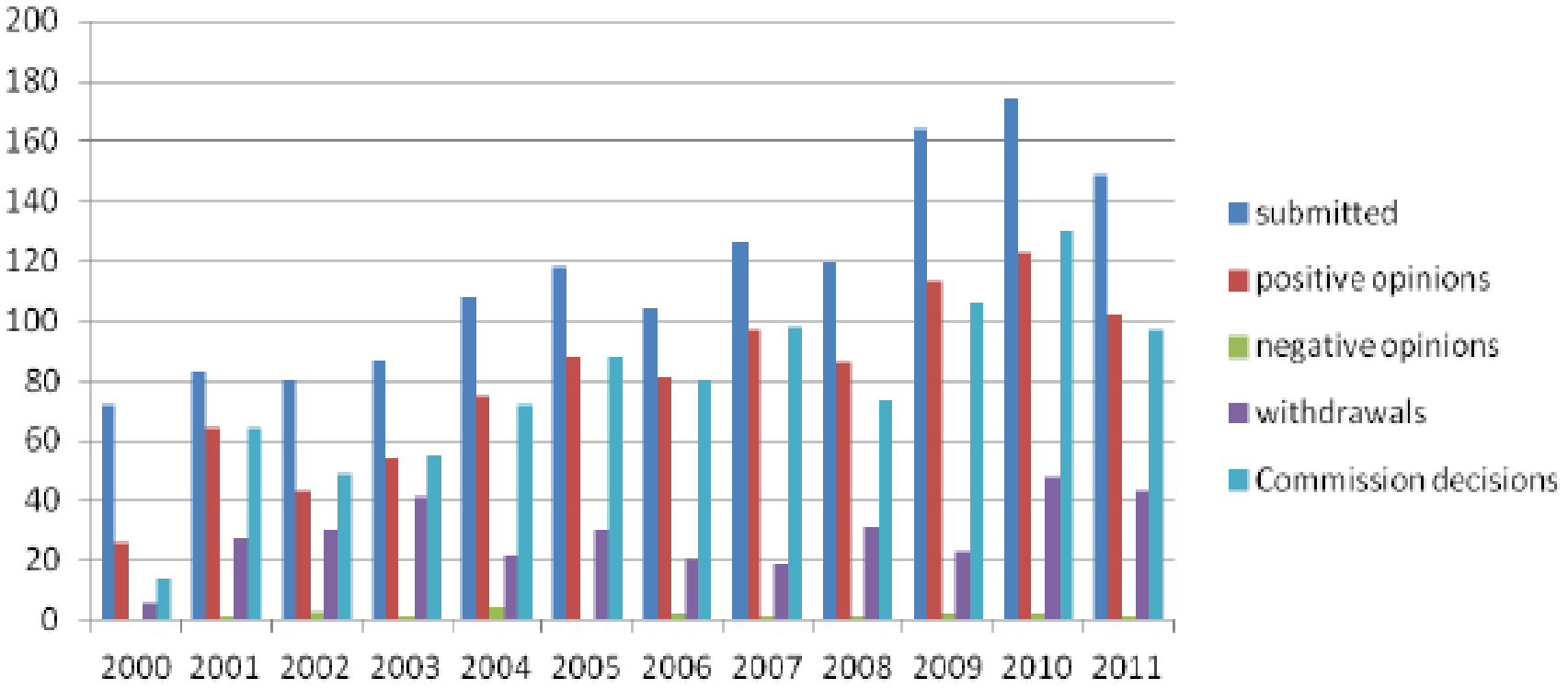
Rho®
Giving flight to research.

Some Statistics

1449	• Applications submitted since 2000 • 166 applications in 2011
1005	• Positive opinions adopted by COMP since 2000 • 111 positive opinions in 2011
68	• Applications receiving marketing authorisation since 2000 • 5 applications were approved in 2011
>50%	• Products with positive opinion are for pediatric conditions

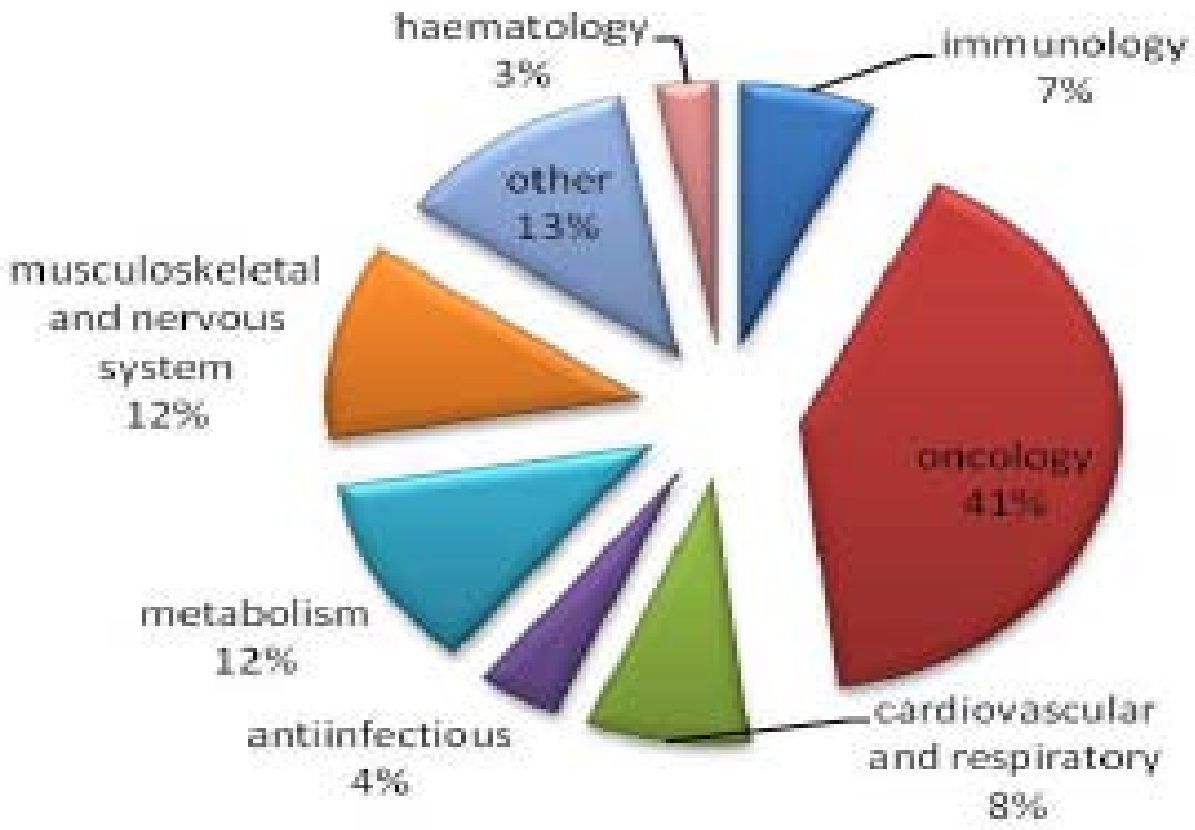
Rho®
Giving flight to research.

Some Statistics



Rho
Giving flight to research.

Some Statistics



Rho
Giving flight to research.

EU and US Collaboration

- Common application form
- Monthly teleconferences between agencies
- Still have separate opinions
- 90% concordance in approvals
- Differences mostly explained by differences in legislation

Rho®
Giving flight to research.

Questions?

Rho®
Giving flight to research.