EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Conditional Marketing Authorisations in the European Union

FDA ODAC meeting, Silver Spring – 08 February 2011

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CONTENTS

1. EU Regulations and Guidance

Regulatory Background

- March 2004: Review of EU Pharmaceutical Legislation

  Art 14(7)*: "Following consultation with the applicant, an authorisation may be granted subject to certain **specific obligations**, to be reviewed annually by the Agency.
  Such authorisation shall be **valid for one year** [*instead of 5*], on a renewable basis."

  Motivation*: "*In order to meet, in particular, the legitimate expectations of patients and to take account of the increasingly rapid process of science and therapies.*"

- March 2006: European Commission implementing Regulation 'on the Conditional Marketing Authorisation' adopted

* Art 14(7) and Recital 33 of Regulation (EC) No 726/2004 of 31 March 2004

Commission Regulation and CHMP Guideline on "Conditional Marketing Authorisation" (MA)*

- **Scope**: medicinal products for
  - Seriously debilitating or life-threatening diseases
  - Emergency threats (WHO, EU Commission)
  - Orphan medicinal products

- **Requirements**

  A Conditional MA may be granted when, although comprehensive clinical data have not been provided, all of the following requirements are met:

  a) Benefit/Risk balance is positive

  b) It is likely that comprehensive clinical data will be provided

  c) Unmet medical needs will be fulfilled

  d) Benefit to public health of immediate availability outweighs risks that additional data are still required

* Regulation (EC) No 507/2006 of 29 March 2006; draft CHMP Guideline EMEA/509951/2006 of 5 December 2006

- Conditional MA will be subject to **specific obligations** to complete ongoing studies, or to conduct new studies with a view to confirming the positive Benefit/Risk balance.

  Applicant to provide reassurance on the **feasibility** and quality of additional studies to be performed

  "*where (timely) completion of further studies required for the confirmation of the Benefit/Risk can not be expected, this may lead to a negative opinion on the granting of a conditional MA*"

- Financial **penalties** in case of infringement of the specific obligations

- Nature of approval, obligations and timeframes **publicly available**

- Conditional MA only for **initial MA** Applications, not for variations (supplements)

- Conditional MA **valid for one year**, renewable

- **Renewal of Conditional MA:**
  - confirm the Benefit/Risk balance
  - review status of the Specific Obligations

  ➔ MA Holder to submit:

  · Overview of data submitted since the granting of Conditional MA, status / outcome of assessment

  · Specific Obligation data and/or PSUR data, when due at renewal

  · Interim report on the status of the Specific Obligations (*synopsis, accrual, event rates, adverse events, expected timing of endpoint analyses, study conduct and compliance, issues which may impact on feasibility or timing of study*)

  ➔ CHMP to assess renewal application within 90 days
  Confirm Benefit-Risk balance or recommend regulatory action
  May modify 'label' (SmPC), Specific Obligations and timeframes

- Upon fulfilment of all specific obligations, the conditional MA may **convert** to a 'normal' MA

"MA Under Exceptional Circumstances"

- Available since the start of EMA's Centralised Procedure
  Confirmed in the 2004 Review of EU pharmaceutical legislation*

- Applicant **unable** to provide comprehensive clinical data because of:
  - rarity of the disease
  - present state of scientific knowledge
  - ethical constraints

  → Marketing Authorisation 'under Exceptional Circumstances'

- **"Specific Procedures / Obligations"** - focus on safety studies

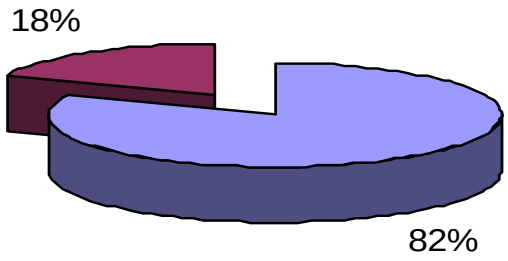
- MA valid for 5 years (renewable), but
  annual re-assessment of the benefit/risk balance by CHMP

* Art 14(8) of Regulation (EC) No 726/2004; previously Art 13(2) of Regulation (EC) No 2309/93

2. EMA Experience

New Marketing Authorisation Applications
Use of 'Exceptional Circumstances' 1995-2005*

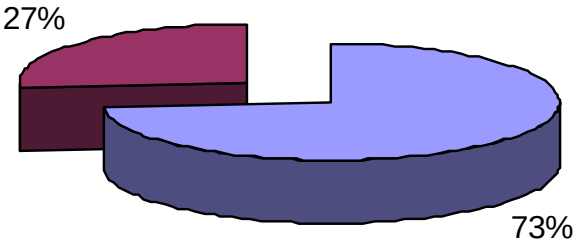
All therapeutic areas (incl oncology)



'Normal' MA

MA under Exceptional Circumstances

Oncology

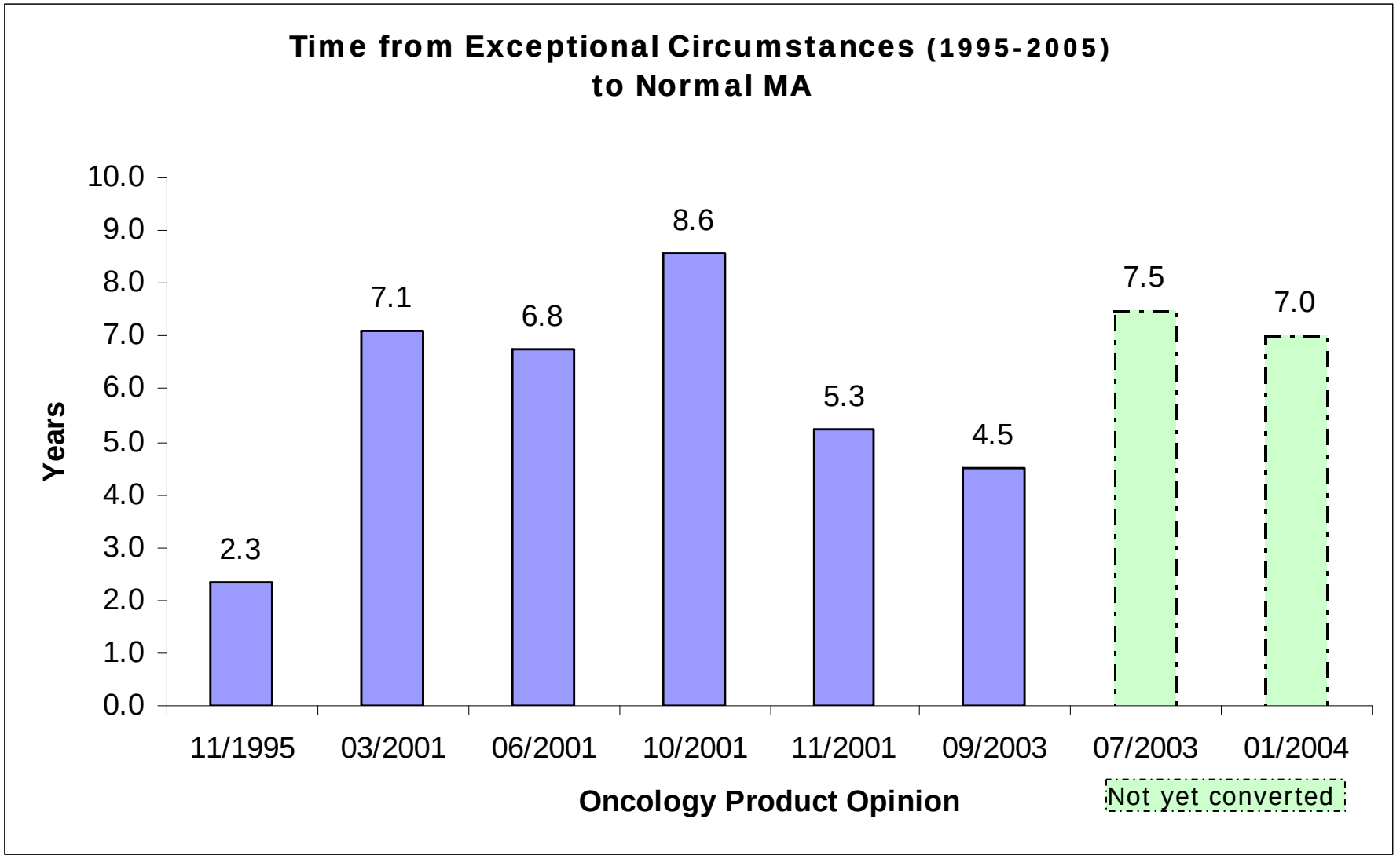


'Normal' MA

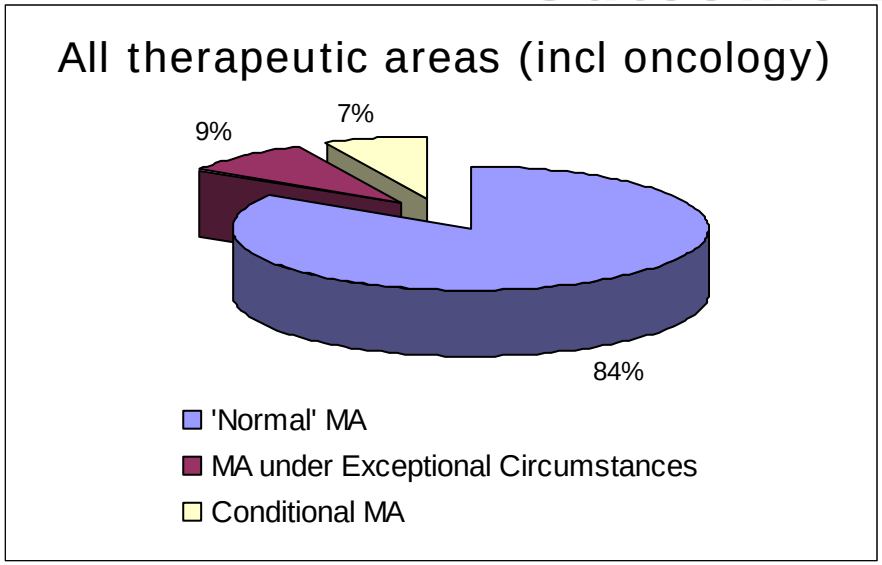
MA under Exceptional Circumstances

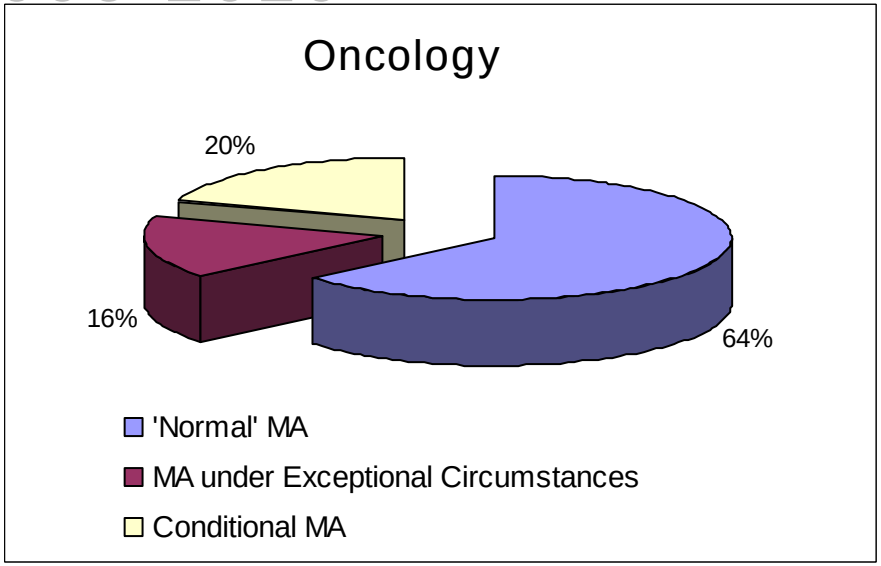
Taxotere (docetaxel)
Foscan(temoporfin)
MabCampath (alemtuzumab)
Trisenox (arsenic trioxide)
Glivec (imatinib)
Xagrid (anagrelide),
Velcade (bortezomib)
Zevalin(ibritumomab)

* CHMP Opinions; excluding duplicates


Time from Exceptional Circumstances (1995-2005) to Normal MA
Years
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
2.3
7.1
6.8
8.6
5.3
4.5
7.5
7.0
11/1995
03/2001
06/2001
10/2001
11/2001
09/2003
07/2003
01/2004
Oncology Product Opinion
Not yet converted

New Marketing Authorisation Applications Outcome 2006-2010*





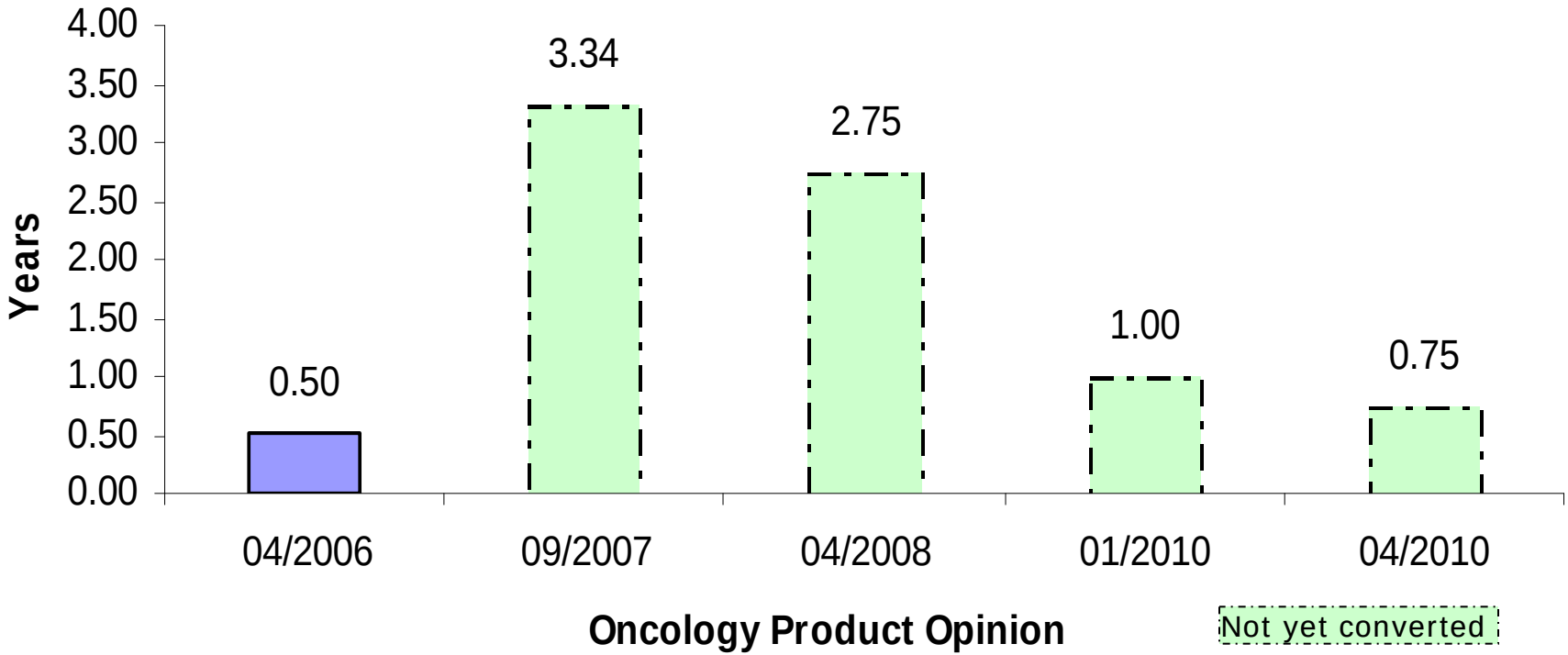
CHMP Opinions* (Oncology)	2006	2007	2008	2009	2010
'Normal' MA	2	5	4	4	1
Except Circum	1 Evoltra(clofarabine)	2 Atriance(nelarabine) Yondelis(trabectedin)	1 Ceplene (histamine)	0	0
Conditional MA	1 Sutent (sunitib)	1 Vectibix (panitumumab)	1 Tyverb (lapatinib)	0	2 Arzerra (Ofatumumab) Votrient (pazopanib)

*CHMP Opinions; Art 8(3) applications only; excluding duplicates

EU Conditional MA – oncology

- **Efficacy data at time of approval**, *e.g.*
  - Phase II single-arm trial(s); ORR endpoint (*Sutent, Arzerra*)
  - Single randomised controlled Phase III trial; TTP or PFS endpoint (*Vectibix, Tyverb, Votrient*)

- **Confirmatory efficacy data requested as Specific Obligation**, *e.g*
  - Updated OS analysis of pivotal trial
  - Results from ongoing Phase III randomised controlled trials; PFS or OS endpoint
  - New randomised controlled Phase III trial, incl. non-inferiority
  - New Phase IV observational study
  - Data on use and performance of KRAS testing kits


Time from Conditional MA (2006-2010) to Normal MA
Years
4.00
3.50
3.00
2.50
2.00
1.50
1.00
0.50
0.00
0.50
3.34
2.75
1.00
0.75
04/2006
09/2007
04/2008
01/2010
04/2010
Oncology Product Opinion
Not yet converted

EU Scientific Advice on Conditional MA

2006-2010: 91 Scientific Advice procedures on Conditional MA
37 for oncology products

- Questions on eligibility for Conditional MA
- Questions on adequacy of efficacy data at time of MA submission
- Questions on adequacy of safety database at time of MA submission
- Questions on design of Specific Obligation studies

Parallel Scientific Advice from EMA and FDA possible

3. Conclusions

- EU legislative framework & guidance on Conditional MA in place. In effect since April 2006.

- Medicinal products **fulfilling unmet medical need**
  For severe, life-threatening or rare diseases
  Different trial design and endpoints than usually expected
  Positive benefit-risk balance to be demonstrated
  'Specific Obligation' data from ongoing and new studies

- **Yearly renewal** for Conditional MA: ensures close monitoring of compliance with post-authorisation data requirements

- Early Access tools (Conditional MA and Except Circum) applied to approx. 2 new oncology products per year.

- Seek **EU Scientific Advice** on Conditional MA **early** during development

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Thank you

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