

# How to improve the success rate of orphan drug development between orphan designation and marketing authorisation

10<sup>th</sup> workshop on partnering for rare disease therapy development

EPPOSI

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Brussels

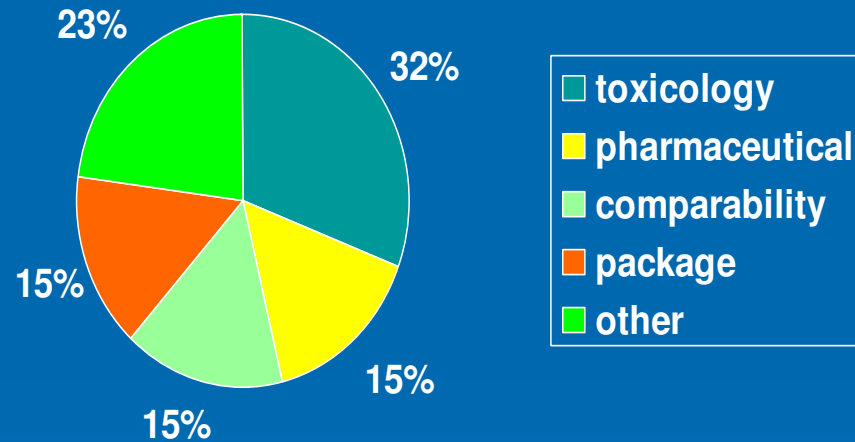
# Using protocol assistance data...

- Protocol assistance is incentive for development after designation
- Issues discussed as indicators of difficult areas during development
- PA is sought if
  - Deviation from guidelines
  - New issues
- But we miss issues for those that never made it to protocol assistance
- Not a full analysis

# Data

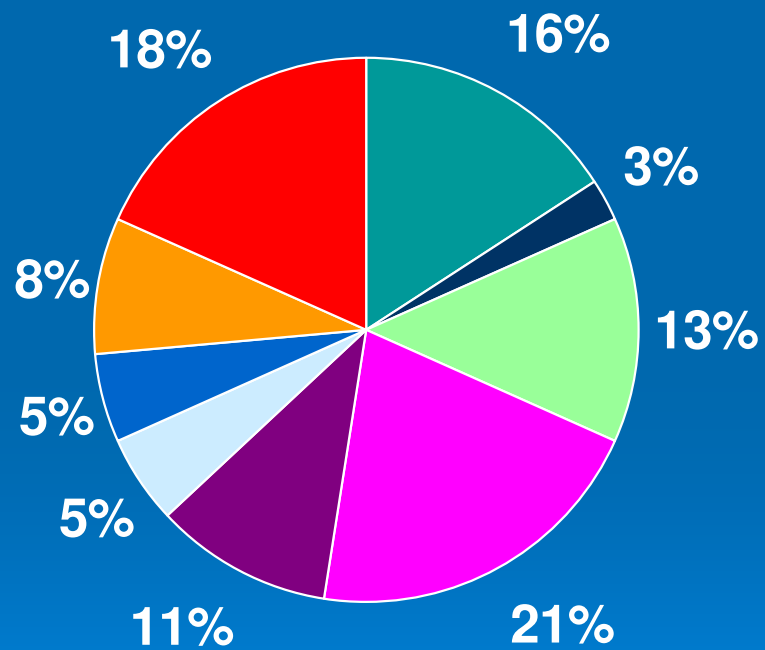
- Analysis of last three years
- Protocol assistance procedures for the areas most frequently scope of procedures
- Five conditions included
- Four therapeutic areas
  - Cancer
  - Respiratory diseases
  - Metabolic diseases
  - Ophthalmology

# Preclinical issues



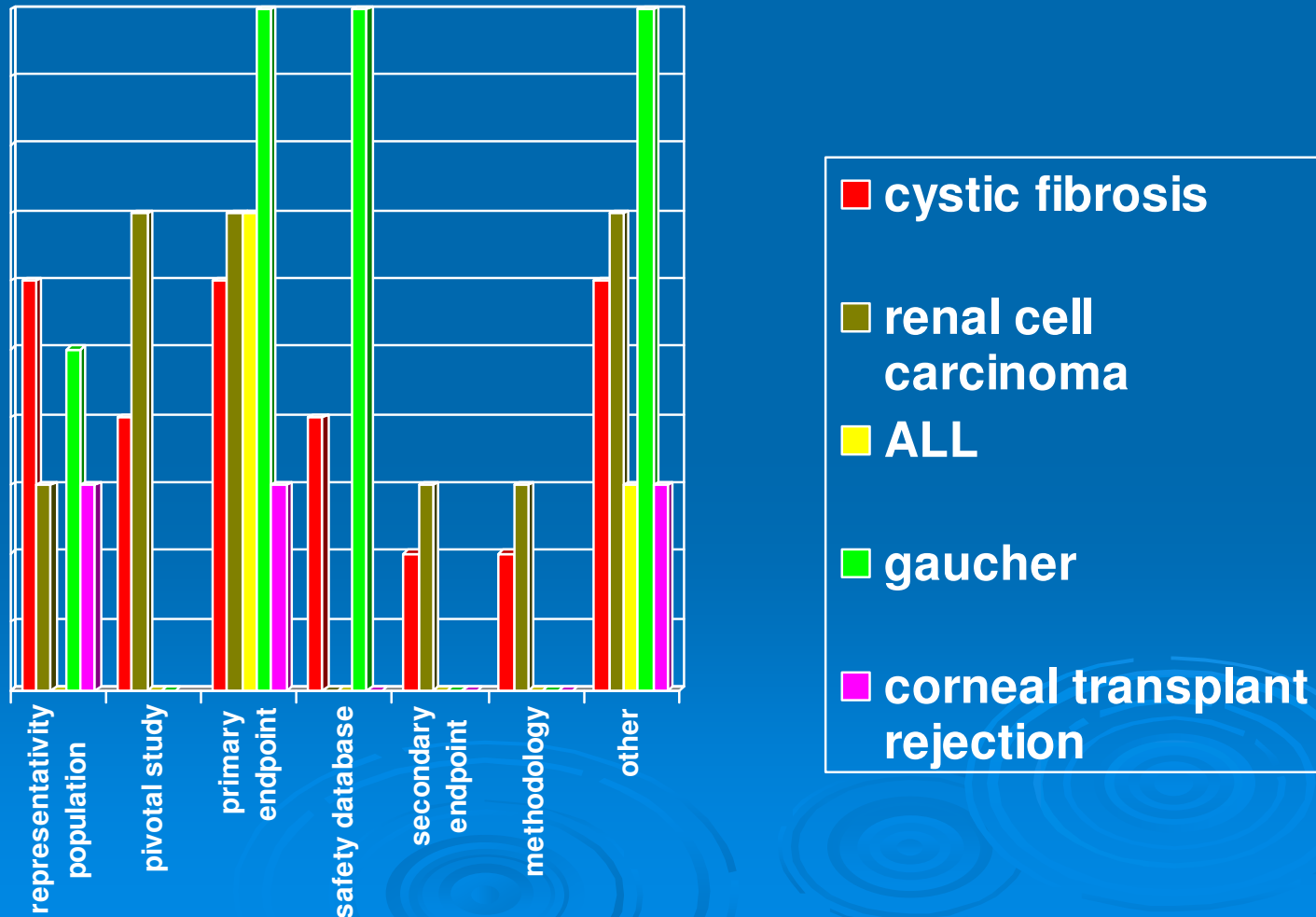
- Issues are not “development limiting”
- Overall agreement is reach at end of procedure
- Overall plan for toxicology studies
- Timing for studies
- Need for further data

# Clinical issues



- representativity population
- use of placebo
- MA based on pivotal
- primary endpoint
- safety database
- secondary endpoint
- statistical plan
- general methodology
- other

# Clinical issues per condition



# Some examples...high risk

- **Following CHMP comments regarding the previously proposed scoring system to capture events of exacerbations, and absence of method validation, the Company proposes to adopt the scoring system used and validated in the XXXXXX clinical study with XXXX published by XXXXXX. The Company would appreciate receiving CHMP advice on the suitability of this proposed scoring method.**
- **CHMP ANSWER**
  - **the data from the published paper is insufficient to consider the scale validated**
  - **the scoring system has not been correlated to validated scales in COPD, like (...). Further, the ability of the scoring system to measure the reduction in the progression of the disease as a result of an effective therapeutic intervention on these factors has not been proven, and the scoring system lacks external validation.**

# Some examples ... flexibility

- *Does the EMEA agree with the definitions of the stable disease parameters for the inclusion criteria and the primary endpoint?*
- **CHMP answer**
- In preparation of the discussion meeting the applicant has revised the definition of stable disease in a way that (...). This is considered acceptable.

# Some examples... yes, but

- **Does the EMEA agree with the proposed dosing strategy in the Phase 3 studies?**
- **CHMP answer**
- In principle the proposed dosing strategy is endorsed. However, while Study XXXX is planned as double-blind with a fixed dose, in study XXXX the applicant considers it necessary to titrate the dose of XXXX according to plasma trough levels, which would exclude the possibility of a blinded design.
- It is recommended to first stabilize patients (...) and to define a rule, how patients should be switched to oral treatment. The burden of the double dummy design (as compared to the current treatment situation) is assumed to be acceptable (...)

- Some conditions have questions on many aspects of development
- One case of follow up after disagreement
- “Regulatory” issues linked to rarity discussed
  - Safety database size
  - Use of pivotal trial as basis of MA
- Major clinical development issues discussed
  - Population
  - Primary (and secondary) endpoints

# How to improve success

- Ask and follow advice
  - As early as possible
  - Use the follow up advice
  - Discuss with Agency if deviation
  - If in doubt ask
- Learn from failures
  - Transparency (?)
  - Example of paediatric regulation on publishing data whatever outcome (?)
- Guidelines: new and revision
  - Lot of room for improvement
    - Complex system of revision

Not even the best advice and the most imaginative development can rescue an inactive product!

- Thank you very much
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- <http://www.emea.europa.eu/htmls/human/sciadvic/Scientific.htm>

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