



Protocol Assistance for Designated Orphan Medicinal Products



What have we learned

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Contents

Protocol assistance

- Main characteristics
- Procedure
- Experience
- Impact on authorisations



PROTOCOL ASSISTANCE

Scientific advice + orphan = protocol assistance

- Protocol assistance is scientific advice for products designated as orphan
- Which is not assistance on protocols and is free

Article 6

Protocol assistance

1. The sponsor of an orphan medicinal product may, prior to the submission of an application for marketing authorisation, request advice from the Agency on the conduct of the various tests and trials necessary to demonstrate the quality, safety and efficacy of the medicinal product, in accordance with Article 51(j) of Regulation (EEC) No 2309/93.
2. The Agency shall draw up a procedure on the development of orphan medicinal products, covering regulatory assistance for the definition of the content of the application for authorisation within the meaning of Article 6 of Regulation (EEC) No 2309/93.



Scientific advice (SA) Protocol assistance (PA)

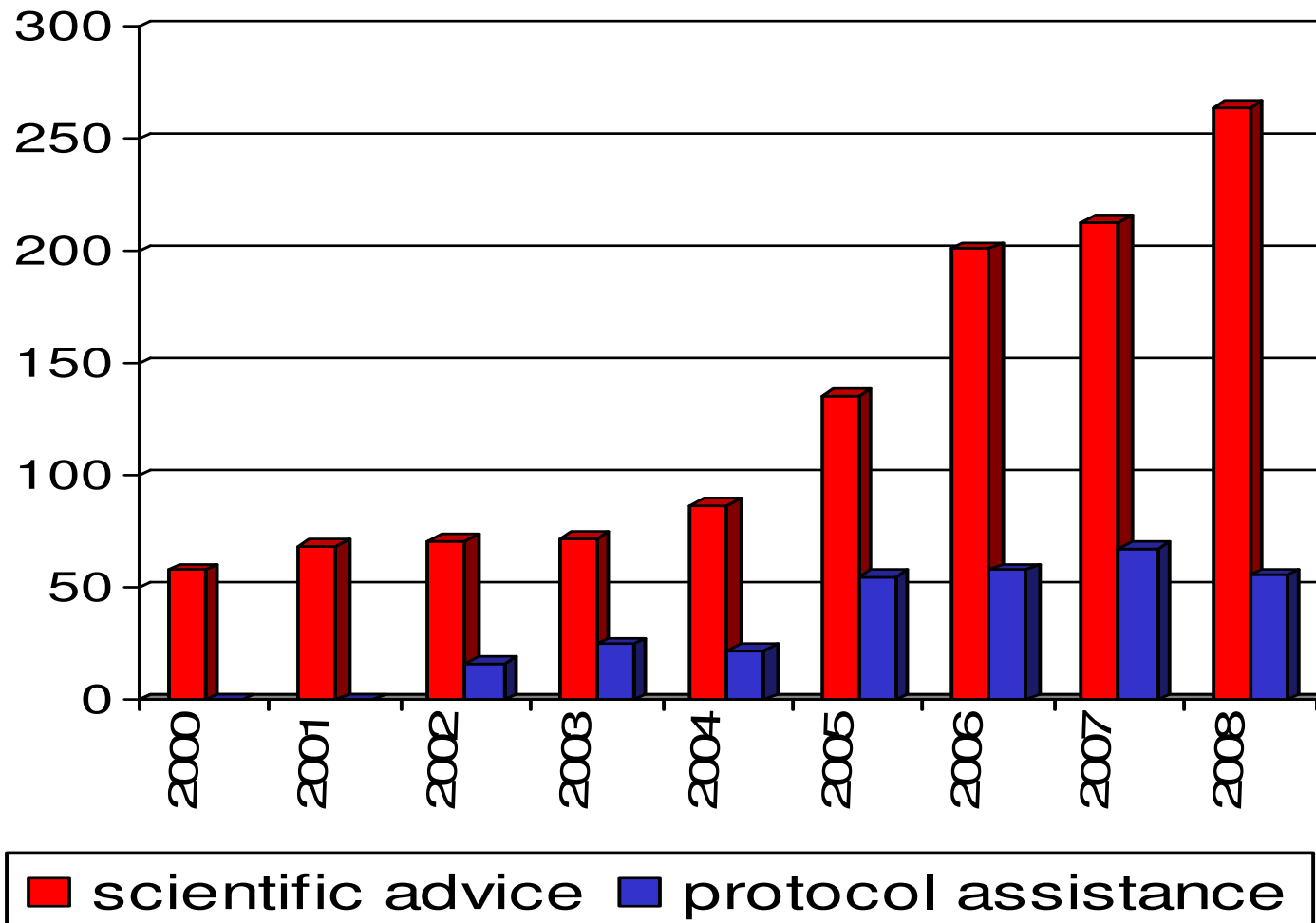
- **Given by Scientific Advice Working Party**
 - Multidisciplinary group of 25 experts (complementary scientific competences)
 - Advice to sponsors on all aspects of drug development: quality, non clinical, clinical
 - Advice on how to demonstrate significant benefit
 - Advice on other orphan related issues (including similarity and superiority issues)
 - Advice on non-product related issues (e.g. on new statistical approach or validation of a scale)
 - Advice on qualification of biomarkers



PA Procedure

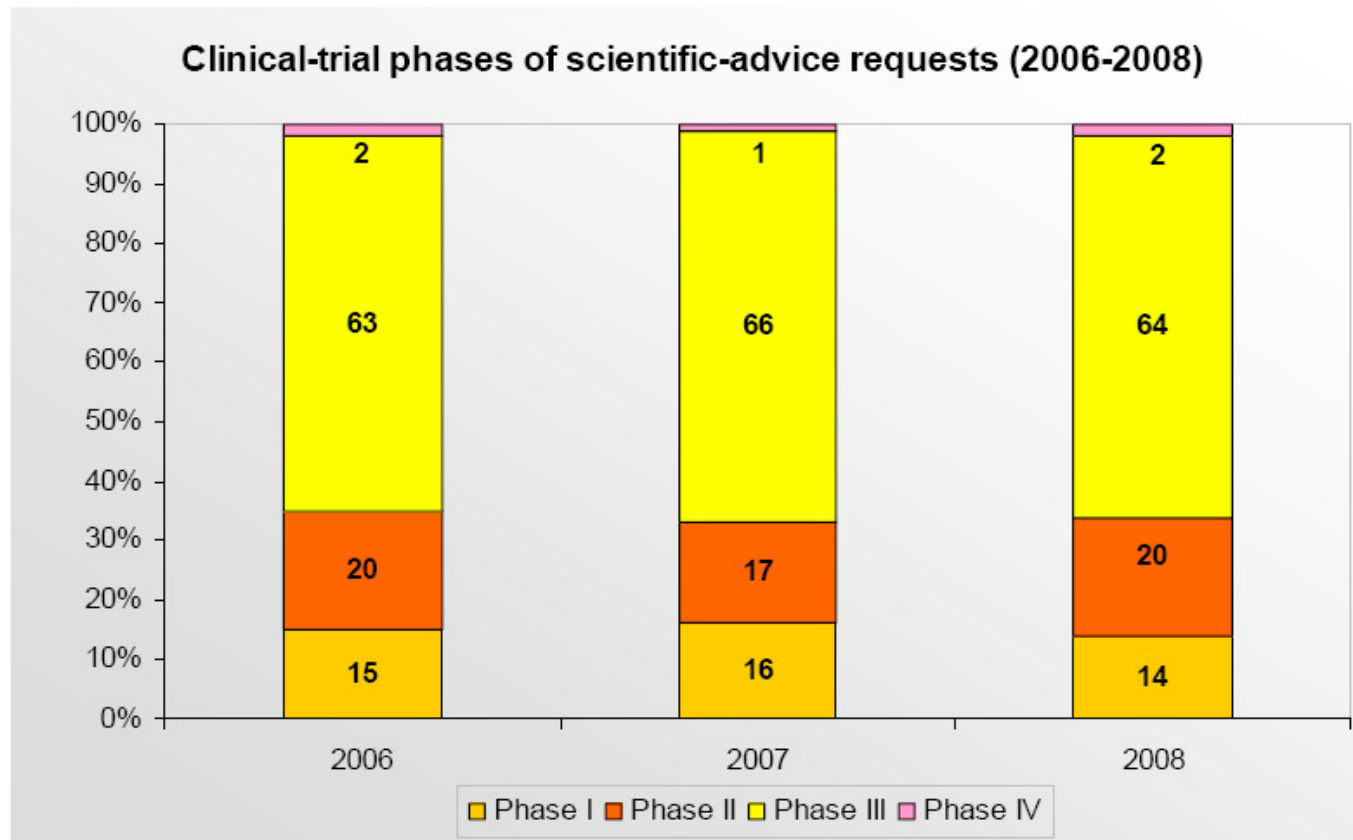
- 70 day procedure (maximum)
 - Possibility of finalisation in 40 days
 - Presubmission meeting
 - Discussion meetings with SAWP (in 50%)
 - Major disagreement
 - Need for additional information
- Final advice letter adopted by CHMP
COMP involved if issues on significant benefit

Scientific Advice- Protocol Assistance





Scientific Advice- Protocol Assistance





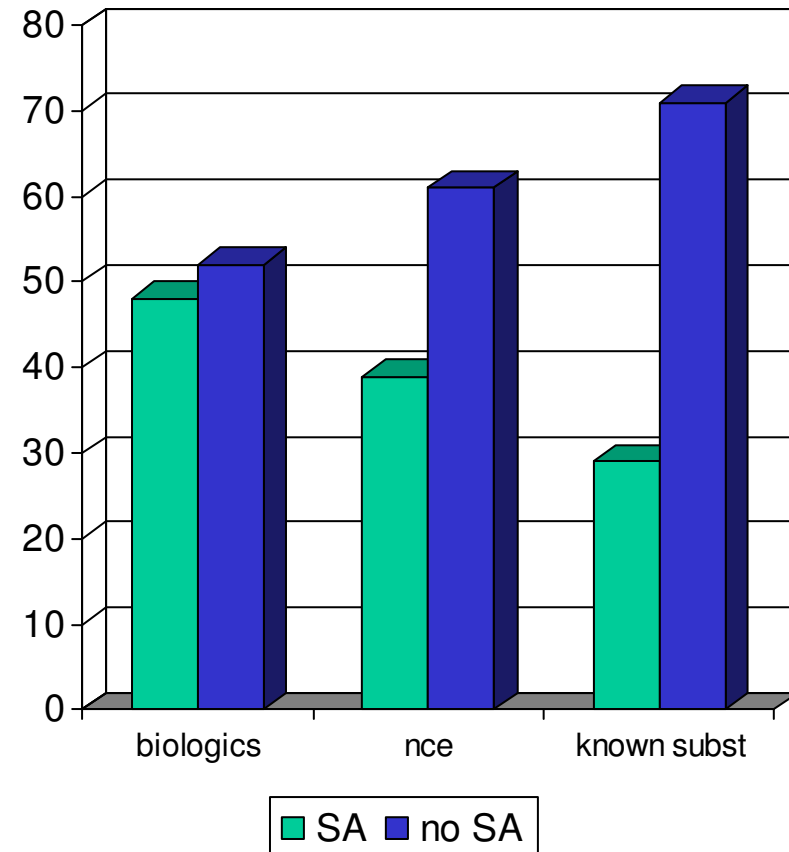
PA/SA and marketing authorisation (MA)

- Analysis four consecutive years
- 192 MA Applications with outcome
 - Positive opinion 140 (72.9%)
 - Negative opinion 10 (5.2%)
 - Withdrawal 42 (21.9%)

 - Orphan drugs 51 (26.6%); of them 21 (41%)
came for PA

Type of products

- MA applications with SA
 - 48% of biologics
 - 39% of new chemical entities
 - 29% of known substances





Characteristics of MA application with positive outcome

- Significant association with positive outcome
 - Company size: OR 2.84 (1.86 to 4.33)
 - Orphan designation: OR 2.48 (1.25 to 4.93)
 - if company size independently analyzed then designation seem not to play a role (success rate similar by company size strata)



Company size and success rate

Size	Success rate
Big Non orphan Orphan	89% 90% 82%
Medium Non orphan Orphan	72% 74% 60%
Small Non orphan Orphan	50% 50% 50%



Success and compliance with SA

- Overall compliance 68%
- Overall RR for success favourable to MA that complied with SA (1.48; 95%CI: 1.31 to 1.67)

- Failure rate 70% non compliant
- Failure rate 2% in compliant

- Highest compliance by big pharma
 - Big 84%
 - Medium 63%
 - Small 36%



Study conclusions

- **Company size is associated with outcome**
 - Limited resources
 - Lack of experience
- **Compliance is associated with positive outcome**



Study conclusions

How to avoid failing of MA

- Many companies come for initial advice late (ongoing phase III)
- Better to come for follow up than disregard advice