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Rare Diseases 360°
Collaborative Strategies to leave no-one behind

9th European Conference on Rare Diseases & Orphan Products
10-12 May 2018 Vienna

Abandoned OMPs

Viviana Giannuzzi

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R&D of medicines for RDs

- Lower knowledge on disease pathophysiology
- Preclinical models not always available
- Geographic dispersion
- Few clinical experts – reference hospitals
- Few patients' epidemiological data
- Small simple size

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R&D of medicines for RDs

Children are 'orphan' 2 times..

Rare diseases often affect children:

- Many rare diseases are genetic
- Start early in life
- Affect growth, sexual and CNS maturation during the developmental process

Few specific information available because:

- Ethical issues (consent, assent, minimise pain and distress etc)
- Methodological issues (small volumes, micro-volumes, placebo, etc)
- Few resources invested
- Use of medicines not specifically tested (off-label, unlicensed)

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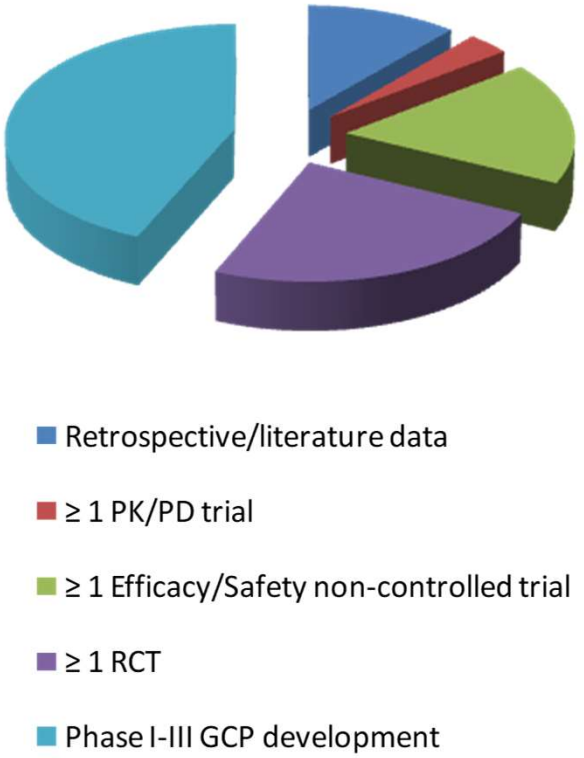
Evidence supporting the Marketing Authorisation of OMPs

Many MAs of OMPs has been granted without a phase I-III scheme

The MA of the following drugs was granted on the basis of bibliographic/retrospective data:

1. Carglumic acid
2. Betaine anhydrous
3. Mitotane
4. Caffeine citrate
5. Hydroxycarbamide
6. Thiotepa
7. Zinc

The maximum level of evidence supporting the MA of ODs approved in Europe



Quantum of Effectiveness Evidence in FDA's Approval of Orphan Drugs

Cataloguing FDA's Flexibility in Regulating Therapies for Persons with Rare Disorders

by Frank J. Sasinowski, M.S., M.P.H., J.D.[1]
Chairman of the Board
National Organization for Rare Disorders

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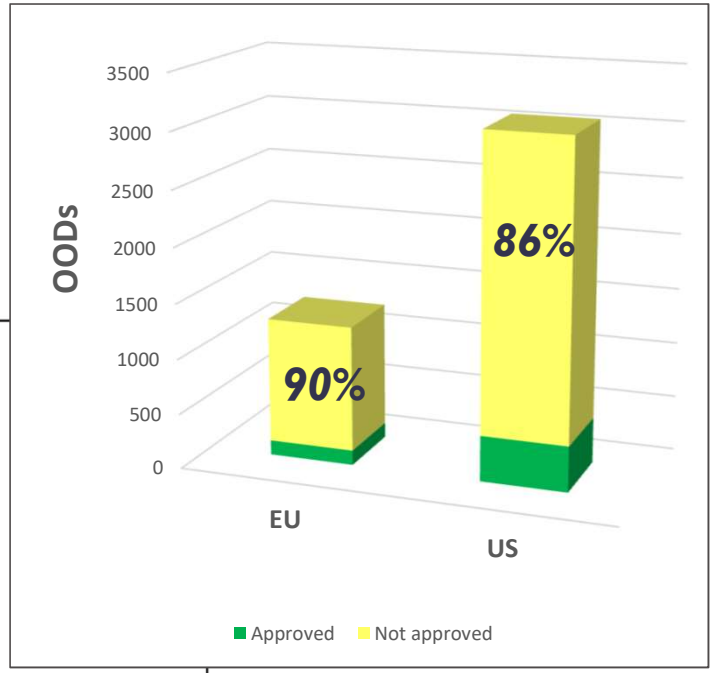
Reaching the market

A large percentage does not reach marketing approval



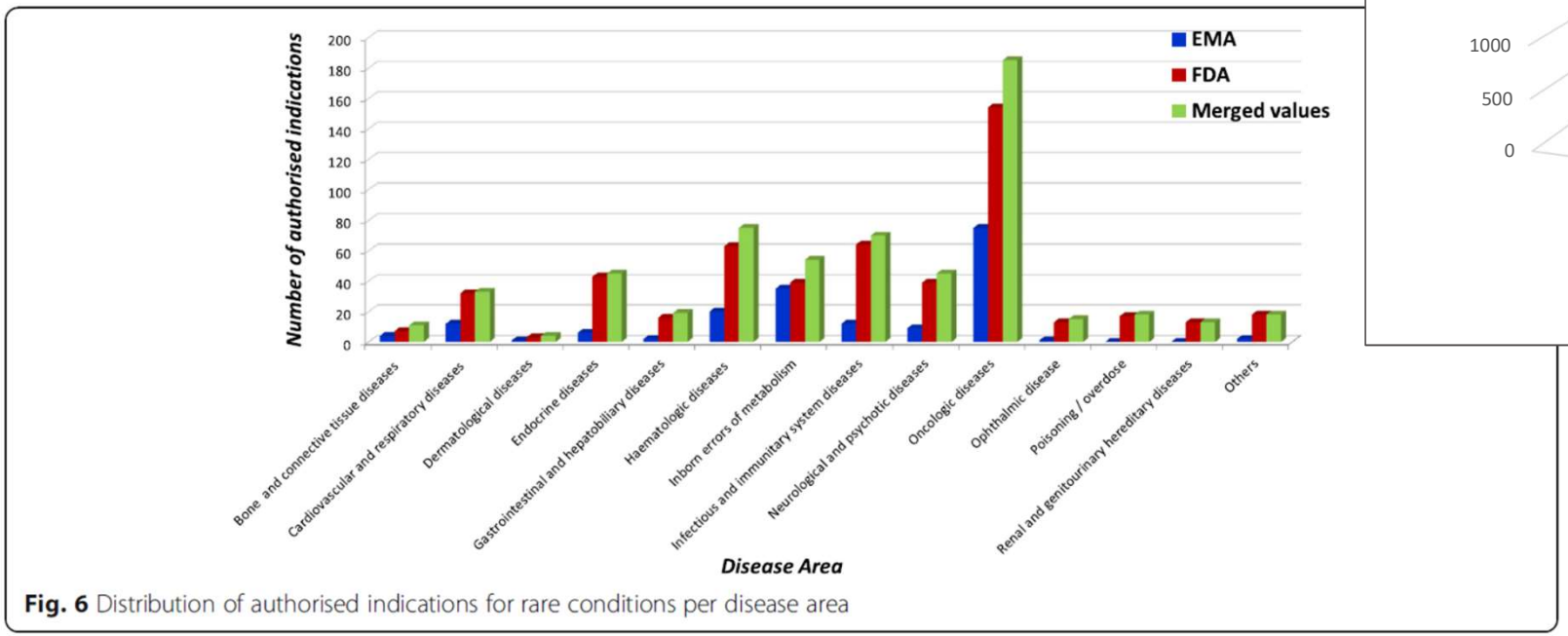


Fig. 6 Distribution of authorised indications for rare conditions per disease area

Giannuzzi V et al. Orphanet Journal of Rare Diseases. 2017 Apr 3;12(1):64

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AIMS

Open Access Research

BMJ Open

Failures to further developing orphan medicinal products after designation granted in Europe: an analysis of marketing authorisation failures and abandoned drugs

Viviana Giannuzzi,[1] Annalisa Landi,[1] Enrico Bosone,[2] Floriana Giannuzzi,[3] Stefano Nicotri,[3] Josep Torrent-Farnell,[4] Fedele Bonifazi,[1] Mariagrazia Felisi,[5] Donato Bonifazi,[5] Adriana Ceci[1]

- To identify
  - OMPs designated by the EMA that failed to reach the MA
  - the reasons for their failure
- To investigate
  - the stage of the R&D process at the time of its interruption
  - possible factors influencing the failure

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METHODOLOGY

EuOrphan

SOURCES: EMA Register of designated Orphan Medicinal Products and EPARs; EC Community Register of medicinal products; FDA Orphan Drug Designations and Approvals; Orphanet; EMA PIP opinions

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

FDA

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Since 2008 volutarly managed and updated by Gianni Benzi Foundation

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OMPs with a MA

Active substance designated as OMP

Orphan condition and indication

- therapeutic area,
- genetic nature,
- paediatric interest

MA refusals and withdrawals

Non-OMPs with a MA

Orphan-like drugs with a MA

Date of designation

First and current sponsors

MAH

Date of MA

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Methodology: SAMPLE

- OMPs designated in EU (2000-2012)
- Medicinal products approved for a rare condition through the EU centralised procedure

1. ***Drug development successfully completed*** ⇨ MA issued by the EC
2. ***Failure*** ⇨ an OMP not reaching marketing approval because:
   a) MA refused or withdrawn (MA failures)
   b) R&D process interrupted by the sponsor (abandoned)

- no clinical trial published during the last 3 years

or

- published trials, but development declared terminated, or inactive sponsor

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Methodology: SOURCES

Table 1 Sources used for the analysis and information investigated

	Source	Information
	EuOrphan (EMA, Orphanet)	▶ Active substances designated as OMP ▶ ODDs with an MA ▶ ODDs withdrawn with an MA ▶ Dates of designation ▶ Rare condition(s) ▶ Orphan indication(s) ▶ First and current sponsors ▶ MA refusals and MAA withdrawals ▶ Reasons for withdrawals or refusals ▶ Clinical trials and other evidence supporting the MA ▶ Possible competitors, that is, other OMPs for the same indication
	Clinical trial databases (EU Clinical Trials Register and Clinicaltrials.gov)	▶ Published clinical trials ▶ Reasons for prematurely ended clinical trials
*	PubMed	▶ Published clinical trials and other studies in literature ▶ Efficacy and safety data
	Sponsor-sourced information (company websites and pipelines, direct communications with the sponsors)	▶ Sponsor type (commercial or non-commercial) ▶ Stage of development of the drug ▶ Reasons for failures

EMA, European Medicines Agency; MA, marketing authorisation; MAA, MA application; ODD, orphan drug designation; OMP, orphan medicinal product.

Few publicly available information

* *Search strategy:*
- Keywords derived from MeSH vocabulary thesaurus:
(MeSH <drug name> AND MeSH <condition name>) OR (<drug name> AND <condition name>)
- synonyms or acronyms used when relevant

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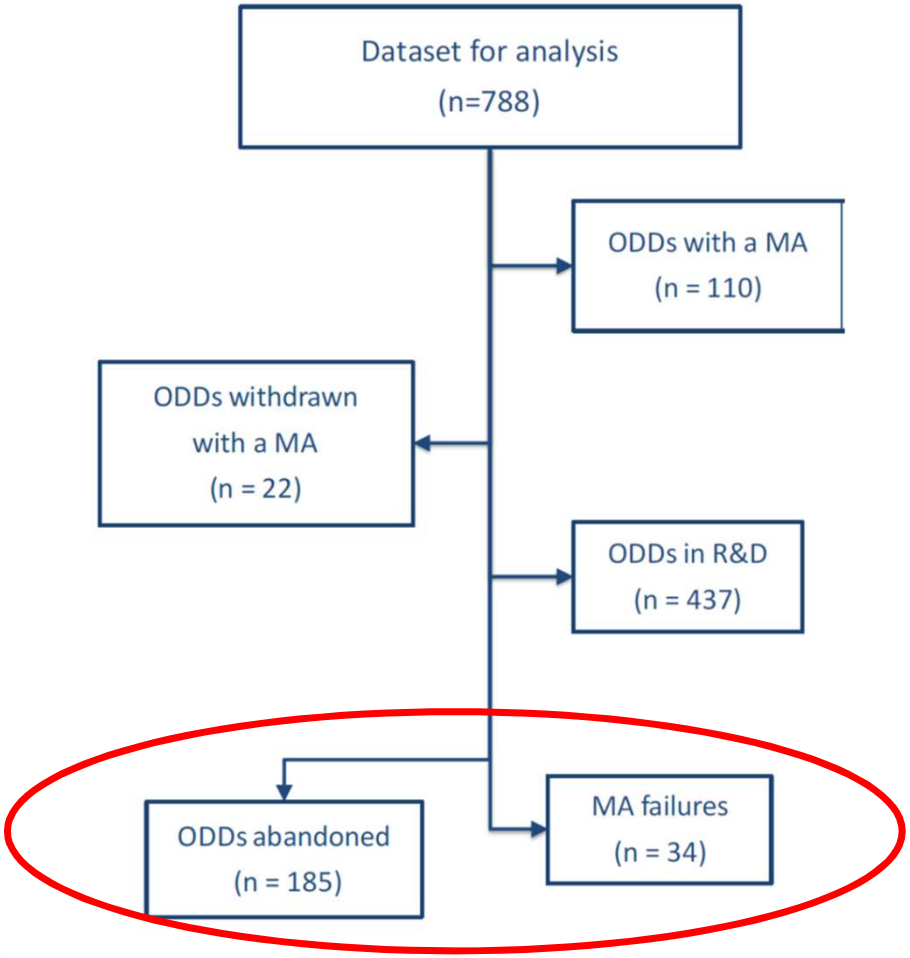
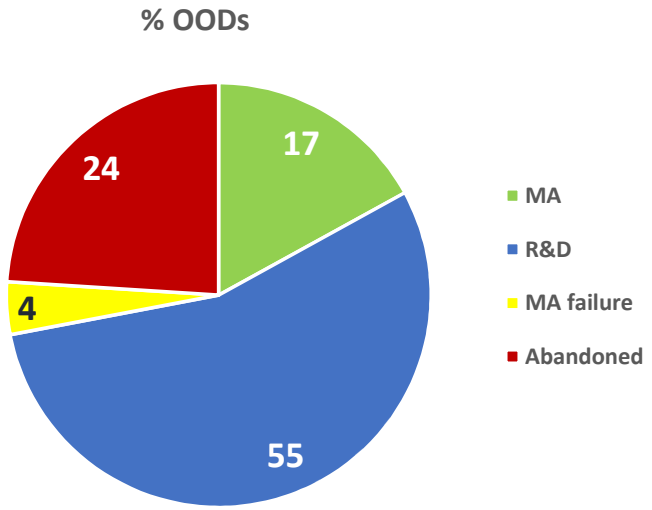
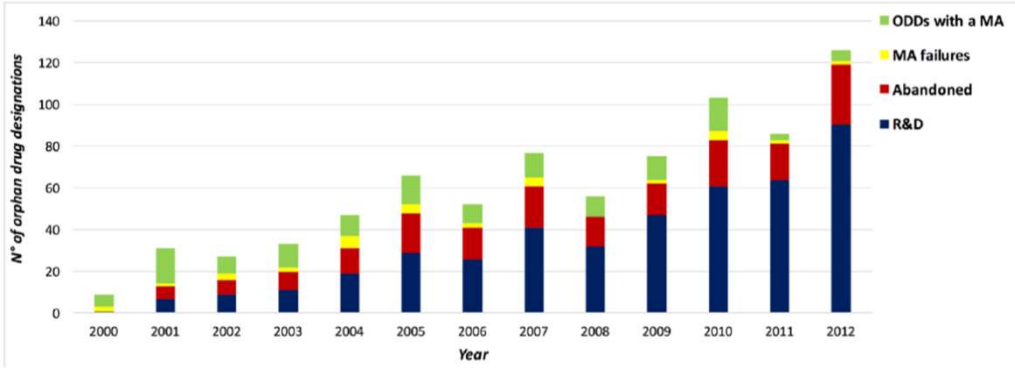
RESULTS



27.8% failures





Distribution of orphan designations by year

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Stage of development

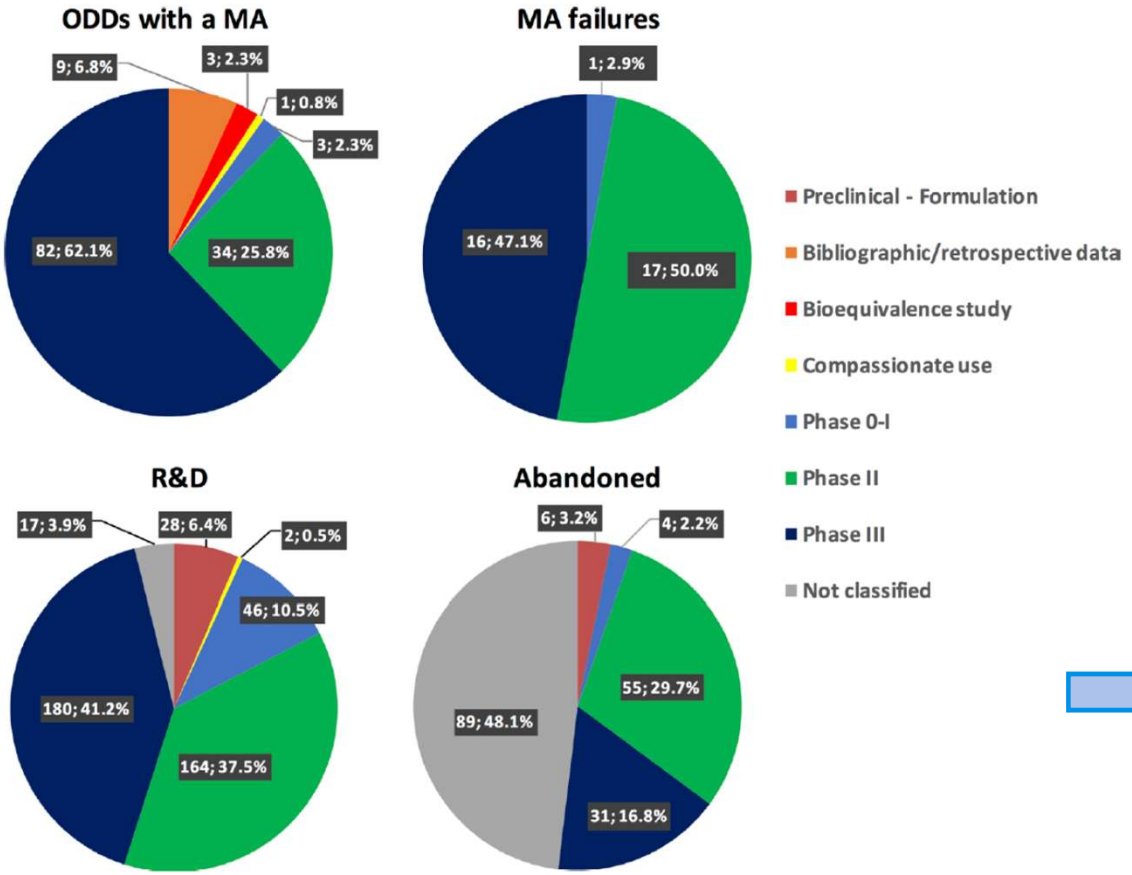

Figure 2 Stage of development reached by orphan drug designations (ODDs) with a marketing authorisation (MA) and MA failures (on the top) and ODDs resulting in research and development (R&D) and abandoned (on the bottom). Statistical differences between stages of development were determined using a χ^2 test (*p<0.01).

OMPs completing/reaching phase III have a reduced risk of failure

Most of the failures does not reach the clinical phase (no literature, trial databases or sponsor data for 48%)

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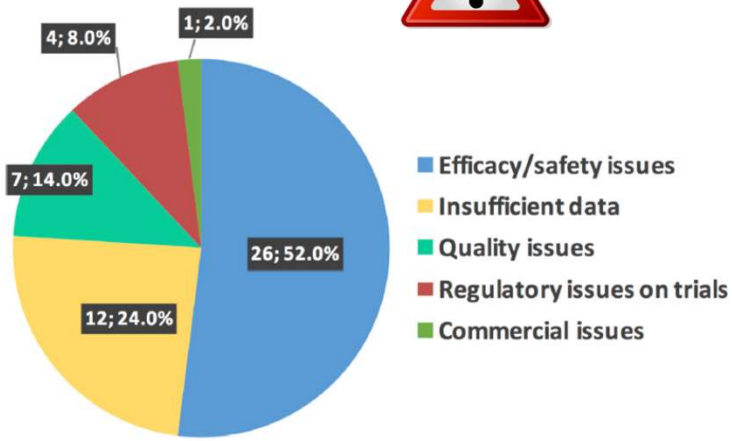
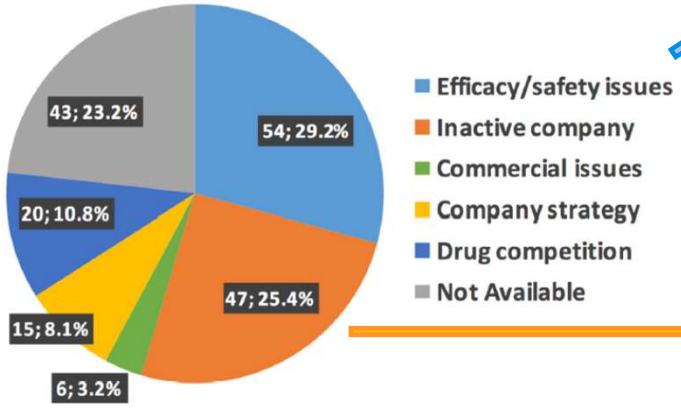
Reasons for failure





stopped in

- preclinical phase (20%)
- phase I-II trials (48%)

R&D failure?

42.5% oncologic ODDs failed for efficacy/safety issues

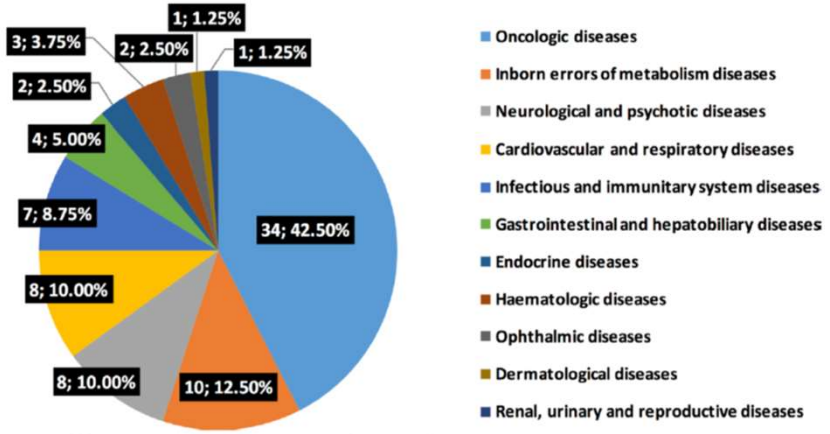


Figure 4 Failures for efficacy and safety issues across therapeutic areas.

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Risk factors

Table 2 Orphan drug designations by risk factors

Risk factors	ODDs with an MA (n)	R&D (n)	Failures (n)			% Failures
			MA failures	Abandoned	Total	
Age-related type of condition						
Not affecting children	24	102	8	45	179	29.6%
Affecting children	108	335	26	140	609	27.3%
Therapeutic area						
Cardiovascular and respiratory diseases	10	37	3	25	75	37.3
Dermatological diseases	1	8	1	4	14	35.7
Endocrine diseases	6	16	1	4	27	18.5
Gastrointestinal diseases	2	11	0	6	19	31.6
Haematologic diseases	12	35	0	8	55	14.5
Inborn errors of metabolism diseases	32	37	6	16	91	24.2
Infectious and immunitary system diseases	8	58	1	19	86	23.3
Neurological and psychotic diseases	9	54	2	20	85	25.9
Oncologic diseases	49	147	17	74	287	31.7
Ophthalmic diseases	1	22	1	4	28	17.9
Poisoning/overdose diseases	0	5	1	0	6	16.7
Renal, urinary and reproductive diseases	0	3	1	1	5	40
Others	2	4	0	4	10	40
Sponsor type						
Commercial	132	405	34	178	749	28.3
Non-commercial	0	32	0	7	39	17.9
Sponsorship transferred	40	117	16	53	226	30.5

MA, marketing authorisation; ODD, orphan drug designation; R&D, research and development.

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Conclusions

- Completing the R&D process still remains a challenging issue for orphan medicines ⇨ *28% failures*
- The main reasons for failures are safety and efficacy issues
- Most of the failures does not reach the clinical phase
- The availability of public data should be improved without compromising personal data and commercial protection

….Might a machine learning create an algorithm to predict failures or successes?

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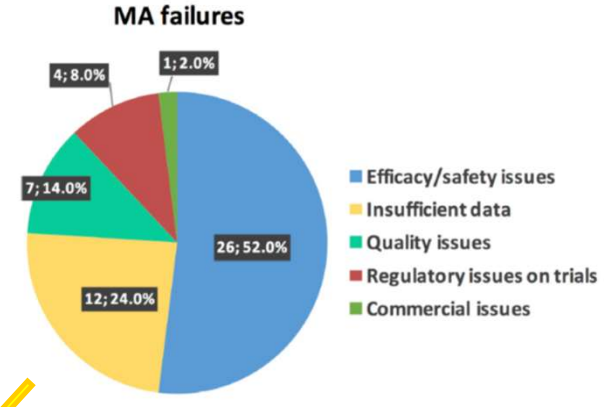
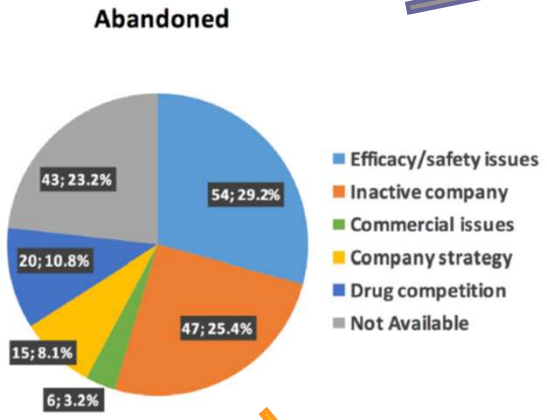
How to reduce the risk for failure?

- *Networking & collaboration*
- *Regulatory support*
- *Public data*





- *Methodology to gain the reliable evidence supporting the MA*
- *Incentives – economic support*

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How to reduce the risk for failure?

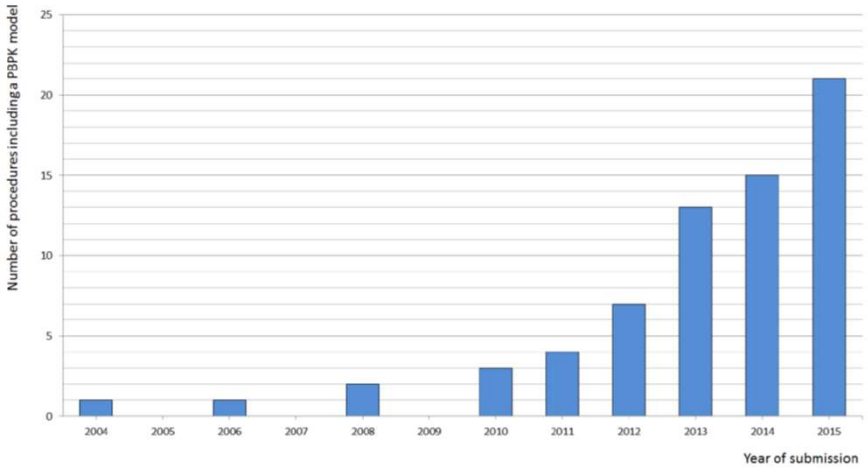
Clinical trials preformed with inherited neurometabolic diseases

IMP	Indication	Type of study	Study design	Sample size
Laronidase	MPS I	PK-PD	Open label	10
		Efficacy	**Double-blind placebo-controlled**	**45**
		Long-term efficacy	Open label	45
Imiglucerase	Gaucher disease	Efficacy	Matched-pair dose comparison	10
		Efficacy	**Double-blind active-controlled**	**30**
		Long-term efficacy	Open label	30
Galsufase	MPS VI	**Efficacy**	**Double-blind placebo-controlled**	**39**
		Efficacy	Double-blind dose-comparison	7
		Long-term efficacy	Open label	10
		Clinical symptomatology	Survey	121
Velaglucerase alfa	Gaucher disease	Safety only	Open label	12
		Long-term safety	Open label	10
		Efficacy	**Double-blind baseline-comparison**	**25**
		Efficacy	**Double-blind active-controlled**	**34**
		Safety only	Open label	40
Miglustat	Gaucher disease Niemann-Pick D	**Efficacy**	**Open label**	**28**
		Efficacy (dosage regimen)	Open label	18
		Efficacy	Open label active-controlled	36

2° Health Programme, 2012 12 12 (2015)

INNERMED Inherited NeuroMetabolic Diseases Information NETWORK

- *Methodology to gain the reliable evidence supporting the MA*



Luzon et al., Clin Pharmacol Ther. 2016

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