EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Cystic fibrosis endpoints:

Difficulties encountered in the Orphan procedures

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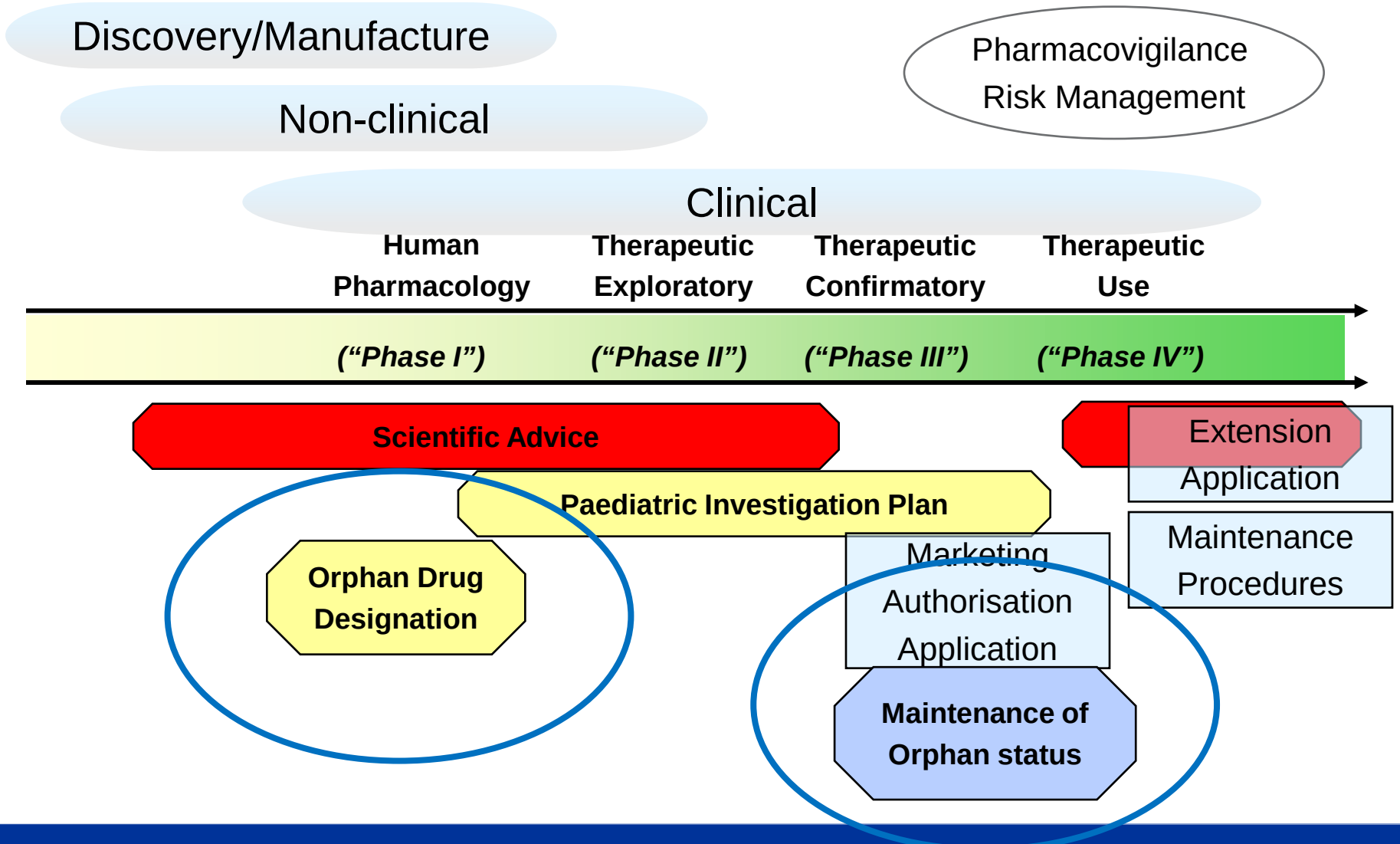
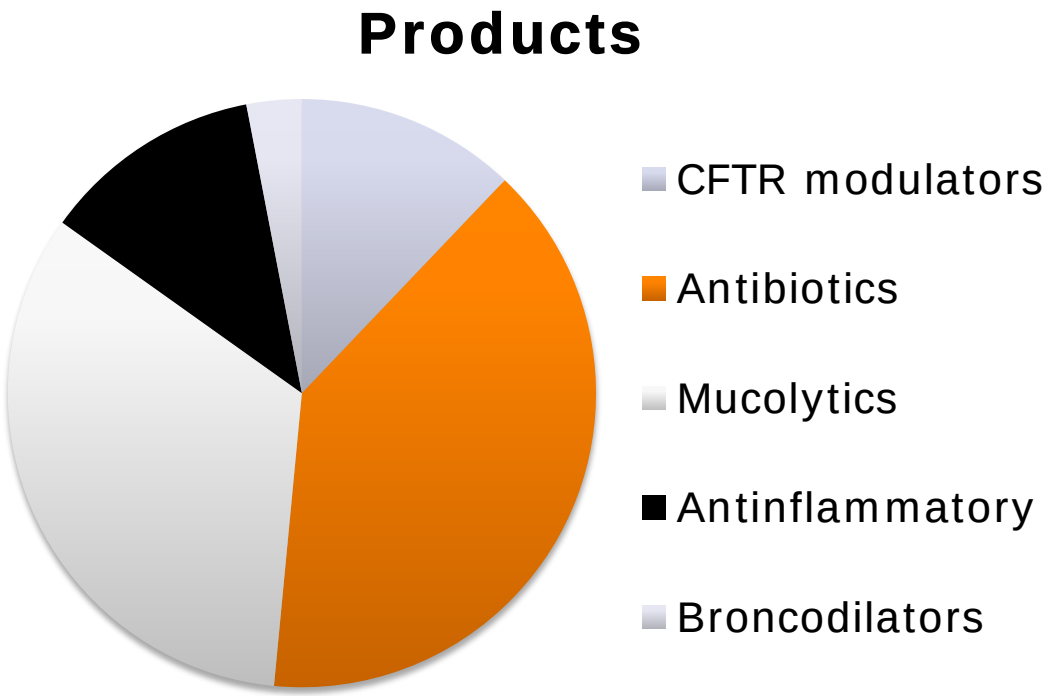
Outline

1. Orphan procedures
2. Significant benefit
3. Endpoints at orphan designation (preclinical)
4. Endpoints at marketing authorization confirmation of orphan status (clinical and major contribution to patient care)
5. Need-lists for “orphan” endpoints

Drug Development Overview



Designated orphan products for CF (n = 38)



Only 4 have marketing authorization

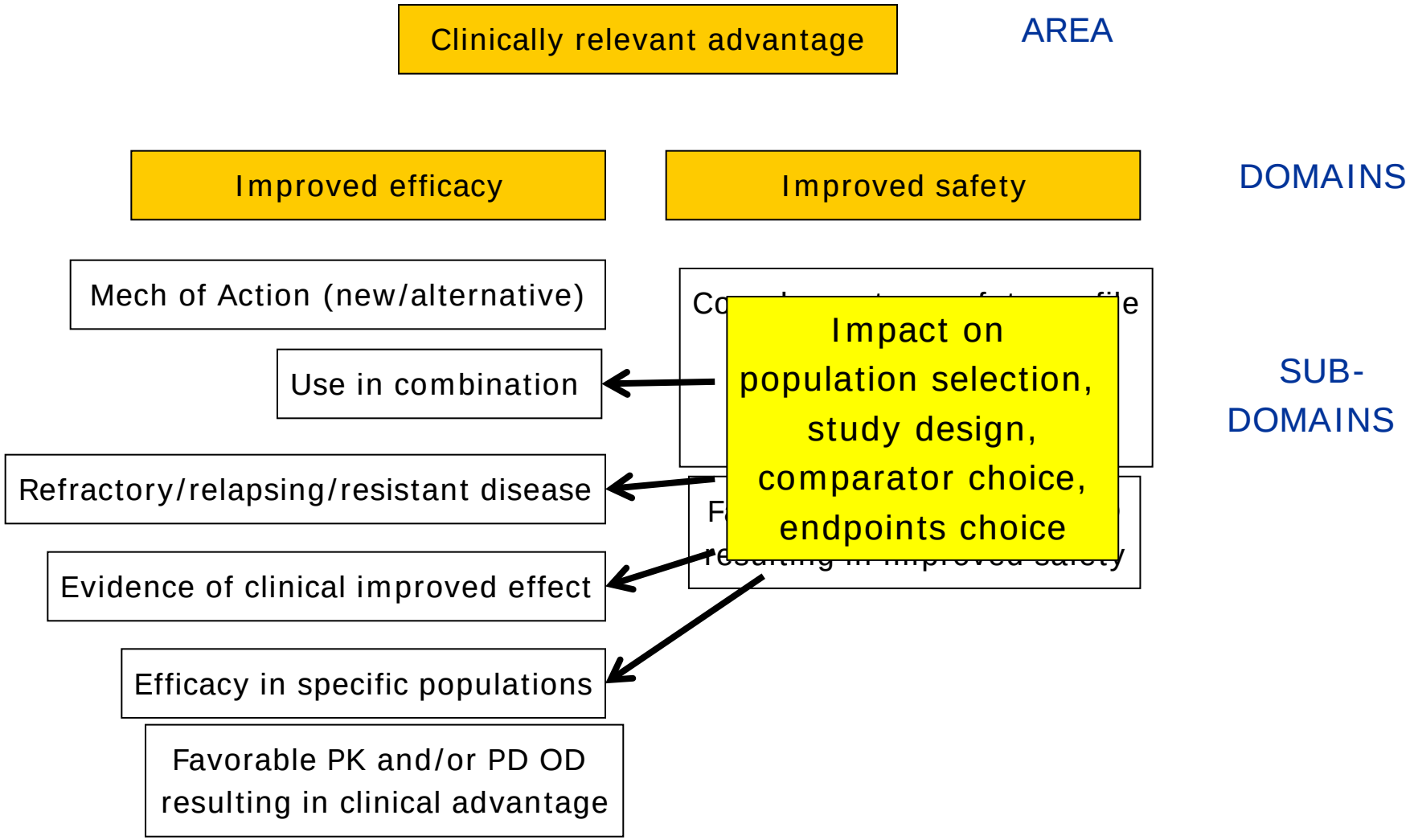
Criteria for Orphan Status

At designation (OD) and at marketing authorization (MA)

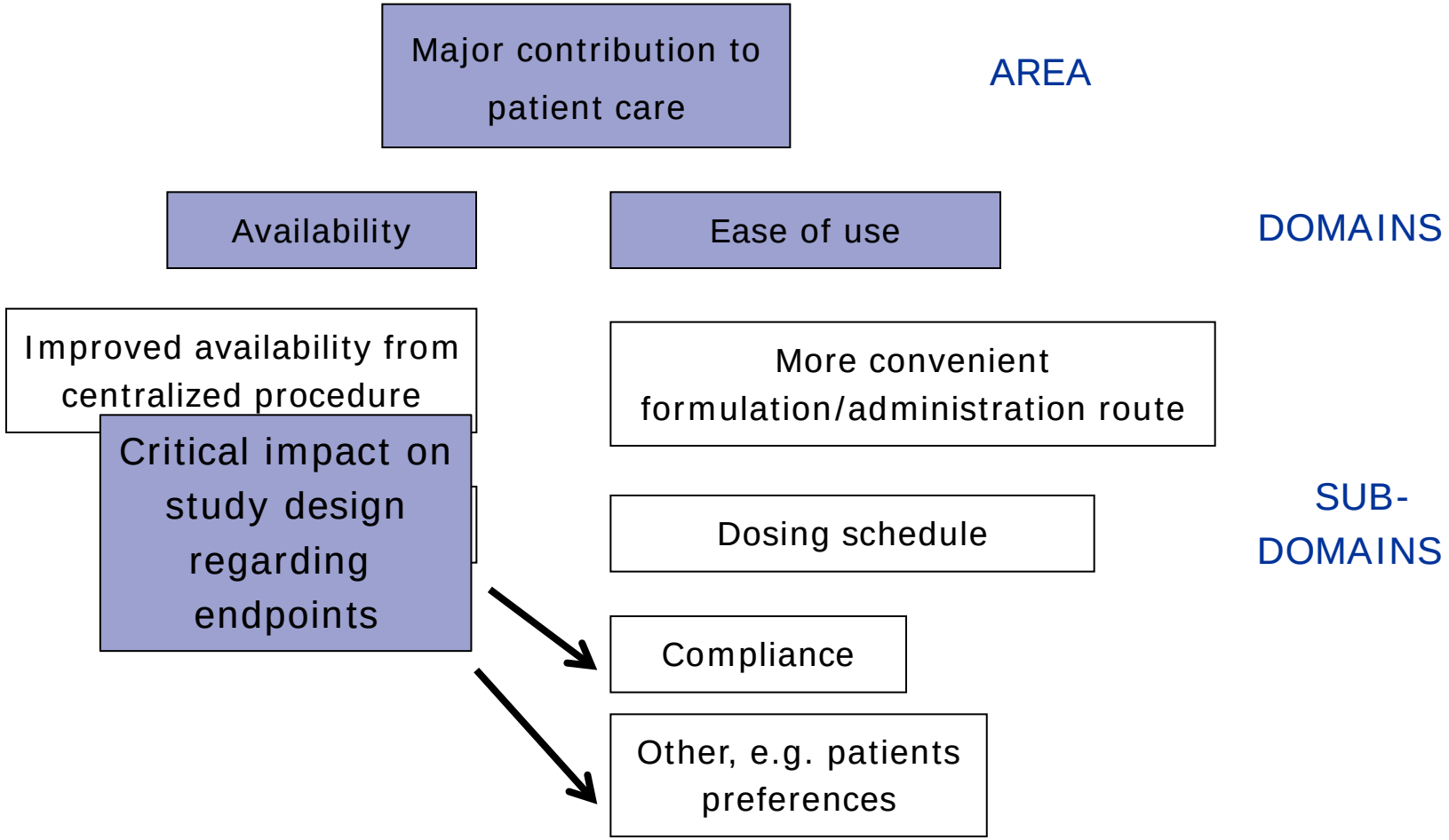
- Prevalence
- Seriousness
- Significant benefit **if needed**

Usually preclinical endpoints at OD, and clinical at MA

Scientific aspects of significant benefit (I)



Scientific aspects of significant benefit (II)



Comparators for significant benefit

- Significant benefit to be discuss taking into account satisfactory treatments for the condition
- **Satisfactory =** all authorized medicinal products for that condition (in at least 1 MS); any treatment (including e.g. surgery, RT, diet) which is considered satisfactory in the standard of care of that condition
- **All comparators or relevant comparators?**
- Different number of comparators at OD and MA to be taken into account
- Often different comparators for different grounds/domains of significant benefit

Endpoints

at orphan designation

Which level of evidence at Orphan Designation ?

- Based on scientifically supported assumptions and hypotheses
- Usually evidence from good pharmacodynamic animal models (e.g. transgenic animals, knock-out animals, animals carrying specific mutations, etc.)
- Sometimes based on cell cultures experiments or “proof of principle” clinical data

Better when supported by preliminary clinical data

Case by case

Mucolytics

- ex-vivo frog palate (increased velocity *vs.* Ringer's lactate, or other products)
- increased mucocyliary clearance carboxymethylcellulose gel guinea pig trachea (increased velocity *vs.* liposome control)
- ex-vivo viscoelasticity of sputum from CF subjects (rheometer)
- velocity of mucin from procine stomach (but vs several other mucolytics and combined with antibiofilm activity)

Stronger when: compared with currently authorized products; more than one model

Evidence and comparisons needs increasing with number of authorized products (and designations!)

CFTR modulators

Correctors

- in vitro HBEC, open probability of product-corrected F508del-CFTR similar to wild-type and higher than temperature-corrected
- preliminary results on sweat chloride decline questioned → poor proxy of clinical activity

Potentiators

- In vitro, different cells systems: (NIH3T3) FRT, (native HBEC). Single channel patch clamp electrophysiology: channel open probability

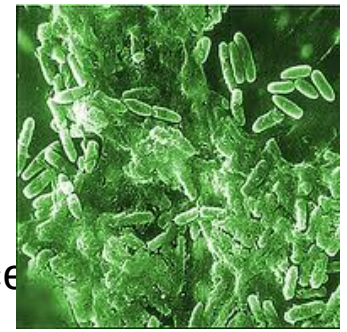
Antibiotics

Antibacterial activity

- *in vitro* MIC (minimum inhibitory concentration) on different Pseudomonas a. and on other relevant pathogens associated with CF

- *in vitro* MIC in situations resembling the CF airways micro-environment (high ionic concentrations and mucin)

Antibiofilm activity



- microfluidic BioFlux 800 flow cell system

- post-antimicrobial effect: delayed bacterial growth and reduce metabolic activity of the biofilm

All questioned…..which relevant endpoints for antibacterial and antibiofilm activity? Clinical relevance?

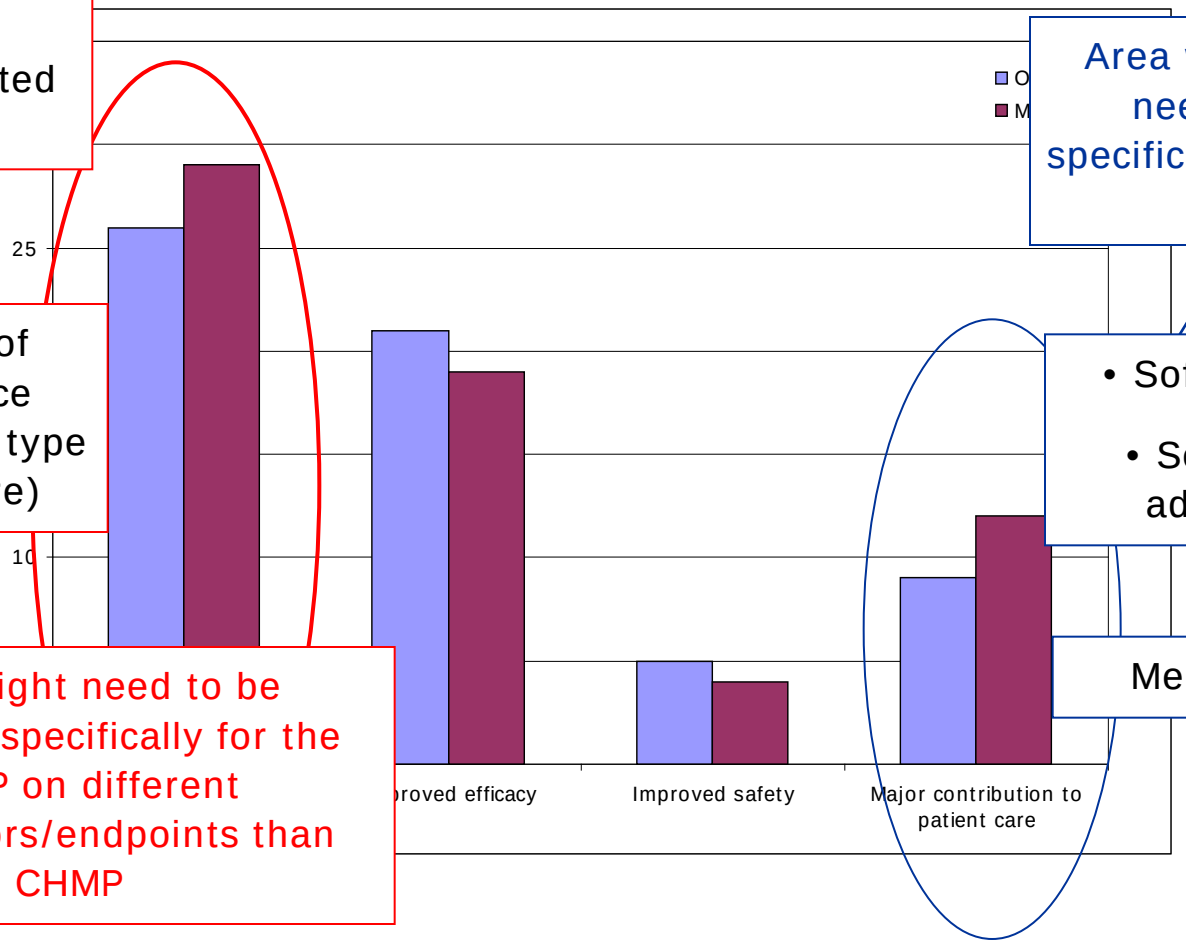
Endpoints for maintenance of orphan status at marketing authorization

Main areas of significant benefit

Judgement on E&S at MA linked to evidence submitted to the CHMP

Variable level of clinical evidence (e.g. prevalence, type of MA procedure)

Data might need to be generated specifically for the COMP on different comparators/endpoints than CHMP

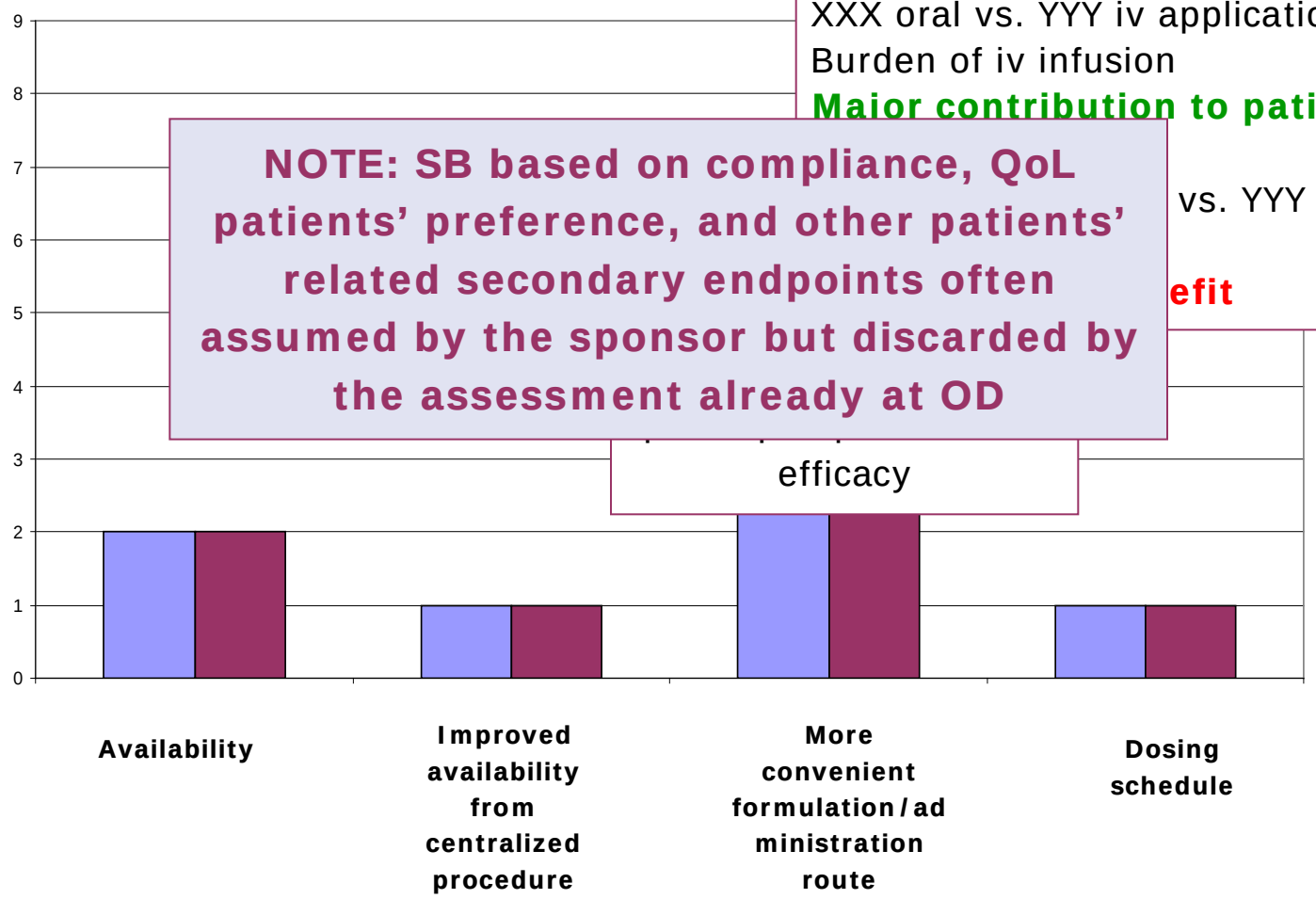


Area with highest need of data specifically generated for SB

- Soft endpoints
- Self-evident advantages

Methodology?

Major contribution to patient care



CFTR potentiator: Ivacaftor

- First-in class authorized and new mechanism of action
- Targeting G551D-CFTR gating mutation

Orphan designation

- Single channel patch clamp electrophysiology: channel open probability *in vitro*

Orphan status at marketing authorization

- significant improvement in lung function; decrease in the number of pulmonary exacerbations (same data as for MA, no need of comparators)
- innovative mechanism of action (disease modifying potential)

Inhaled antibiotic (nebulized): aztreonam

- First inhaled orphan authorized
- Different molecule from nebulized TOBI (non centralized)

Orphan designation

- shorter nebulisation periods (documented) and possible impact on compliance (suggested by the sponsor, no data → assumptions accepted
- Resistance pattern different from that of TOBI and aminoglucosides → assumption accepted (literature, evidence?)

Orphan status at marketing authorization

"*The present data are also insufficient to resolve the raised concerns with regard to the risk of acquired resistance*" (CHMP AR)

- Different resistance pattern → discarded
- shorter nebulisation periods vs. TOBI → accepted
- *Vs* IV antibiotics: new alternative route of administration of antibiotic regimen, alleviating the patient burden of i.v. administration

Inhaled antibiotic: tobramycin inhalation powder

- SB based on major contribution to patient care

Orphan designation

- Shorther administration time, portability → accepted; better compliance, reduction of environmental exposure to the drug, likelihood of treating patients → discarded
- efficacy and safety from TOBI treatment would have to be kept with tobramycin inhalation powder (basis for non-inferiority)

Orphan status at marketing authorization

- Administration time (TIP 5.6 min; TOBI 19.7 min)
- Portability (weight of TIP device is 20 mg, does not need electricity vs nebuliser weight 1.3-1.8 kg)

"Weak" significant benefit: self-evident advantages, soft end-points

Ease of administration:needs to be justified

- pills vs injection
- Inhaler vs Nebuliser (quantify, no need of specific-endpoints)
- Ready to inject vs need to reconstitute (sterile)
- Easy to carry medicines (not requiring storage in the fridge)...how to justify the significant benefit?

Other major contribution to patient care

- patient's preference
- compliance
- Quality of Life

"Need-list" for orphan designation

- Identification of the "ideal" pre-clinical models and endpoints ("*bar gets higher*").
- Valid endpoints in animal models, particularly when only one proof of concept is presented
- Efficacy endpoints for mucolytic and antibiotic activity (antibacterial, antibiofilm?
- Similar views from COMP and SA/CHMP on resistance endpoints *in vitro* (accepted as assumptions of significant benefit only when other preclinical advantages are present)

“Need-list” for maintenance of orphan status at MA

- Elaboration of soft and secondary endpoints such as quality of life, patients’ preference, compliance (e.g. for significant benefit based on portability, ease of use)
- Claimed better resistance profile difficult to support with clinical data: which endpoint when lower generation of resistance is the main claim for significant benefit?
- Elaboration of endpoints linked to efficacy/safety rather than ease of use, for products based on formulations (direct comparison with the authorized formulation), whenever possible

Thanks for your attention

Questions