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Application for marketing authorisation of orphan drugs - the European experience -

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Authorisation of Orphan Drugs in Europe History (1)

- Pre 1998 and ongoing
  - Marketing authorisation through national approval and mutual recognition
- 1998 Commission proposal for Community Procedure
  - Designation of orphan drug status
  - Incentives for development and authorisation
    - Market exclusivity

Authorisation of Orphan Drugs in Europe History (2)

- 1998 Commission proposal for Community Procedure
- 2000 OrphanDrugs Regulation 141/2000 (EC)
  - Designation criteria (COMP evaluation, EC decision)
    - Prevalence ≤5/10,000
    - Life-threatening or chronically disabling disease
    - No satisfactory method or ”significant benefit”
  - Incentives for development and authorisation
    - Fees, Protocol Assistance
    - Market exclusivity in indication 10 years
      - for ”similar” substance unless ”clinically superior”
  - Marketing authorisation (CHMP evaluation, EC decision)
    - Full access to Community MA procedure
    - ”Normal” evaluation criteria (Q,S;E)

Authorisation of Orphan Drugs in Europe History (3)

- 1998 Commission proposal for Community Procedure
- 2000 OrphanDrugs Regulation 141/2000 (EC)
- 2001 First Community marketing authorisations of designated orphan drugs
  - Fabrazyme
  - Replagal

Authorisation of Orphan Drugs in Europe History (4)

- 1998 Commission proposal for Community Procedure
- 2000 OrphanDrugs Regulation 141/2000 (EC)
- 2001 First Community marketing authorisations
- 2005 Revised pharmaceutical legislation
  - Centralised Procedure compulsory for orphan drugs

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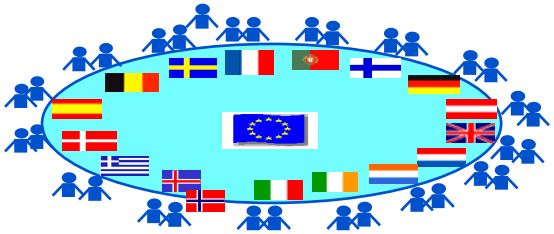
The Centralised European Procedure

EMEA: European Medicines Agency, **CHMP**: Committee for Medicinal Products for Human Use;
COMP: Committee for Orphan Medicinal Products;
BPWG: Working Group on Blood Products; **BWP**: Biotech Working Party; **EWP**: Efficacy Working Party; **PhVWP**: Pharmacovigilance Working Party; **QWP:** Quality Working Party; **SAWP**: Scientific Advice Working Party
SWP: Safety Working Party

EU Commission
(DG3 Industry/Pharmaceuticals/Cosmetics)
Standing Committee

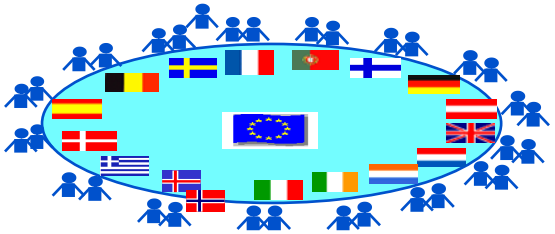
EMEA

CHMP



CHMP's working parties :
BPWG, BWP, EWP,
PhVWP, QWP,
SAWP, SWP
Ad hoc groups
External experts (SAG)

COMP



National Competent Agencies Network
Scientific and Regulatory Expertise

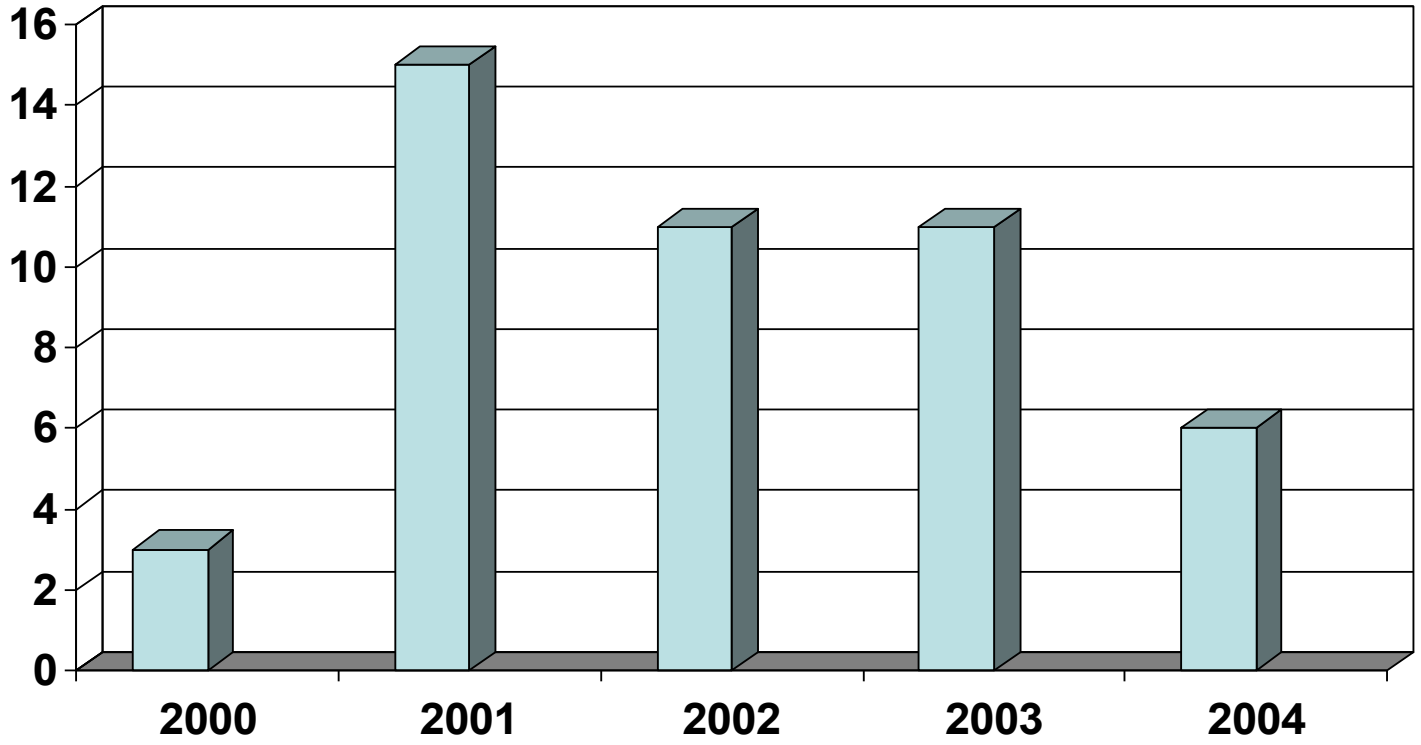
Centralised Procedure
Outcome

- EU marketing authorisation
- One set of product information (SPC, PL)
- European Public Assessment report
- National information from NCA / other bodies to prescribers / patients

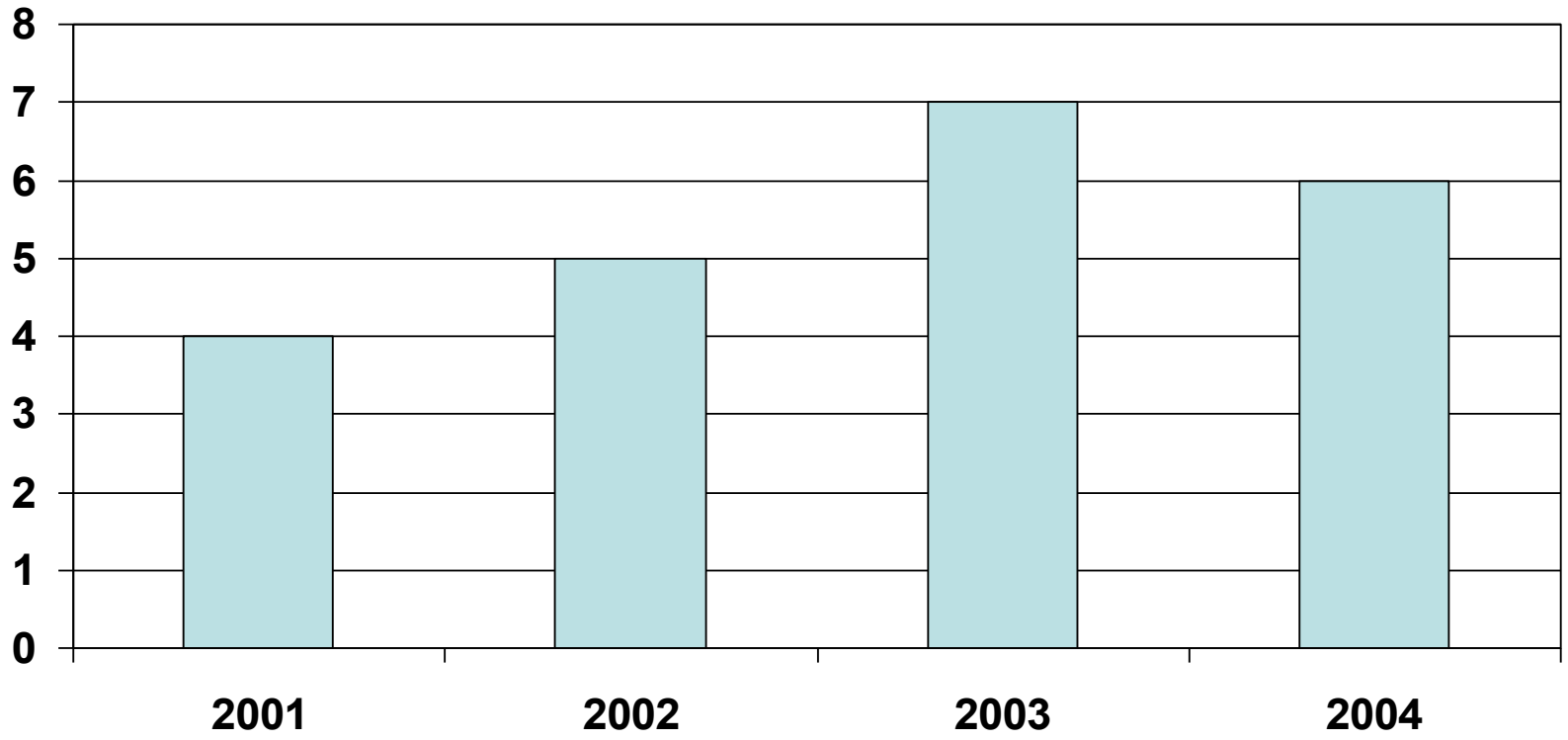
Orphan Designation Applications to COMP

	2000	2001	2002	2003	2004	Total
No. of applications submitted	72	83	80	87	80	402
Positive COMP Opinions	26	64	43	54	61	248
Commission Designations	14	64	49	55	43	225
Final Negative COMP Opinions	0	1	3	1	2	7
Withdrawals after Submission	3	25	24	35	15	119

Submission of Orphan MAAs to EMEA



Orphan CHMP Opinions over time



Approved Orphan MAAs (I)

End 2004

★ **Seventeen authorisations granted to date**

- ➢ Fabrazyme for Fabry disease
- ➢ Replagal for Fabry disease
- ➢ Glivec for chronic myeloid leukaemia
- ➢ Tracleer for pulmonary arterial hypertension
- ➢ Trisenox for acute promyelocytic leukaemia
- ➢ Somavert for acromegaly
- ➢ Zavesca for Gaucher disease
- ➢ Carbaglu for hyperammonaemia
- ➢ Aldurazyme for Mucopolysaccharidosis
- ➢ Busilvex (iv) for haematopoietic progenitor cell transplantation
- ➢ Ventavis for pulmonary arterial hypertension

Approved Orphan MAAs (II)

End 2004

★ **Seventeen authorisations granted to date**

- Onsenal for Familial Adenomatous Polyposis
- Photobarr for Barrett's oesophagus
- Litak for hairy cell leukaemia
- Lysodren for adrenal cortical carcinoma
- Pedea for patent ductus arteriosus
- Wilzin for Wilson's disease
- Xagrid for essential thrombocythaemia

Other outcomes of Orphan MAAs end 2004

Two negative opinions

- Serostim for AIDS wasting
- Yondelis for soft tissue sarcoma

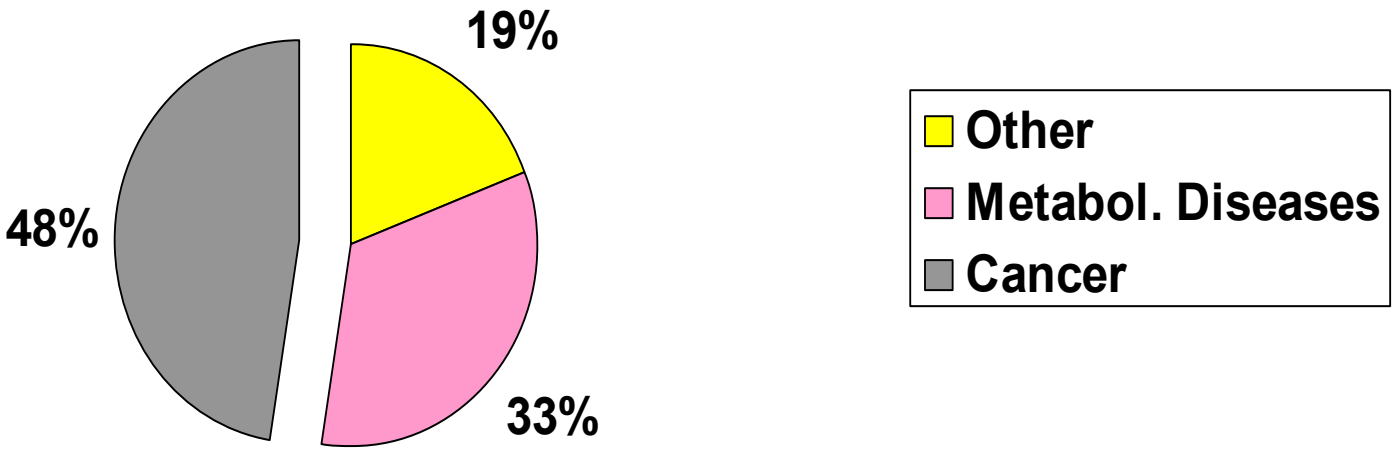
Seven applications for MA withdrawn

- for amyotrophic lateral sclerosis
- for methanol poisoning
- for advanced cutaneous T cell lymphoma
- for erythema nodosum leprosum
- for pulmonary arterial hypertension
- for multiple myeloma
- for Wegener's granulomatosis

Eleven centralised applications in review process

Four applications filed through Mutual Recognition

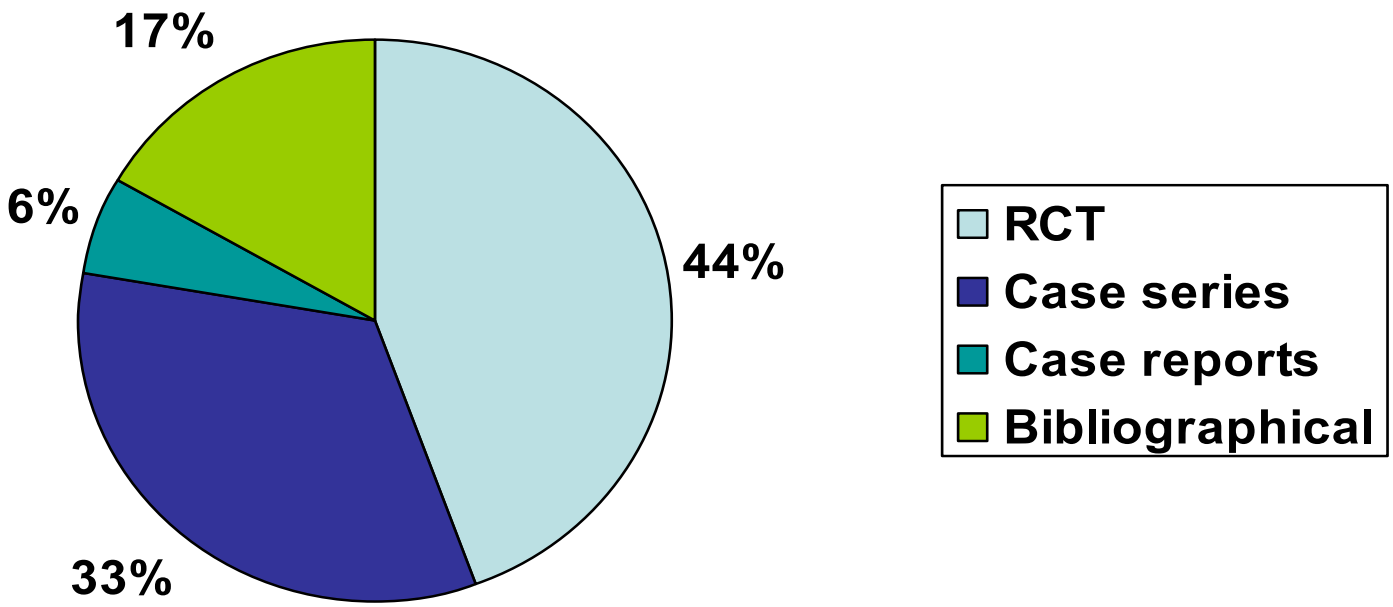
Orphan CHMP opinions



Challenges

1. Regulatory decision on (very) small databases
   - MA should be based on ”normal” requirements

Overview clinical studies in positive CHMP opinions



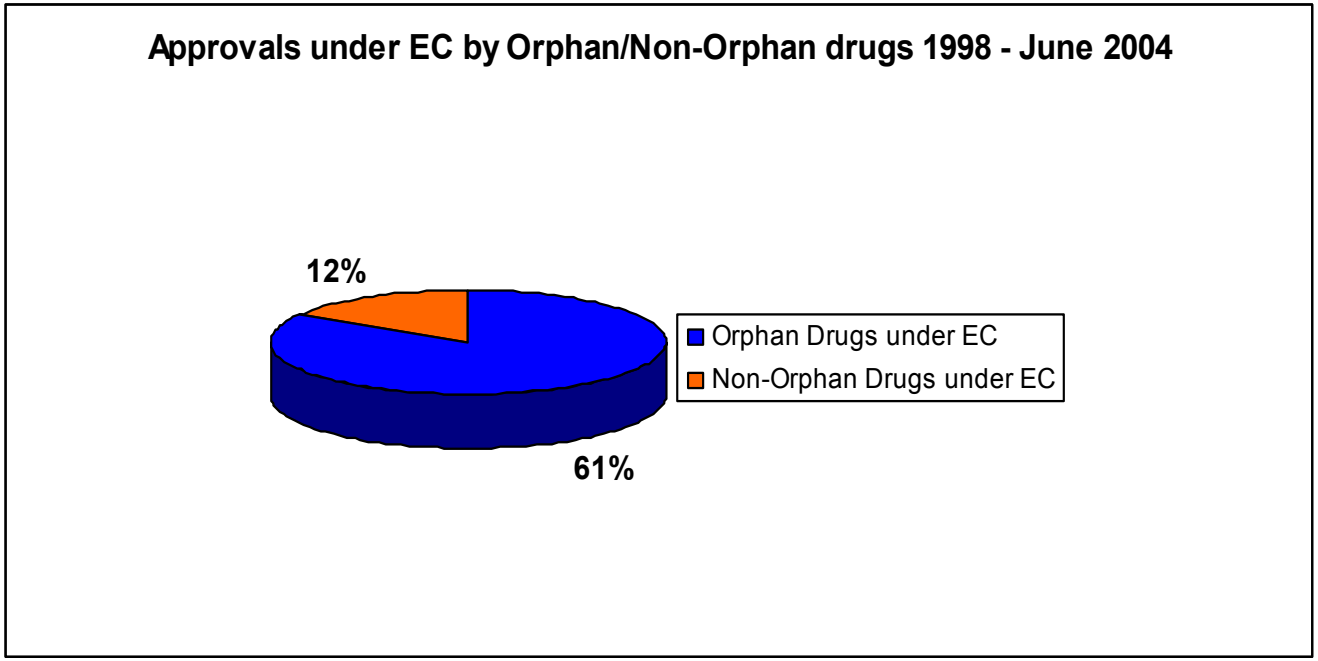
Overview clinical studies in positive opinions

	Efficacy Patients (active)	Safety patients
Fabrazyme	58 (29)	73
Replagal	41 (21)	43
Trisenox	52	251
Tracleer	246 (166)	174
Zavesca	82	96
Somavert	157 (111)	167
Carbaglu	12	20
Busilvex	102	103
Aldurazyme	45 (22)	55
Wilzin	191 bibliographic	255
Orfadin	207 compassionate	>500
Litak	63	523

Challenges and tools

1. Regulatory decision on (very) small databases
   - Restricted authorisation
     - Approval under Exceptional Circumstances
     - Conditional Approval
     - EU Compassionate Use

Approved under Exceptional Circumstances 1998 – June 2004



Challenges and tools

1. Regulatory decision on (very) small databases
   - Restricted authorisation
     - Approval under Exceptional Circumstances
     - Conditional Approval
     - EU Compassionate Use
   - Improving methods for data interpretation and study designs
     - Work within CHMP Efficacy Working Party
     - Implementation through Protocol Assistance

Challenges

2. Prospective learning from post-marketing experience

Challenges and tools

2. Prospective learning from post-marketing experience
   - Making Marketing Authorisation a (new) Starting Point
     - Constructive / Feasible Obligations
       - Aiming at maximal data generation on targeted issues
       - Interaction with Scientific Advice / Protocol Assistance
     - Some degree of across-products perspective

Tracleer (bosentan)

- Endothelin receptor antagonist for PAH
- Pivotal study vs. PLA
  - Significant effect in primary endpoint: 6 min walking distance in patients with PAH stage III
  - Safety concern: High incidence of LFT elevation of unclear significance
- SO Pharmacovigilance: TRAX PMS system
  - Centralised supply (per country)
  - Identification of prescribers
  - Information to identified prescribers
  - Solicited, selective AE reporting to Internet-based system

Tracleer (bosentan)
5th TRAX report March 2004

Country	Centres currently participating in TRAX PMS	Known TRACLEER-treated patients	Entered into TRAX PMS	% of patients enrolled in TRAX database
TRACLEER commercially available				
Austria	17	91	60	66 %
Denmark	3	13	13	100 %
Finland	5	7	7	100 %
France	159	794	705	89 %
Germany	185	876	724	83 %
Greece	34	156	140	90 %
Ireland	2	50	45	90 %
Italy	56	435	365	84 %
The Netherlands	25	126	120	95 %
Norway	3	21	15	71 %
Sweden	26	90	84	93 %
Spain	2	302	24	8 %
The United Kingdom	13	480	463	96 %
Total	**530**	**3 441 ***	**2 765**	**80 %**

Challenges and tools

3. Prospective interaction during product development
   - Improved use of Protocol Assistance
     - New therapies/technologies
     - Small and medium-sized enterprises
     - Transparency and proactivity
     - Increased expert consultation
       - including patient representatives

Challenges and tools

4. Issues of ”signficant benefit”, ”similarity” and ”clinical superiority”
   - Significant benefit – COMP
   - Similarity/superiority – CHMP
     - EC draft guideline released for consultation

Orphan Drugs- the European experience from CHMP level

- Orphan Drug Regulation is a working legal basis
  - Large influx of products to Community Register
  - Reasonable number of MAA with reasonable success rate
    - Worthwhile addition to patient care

- Licensing Procedure functional - in evolution
  - Able to produce consistent and predictable decisions
  - Can improve on Protocol Assistance use and performance
  - May benefit from additional regulatory tools
    - conditional approval
  - Will gain from improved quality and focus of post-marketing obligations
    - importance of external expertise