EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Ophthalmology Workshop EMA 27-28 October 2010

The orphan perspective

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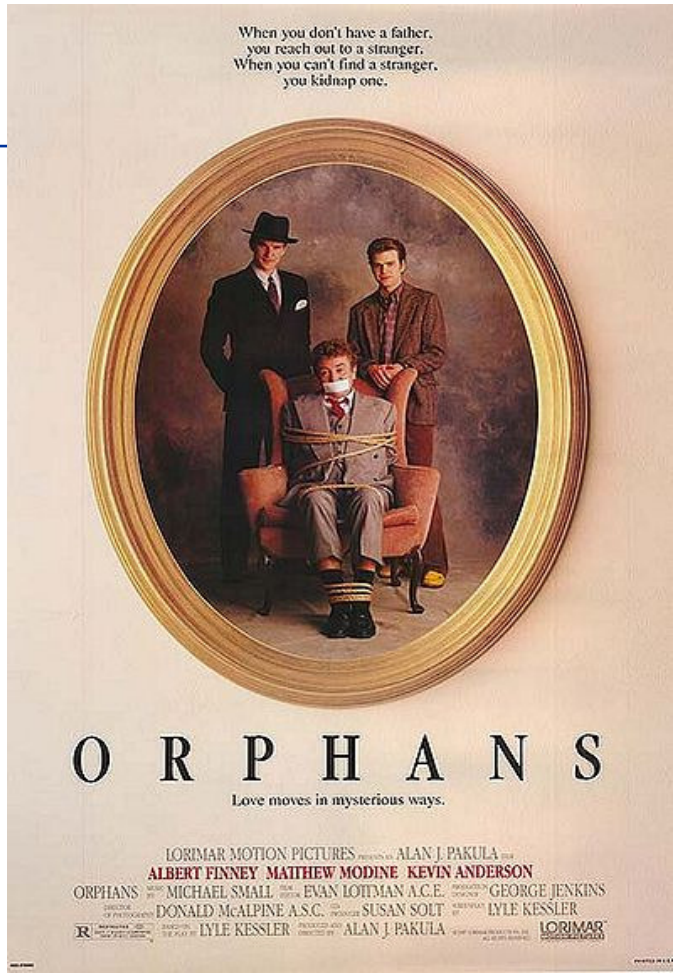
The orphan perspective

1. Criteria and incentives for orphan designation
2. ”Ophthalmological orphan drugs”
3. Criteria for designation – case studies for eye disorders
4. Problems in designation
5. Conclusions

Disclaimer: "The views presented are those of the individual and may not be understood or quoted as being made on behalf of the EMA or reflecting the position of EMA or one of its committees or working parties"

Why an OD framework?

- How do you draw attention to non-profitable conditions?
- Procedure to recognise drugs intended for development for rare diseases
- Provides incentives for their development and marketing



Adopted from http://uk.movieposter.com/poster/MPW-33529/Orphans.html

What is at stake? (Incentives)

Economic / marketing

- Fee reduction / exemption
- Market exclusivity

Product development

- Protocol assistance

EU-wide marketing authorisation

National incentives

Procedure or service	Fee reduction applicable to	Percentage fee reduction
Protocol assistance, initial and follow-up requests	SME sponsors	100%
	Non-SME sponsors	75%
Pre-authorisation inspection	All sponsors	100%
Initial marketing authorisation application	SME sponsors	100%
	Non-SME sponsors	10%
Post authorisation applications and annual fee, in the first year from granting of a marketing authorisation	SME sponsors	100%

Table from document EMA/60514/2011

Criteria – evaluated by the COMP

Rarity (a condition affecting no more than 5 in 10,000) / Insufficient Return of investment

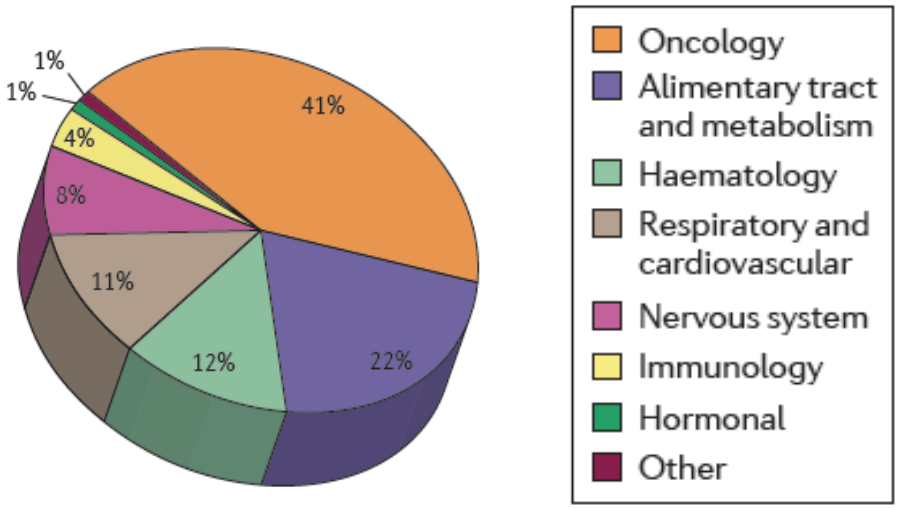
Seriousness (Life –threatening or chronically debilitating)

Medical plausibility an implicit criterion ("intended for…")

Exisiting Methods: If satisfactory methods exist the sponsor should establish that the product will be of **significant benefit**

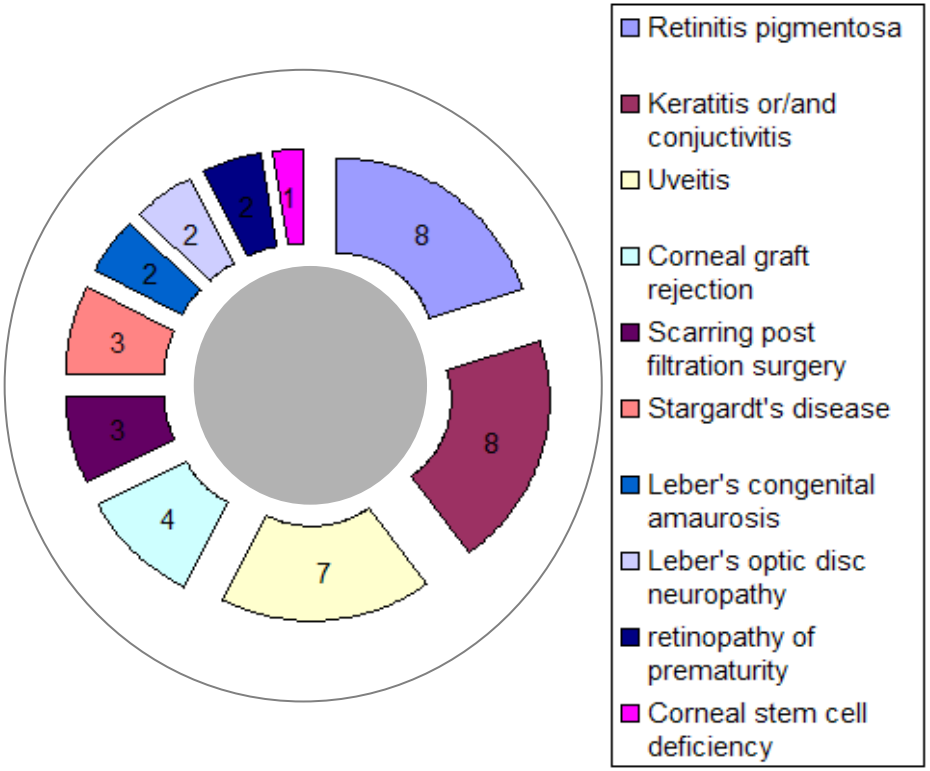
Review at the Marketing Authorisation stage

How many orphan eye products on the market?



Distribution of orphan drug marketing authorizations by therapeutic area
(Adopted from Nature reviews, Drug Discovery, volume 10 May 2011 341-9)

How many orphan designations?



The case of RP

Active substance	Disease / condition	Date of decision
4,7,10,13,16,19-Docosahexaenoic acid	Treatment of retinitis pigmentosa	02/11/2006
9-*cis*-Retinyl acetate	Treatment of retinitis pigmentosa	13/05/2011
Adeno-associated viral vector containing DNA encoding an RNAi targeting rhodopsin / adeno-associated viral vector containing a rhodopsin gene	Treatment of rhodopsin-linked retinitis pigmentosa	17/12/2010
Adenovirus associated viral vector serotype 4 containing the human RPE65 gene	Treatment of retinitis pigmentosa	13/11/2007
Allogeneic human umbilical cord tissue-derived cells	Treatment of retinitis pigmentosa	01/04/2008
Lentiviral vector containing the human *MYO7A* gene	treatment of retinitis pigmentosa in Usher syndrome 1B	23/03/2010
Recombinant human proinsulin	Treatment of retinitis pigmentosa	10/02/2009
Recombinant human rod-derived cone viability factor	Treatment of retinitis pigmentosa	28/11/2007

From the Agency's website

RP case study: a distinct condition?

"Recognised distinct medical entities would generally be considered as valid conditions…in terms of their specific characteristics, e.g. pathophysiological, histopathological, clinical…" (Guideline ENTR/6283/00 Rev3)

"A subset…could be considered as a valid condition…if such characteristics are essential for the medicinal product to carry out its function" (Guideline ENTR/6283/00 Rev3)

RP case study: medical plausibility (1)

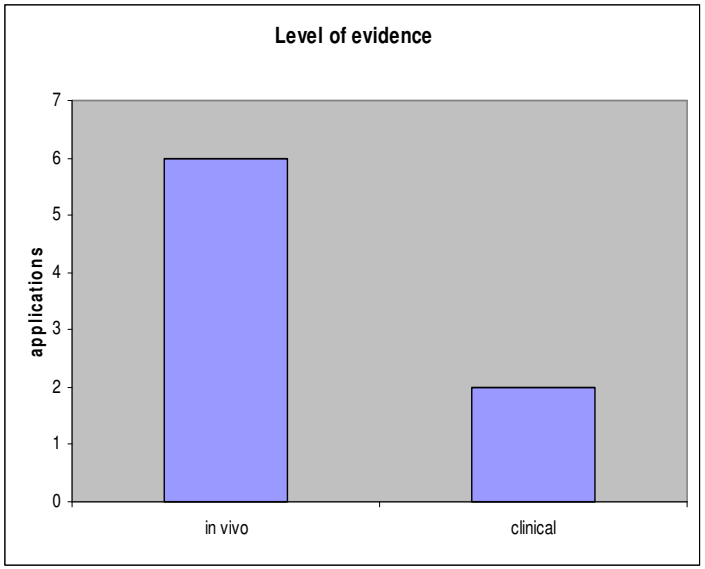
"The sponsor shall submit an application at any stage of the development of the medicinal product before the application for marketing authorisation is made" Reg (EC) No 141/2000

Retinitis Pigmentosa			*genetic basis*	*phenotype and progression*
rd mouse	Natural	1978	Heterozygous deficiency in cGMP PDE subunit	Early and rapid (<10 days) retinal degeneration, ERG perturbation until 2 months age.
rd10 mouse	Natural	2007	Missense homozygous mutation in the PDE6Brd 10 gene (beta-subunit of rod PDE)	Retinal degeneration, with sclerotic retinal vessels at 4 weeks of age. Delayed phenotype.
Rpe65-/- mouse	Transgenic	1998	Mutation in retinal epithelium specific protein	Early loss of cone photoreceptors, altered expression of ECM constituents and cytoskeletal proteins. No rod loss.
RCS rat	Natural	1962	Mutation of receptor tyrosine kinase (Mertk) (mutation in human gene causes RP)	Phagocytis of PR affected PR degeneration by the third week of age, leading to blindness at 3 months.
P23H rat	Transgenic	2002	Heterozygous mutation in rhodopsin P23H gene	PR degeneration and abnormal rod function, measured at day 21, and progressive for several months
Rpe65-/- dog (briad)	Natural	1999	Mutation in retinal epithelium specific protein	Vision defects begins at 5weeks of age, affecting mainly rod, and leading to loss of vision similar to human

Table extract adopted from G.Vaquer EMA internal report 2009

RP case study: medical plausibility (2)

Proof of concept study with the product as proposed on the condition as applied for, in either a valid preclinical model or in preliminary clinical settings



RP case study: severity

Seriously debilitating or life-threatening

> Retinitis pigmentosa is a long-term debilitating disease because it causes the patient's sight to get worse, eventually leading to blindness.

SAMPLE from the EMA website

RP case study: prevalence

- Sponsors advised to consider the Points to consider document on "calculation and Reporting of the prevalence of a condition for orphan designation" (EMEA/COMP/436/01)
- Clear methodology, clear conclusion

What is the estimated number of patients affected by the condition?

At the time of designation, retinitis pigmentosa was estimated to affect less than 3 in 10,000 people in the European Union (EU)*. This is equivalent to a total of fewer than 152,000 people, and is below the ceiling for orphan designation, which is 5 people in 10,000. This is based on the information provided by the sponsor and the knowledge of the Committee for Orphan Medicinal Products (COMP).

SAMPLE from the EMA website

RP case study: significant benefit

- Need for SB justification is conditional on the existence of satisfactory (authorised) methods for diagnosis prevention or treatment
- No medicinal products authorised at the time of designation, an argumentation on why the current methods are not considered satisfactory needed

Uveitis case study

Active substance	Disease / condition	Date of decision	Decision	Medicine name
Cyclo {{(E,Z)-(2S,3R,4R)-3-hydroxy-4-methyl-2-(methylamino)nona-6,8-dienoyl}-L-2-aminobutyryl-N-methyl-glycyl-N-methyl-L-leucyl-L-valyl-N-methyl-L-leucyl-L-alanyl-D-alanyl-N-methyl-L-leucyl-N-methyl-L-leucyl-N-methyl-L-valyl}	Treatment of chronic non-infectious uveitis	14/09/2007	Positive	
Dexamethasone (intravitreal implant)	Treatment of non-infectious uveitis affecting the posterior segment of the eye	04/08/2010	Withdrawn	
E. Coli heat-shock protein 70 with bovine retinal S-antigen	Treatment of autoimmune uveitis	24/01/2006	Positive	
Fluocinolone acetonide (prolonged-release intravitreal implant)	Treatment of non-infectious uveitis affecting the posterior segment of the eye	06/03/2005	Positive	
HLA-B27-derived peptide (amino acid 125-138)	Treatment of autoimmune uveitis	02/09/2004	Positive	
Recombinant human monoclonal antibody to human interleukin (IL)-17A of the IgG1/k class	Treatment of chronic non-infectious uveitis	02/02/2010	Positive	
Sirolimus	Treatment of chronic non-infectious uveitis	30/08/2011	Positive	

From the Agency's website

Significant Benefit: Uveitis case study

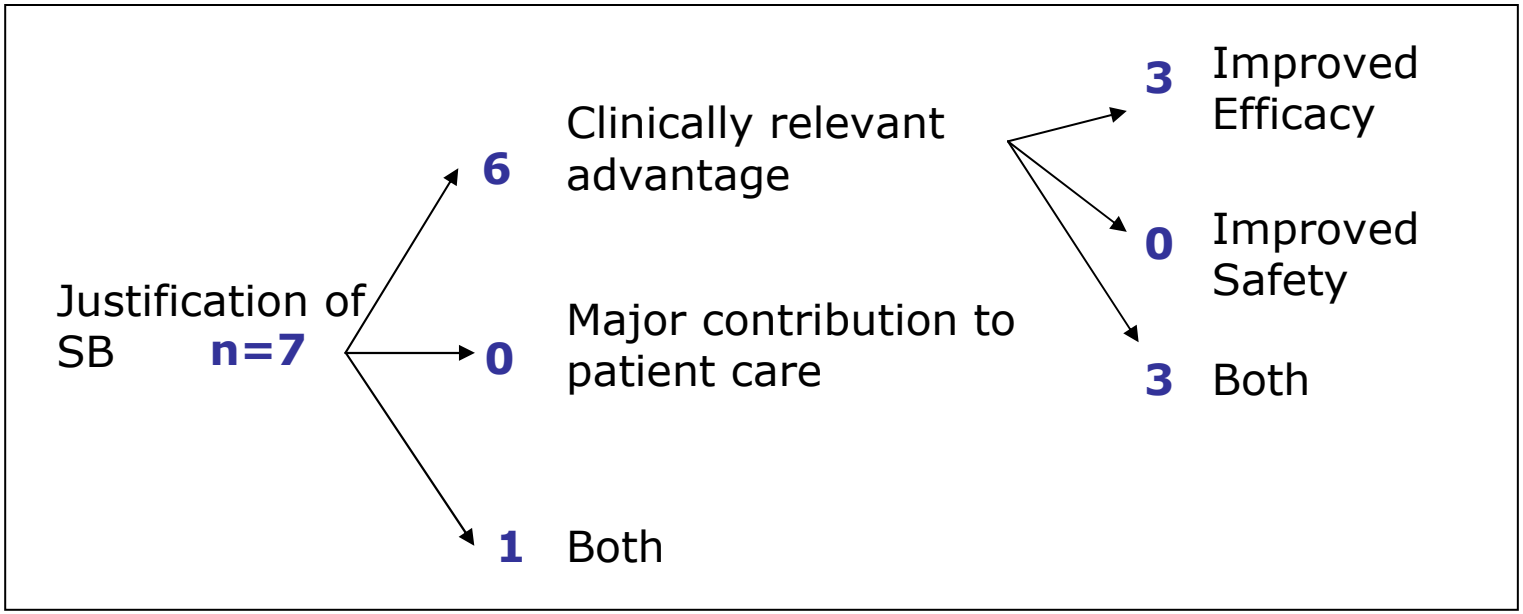
Establishing the basis for a comparative discussion.

- Drugs authorised for the treatment of the condition: corticosteroids and several immunosuppressive agents (e.g. antimetabolites, T-cell inhibitors)

Arguments for justification: a clinicaly relevant advantage or major contribution to patient care

- Well justified assumption has to be reviewed at the MA stage
- A clinically relevant advantage (e.g. a potential for improved efficacy, safety, relevant PK properties) or a major contribution to patient care (e.g. formulation improvement, considerably improved access)

Significant Benefit: Uveitis case study



Withdrawals during evaluation

- Only a couple applications vs. 40 positive opinions
- Challenges in distinct entity delineation (and consequently issues with prevalence)
- Is it a distinct entity or a common complication of several underlying diseases?
- Challenges in significant benefit?

Adopted from www.jpl.nasa.com

Committee on Orphan Medicinal Products (Gate opener)

OD application may be submitted at any stage of development

If unsuccessful re-application is possible (any stage of development!)

Concluding remarks

- A gap between orphan designation and marketing authorisations for eye disorders
- Applications for designation so far very successful for ophthalmological products
- Designations may be granted at any stage of development provided the criteria are met
- Prospective applicants invited to submit an intent to file and arrange for a pre-submission meeting TC/F2F

Thanks very much!

More information at

http://www.ema.europa.eu/ema

- special_topics
- medicines for rare diseases

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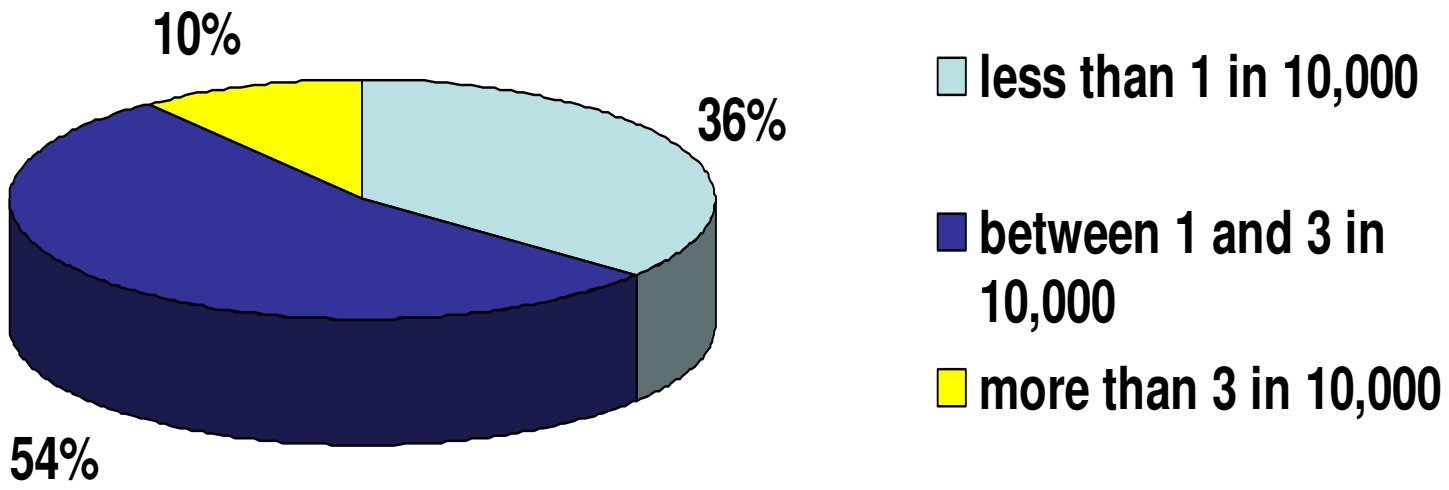
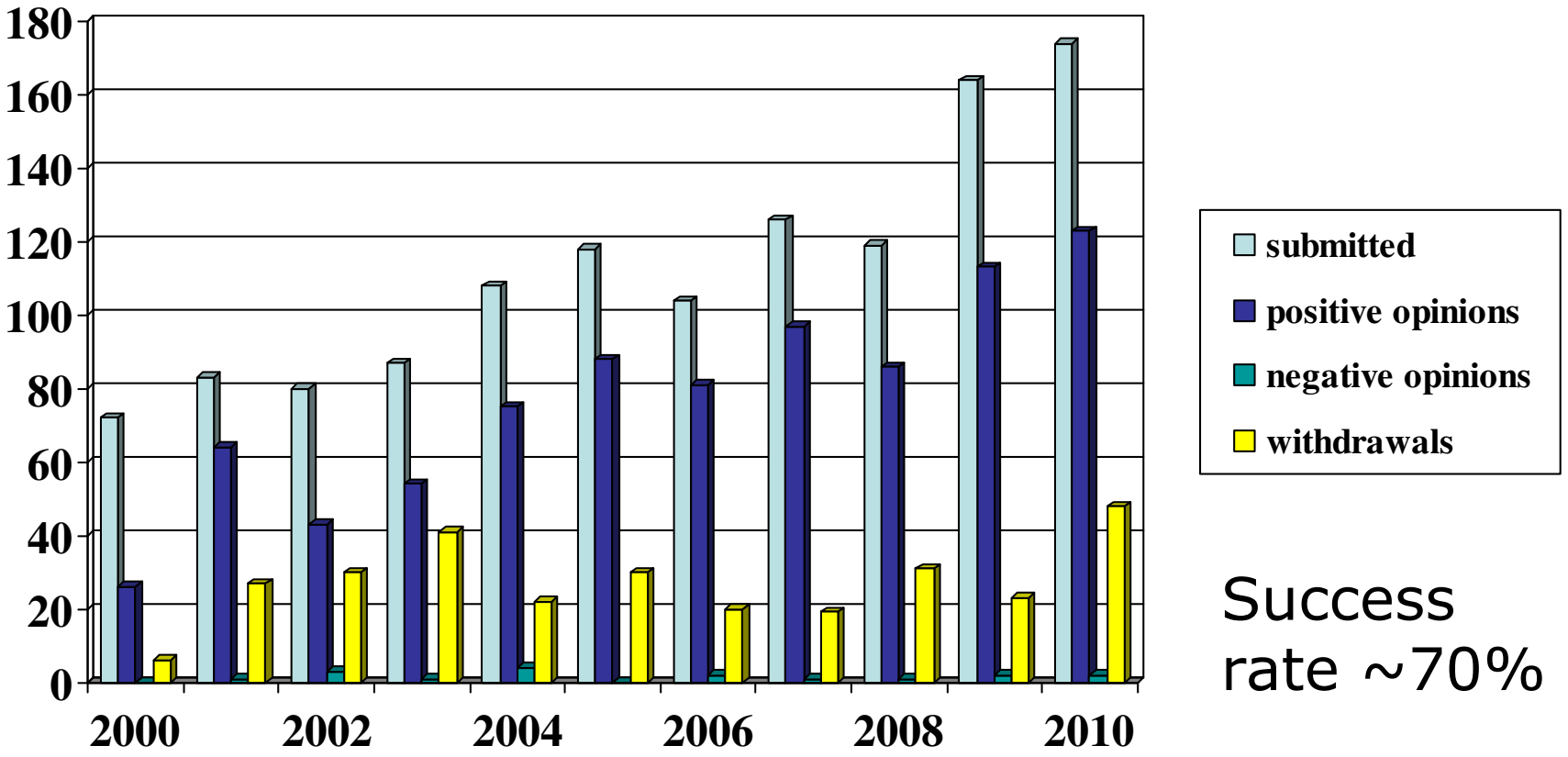
Backup slides

Prevalence Designated Conditions – Jan 2011



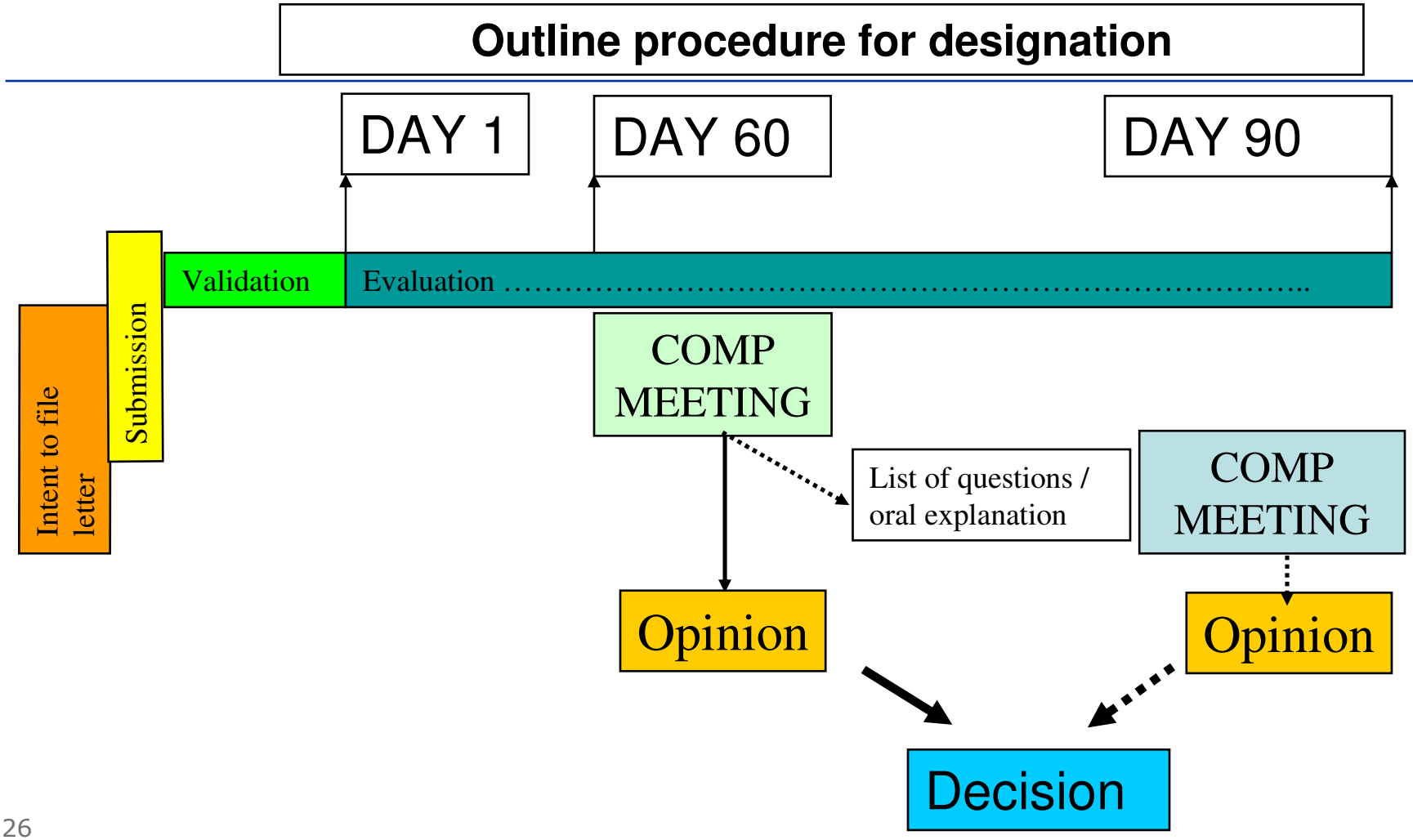
Outcome of designations - Jan 2011



Success rate ~70%

Procedure for Designation

- Pre-submission teleconference / face to face meeting
- Submission of electronic Application to Agency
- Maximum of 90 days for review by (may be done in 60 days)
- Scientific Opinion on Criteria
- Oral explanations in front of Committee if doubts (list of questions)


Outline procedure for designation
DAY 1
DAY 60
DAY 90
Intent to file letter
Submission
Validation
Evaluation ……
COMP MEETING
List of questions / oral explanation
COMP MEETING
Opinion
Opinion
Decision