CLINICAL TRIALS AND RARE DISEASES

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DISCLOSURE

- I RECEIVE UNRESTRICTED GRANTS AND TRAVEL HONORARIA FROM ACTELION, BIOMARIN, GENZYME PTC, SHIRE, SYNAGEVA.

- I HAVE NO ECONOMICAL OR STOCK MARKET INTERESTS ON ANY RARE DISEASE PRODUCT

CLINICAL TRIALS

- Clinical trials are research studies that test how well new medical approaches work in people. Each study answers scientific questions and tries to find better ways to prevent, screen for, diagnose, or treat a disease. Clinical trials may also compare a new treatment to a treatment that is already available.

- 50% of Rare Diseases affect children
- 95% of Rare Diseases have no single approved drug treatment
- 35% of the deaths in the first year of life are due to rare diseases
- 30% of children with a Rare Disease will not live up to the 5th year of age

BETTER MEDICINE FOR CHILDREN

- 21% of Europeans are children
- Children are not just small adults
- > 50% of medicines used for children were never or incompletely studied in this population!!! (unlicensed or off label use)

- Situation prior the pediatric legislation
  - Absence of age – and development-related research and lack of suitable products
  - Recurrent off-labe use
  - Economical/ ethical factors
  - Experience prevails evidence

THE EU PAEDIATRIC DRUG REGULATION

- 26 January 2007: European Regulation (EC) No 1901/ 2006
  - (Paediatric Drug Regulation) has the objective to improve the health of European children by facilitating the development, accessibility and safe use of new drugs for children aged 0 to 17 years, through clinical studies
- 2009: The first marketing authorization based on a completed PIP
- 2011: the first Pediatrics Use Marketing Authorisation (PUMA)
- 2013: the first Commission Report
- 2014: Review of the Commission Guidelines
- 2017: the 2nd Commission Report

European Commission

The 2013 report - conclusions

- Promising signs, but further experience needed:
  - **More than 600 Paediatric Investigation Plans in 2013 (now more than 800)**
  - **Around 350-400 clinical trials per year including children (0-18 years)**
  - **Proportion of clinical trials including children has increased, to approximately 10%**
  - **Increase in the PIP studies of neonates and infants ; currently, 30% of the paediatric investigation plans include studies with neonates**
  - **Enpr-EMA - Network of paediatric research networks has been created by the EMA (18 research networks)**
  - **Mixed picture in the field of paediatric oncology**

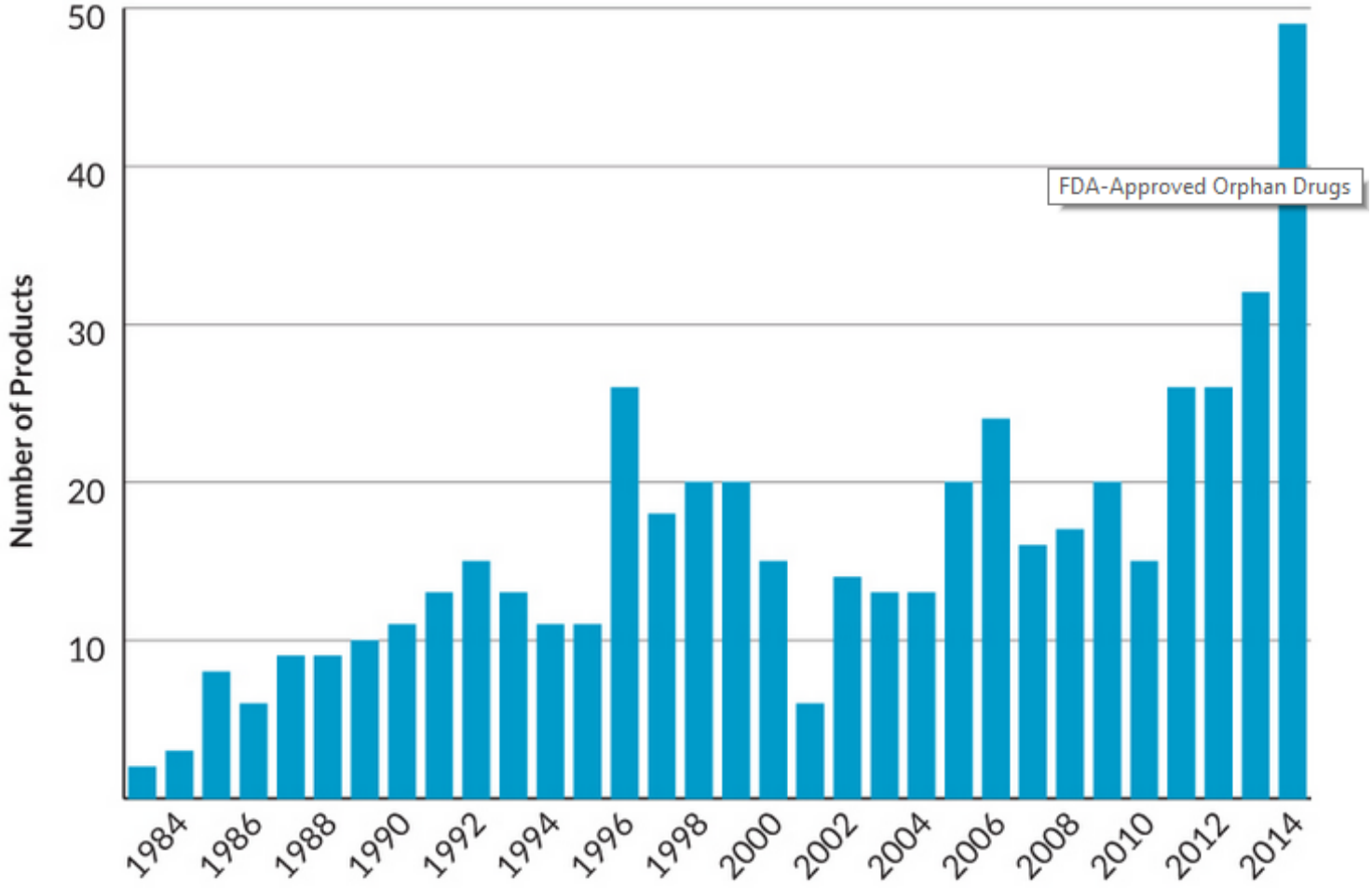
Health and Food Safety

European Commission

Paediatric clinical trials

Number of subjects	2006	2007	2008	2009	2010	2011	2012	2013	2014
Preterm newborns	0	0	0	327	82	2522	1552	3724	4331
Newborns	0	98	5	184	169	1348	2283	1496	1948
Infants and toddlers	530	119	20	54715	2212	13313	62224	13414	39615
Children	2683	706	270	5783	2721	21654	30826	23230	62979
Adolescents	435	36458	285	5801	4831	20206	22680	17300	42353
Sum of above	3648	37381	580	66810	10015	59043	119565	59164	151226
Reference: number of paediatric trials	**340**	**362**	**342**	**406**	**392**	**372**	**401**	**337**	**432**

NUMBER OF APPROVED ORPHAN DRUG BY YEAR



Data Source: FDA Orange Book
Source: FDA Law Blog

EU ORPHAN DESIGNATION BY THERAPEUTIC AREA

	2000-2010	2011	2012	2013
	EMA/279601/ 2010	*2012 Report on the State of the Art of Rare Disease Activities in Europe*	*2013 Report on the State of the Art of Rare Disease Activities in Europe*	*2014 Report on the State of the Art of Rare Disease Activities in Europe*
Applications received	1113	166	197	201
Applications which received positive opinions on orphan designations	760	111	139	136
Number of application which received marketing authorisation per year	/	5	10	7
Total number of application which received marketing authorisation	63	68	78	85
Oncology	45,2%	41%	39&	40%
Musculoskeletal and nervous system	12,4%	12%	11%	8%
Immunology	9,7%	7%	6%	3%
Metabolism	9,7%	12%	10%	20%
Cardiovascular and respiratory	9,4	8	9	13
Anti-infectious	3,3	4	6	/
haematology	/	3	7	9
Other	10,3	13	12	7

KEY CHALLENGES FOR STUDY DESIGN AND STATISTICAL ANALYSIS OF SMALL HETEROGENEOUS POPULATIONS

CT FOR RARE DISEASES INVOLVE VERY SMALL POPULATION OF PATIENTS. This implies the use of non homogenous groups for age and phenotypes which will be finally may negatively impact the understanding of the results of the trial itself.

THE LARGE VARIATION IN SEVERITY, STAGE, IRREVERSIBILITY AND AGE leads to a **very large range at baseline** for many measures of efficacy, making it hard to detect clinical important efficacy changes

THE **LACK OF QUANTITATIVE NATURAL HISTORY INFORMATION** and difficulty using this information in analyzing clinical trial data,

KEY CHALLENGES FOR STUDY DESIGN AND STATISTICAL ANALYSIS OF SMALL HETEROGENEOUS POPULATIONS

The **complexity of disease multitorgan manifestations requires more than one clinical endpoint for one domain** to assess an effective treatment,

the interpretation or calibration of the relative magnitude and **clinical meaningfulness of endpoint changes** in terms of established minimal important clinical differences to understand what effective really means,

the **accurate analysis of safety data** due to the fragmented approach to safety reporting that will miss lower frequency safety events in small populations.

WHAT DO WE NEED TO IMPROVE CLINICAL TRIALS IN RARE DISEASES

BETTER CONTROLLED STUDY DESIGNS ALLOW BETTER ANALYSES: The traditional randomized controlled studies are not suited for small populations. It is difficult to create comparable groups and to adequately assess change between variable groups. Controlled rigorous designs that allow within-patient comparisons and treat all subjects will assess therapies more accurately.

IMPROVED NATURAL HISTORY STUDY DESIGNS AND ANALYSES would allow more efficient interpretation of clinical studies: The lack of natural history information provides little insight regarding how to choose endpoints or how to design and power a clinical study. An improved paradigm for conducting a cost- efficient natural history study and to allow the integrating natural history observational data into clinical trial analyses can enhance the data set value.

BETTER STATISTICAL ANALYSES WILL DEPEND ON MORE EFFICIENT AND EFFECTIVE ENDPOINT DESIGNS FOR EVALUATION OF THE BROADER BASIS FOR CLINICAL EFFICACY: Single clinical endpoints do not adequately cover the breadth of disease. Novel approaches to combine independent multi-domain analysis to better assess efficacy are necessary.

Key challenges for study design and statistical analysis of small heterogeneous populations

INTERPRETATION AND COMBINATION OF CLINICALLY IMPORTANT CHANGES IN ENDPOINTS REQUIRES BETTER USE OF MINIMALLY IMPORTANT DIFFERENCES (MID'S) OR RESPONDER ANALYSES: A systematic approach using natural history and comparable disease information should be developed to an efficient method for translating MID's from common diseases to rare diseases. The MID's may allow the interpretable combination analysis of clinically important changes in multiple domains.

SAFETY EVALUATION IN SMALL POPULATION STUDIES NEEDS TO INTEGRATE KNOWN ADVERSE PHYSIOLOGIES IN DATA COLLECTION AND ANALYSIS: Adverse events are the key tools for safety assessment. Individual symptoms often obscures and fails to capture underlying pathophysiology. In contrast with big numbers study, A small study cannot readily detect recurrent patterns of adverse event responses based existing methods of safety reporting and analysis which could be dramatically improved.

AIMS OF A COORDINATED CLINICAL TRIAL SETTING INSIDE THE ERN (TECHNICAL POINTS)

Development of cost-efficient novel, rigorous controlled STUDY DESIGNS and relevant analyses that are effective in studying efficacy in heterogeneous, small populations

Design of NATURAL HISTORY STUDIES to capture clinical information more cost-efficiently and to help inform on the optimal approach to treatment development

Establishment and use of strategies to more efficiently analyze a broader array of CLINICAL ENDPOINTS for a more comprehensive set of affected clinical domains, set up strategies to identify VALUABLE BIOMARKERS.

Development and evaluation of novel more efficient TOOLS FOR SAFETY evaluation using adverse physiology-related groups and allow the integration of known medical physiology into analyses of safety information to detect recurrent adverse physiologies.

AIMS OF A COORDINATED CLINICAL TRIAL SETTING INSIDE THE ERN (POLITICAL POINTS)

To collaborate with Regulatory Agencies (EMA) and EU (i.e. reg. EU 536/2014,directive 2001/83/EC etc.) to determine a guideline for the setting of Clinical Trial in Rare Diseases.

To collaborate to identify a policy for the scientific independency of the Clinical Trial setting and favour a cosponsorship of Academia in the field of Rare dDseases.

To favour interaction with Member States to uniform the Clinical Trial policy for Rare Diseases

To collaborate with Member States Agencies to speed up the availability of products to patients affected by Rare Diseases.

To collaborate with Family Association to empower patients in participating and counselling the Clinical Trial.

To collaborate with pharmaceutical industries and networks to achieve better results.

Thanks for your attention

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