Conditional regulation of orphan drugs

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My background

- PhD thesis: role of users in innovation
- TU Delft, VU, Dialogic, Rathenau Instituut
- Innovation studies group (UU)

- Demand articulation in emerging tech
- User-driven innovation
- Public-private partnerships
- Innovation and regulation

Perspective: orphans as precursors

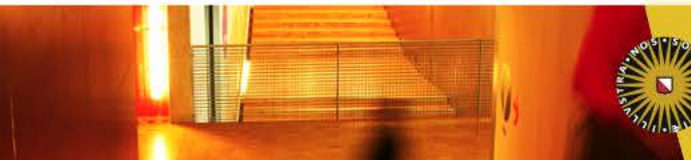
- Orphan drugs as ‘model’ for future of pharma
- Problems show earlier with ‘orphans’
- Examples: personalized medicine and small patient groups, market access problems, etc.

Conditional approvals

Jarno Hoekman; Wouter Boon; Marie De Bruin

Hoekman et al (submitted) Use of the conditional marketing authorisation pathway for oncology medicines in Europe.

Boon et al (2014) Improving the EU system for the marketing authorisation of medicines'. TI Pharma/Escher, http://escher.tipharma.com/fileadmin/media-archive/escher/Reports/Escher_report_IA.pdf)



Conditional marketing authorisation

- Goal:

"In order to meet unmet medical needs... it may be necessary to grant marketing authorisation on the base of less complete data than is normally the case"

[≠ approvals under exceptional circumstances]

- Scope:

(i) Seriously debilitating or life-threatening diseases; (ii) Emergency threats (WHO, EC); (iii) Orphan medicinal products

Evaluation criteria

- positive-risk benefit balance;
- likely that comprehensive risk/benefit data will be provided;
- unmet medical needs are fulfilled;
- benefit of quick access outweighs risk

Specific obligations to be full-filled post-marketing: complete ongoing studies/conduct new studies; yearly renewal of MA in case of positive risk/benefit balance; financial penalties in case of infringement of obligations

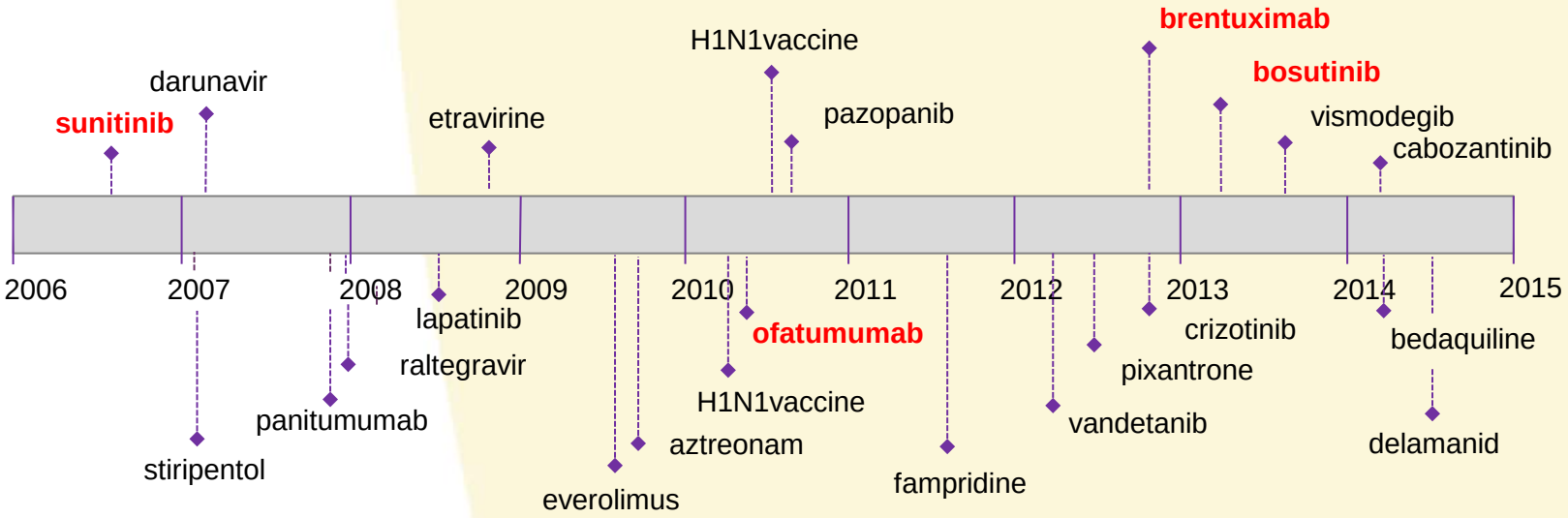
Cancer
12 (52%)

HIV
3 (13%)

23

Other
6 (26%)

Influenza
2 (9%)



Aim of the study

- To provide insight in how the CMA pathway has been used for the authorisation of oncology medicines in the period 2006-2013
- Comparative perspective
  - Examine how use of CMA for oncology medicines compares to (i) use of standard MA for oncology medicines and (ii) authorisation of oncology medicines by FDA
- Process perspective
  - Examine how CMA was used in individual MA procedures of oncology medicines (from scientific advice to conversion to standard MA)

Sample and data

- Sample
  - All new active substances that were granted a first standard MA (n=31) or conditional MA (n=11) at EMA for an oncology indication in the period 2006-2013

- Data sources
  - European Public Assessment Reports
  - Review documents from drugs@FDA
  - Interviews with industry representatives, (former) CHMP members and (former) European Commission officials

Submitted evidence

	Conditional MA (n=11)	Standard MA (n=31)	P-value
# of patients in pivotal study	154 [106-435]	626 [370–808]	<0.001
Pivotal study is RCT	5 (46%)	28 (90%)	0.005
Primary endpoint in pivotal study			
OS	0 (0 %)	19 (61%)	
PFS	3 (27 %)	7 (23%)	
TTP	1 (9 %)	1 (3%)	
Response rate	7 (64%)	4 (13%)	<0.001
# of patients in safety population	876 [357-1572]	1027 [584-1675]	0.606

Timelines

	Conditional MA (n=11)	Standard MA (n=31)	P-value
Development time in days	2074 [1821–2656]	2307 [1866–3615]	0.864
Total assessment time in days	513 [433-569]	390 [296-442]	0.002
Active assessment time in days	203 [183-210]	204 [201-210]	0.437
Clock stop time in days	190 [142-255]	120 [55-159]	0.004
EC decision time in days	84 [69 – 96]	62 [57 – 81]	0.038
Accelerated assessment, n (%)	0 (0%)	6 (19%)	0.312

Time to marketing authorisation

- We observed a significant difference in time to MA since IND submission when comparing all 11 conditionally authorized products (EMA) with all 10 accelerated approved oncology products (FDA): accelerated approved products are faster

Procedures

	Conditional MA (n=11)	Standard MA (n=31)	P-value
Scientific advice, n (%)	8 (73%)	24 (77%)	1.000
SAG-O meeting, n (%)	8 (73%)	9 (29%)	0.029
List of outstanding issues	1 [1-2]	1 [1-1]	0.063
Consensus vote, n (%)	6 (55%)	27 (87%)	0.038
Appeal procedure, n (%)	1 (9%)	0 (0%)	0.262

Post-marketing safety issues

- Post-marketing safety issues:
  - Boon et al (2010): less safety-related withdrawals, more DHCPs for CA&EC products
  - Fear to withdraw for products with no alternative?

- Compliance:
  - US: 40% post-marketing studies to start; # completed studies increases (Fain & Daubresse, 2013)
  - In EU slightly better (Blake et al, 2011)

Request for CMA: industry or regulators?

- 2 out of 11 requests by companies before start of MA
- 1 upfront requests denied because of lack of unmet medical need
- 1 request by company during clarification meeting at day 120
- 1 request by company around day 150
- 7 proposals by regulators upon or after day 180
- 1 proposal by regulators during appeal procedure

Success accelerated pathways?

- Companies apply ‘wait-and-see’ and prefer standard approval
  - ‘Conditional’ seen as stigma?
  - Not eager to be committed to long-term post-marketing studies
- Evaluation criteria unclear
  - Positive risk-benefit as criteria?
  - What is an unmet medical need?

→ Not well aligned with expectations of patients, healthcare professionals, payers about the function of early-access pathways

Conditional reimbursement

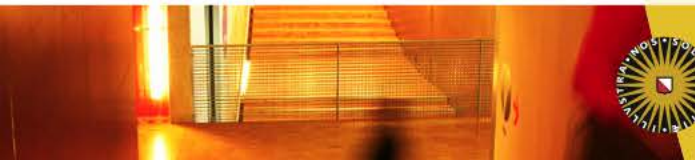
Wouter Boon; Marc Koopmanschap; Luis Martins
i.s.m. Stuurgroep Weesgeneesmiddelen

Boon (2011) Doelmatigheidsonderzoek Weesgeneesmiddelen –analyse en toekomstperspectief (http://www.npzz.nl/wp-content/uploads/2011/08/WGM-Onderzoek-doelmatigheid-Eindversie.pdf)

Boon et al (2015) Governance of conditional reimbursement practices in the Netherlands. Health Policy 119(2), 180-185

Long history of orphan reimbursement

- Since introduction of Taxol (1993)
  - Pressure by patient groups, media, Parliament, firms, hospital boards
  - Medical specialists creating guidelines
  - Ministry creating subsidies and, later, ‘beleidsregels’
- Conditional reimbursement (2007)
- First re-evaluations in 2012; ‘media outrage’



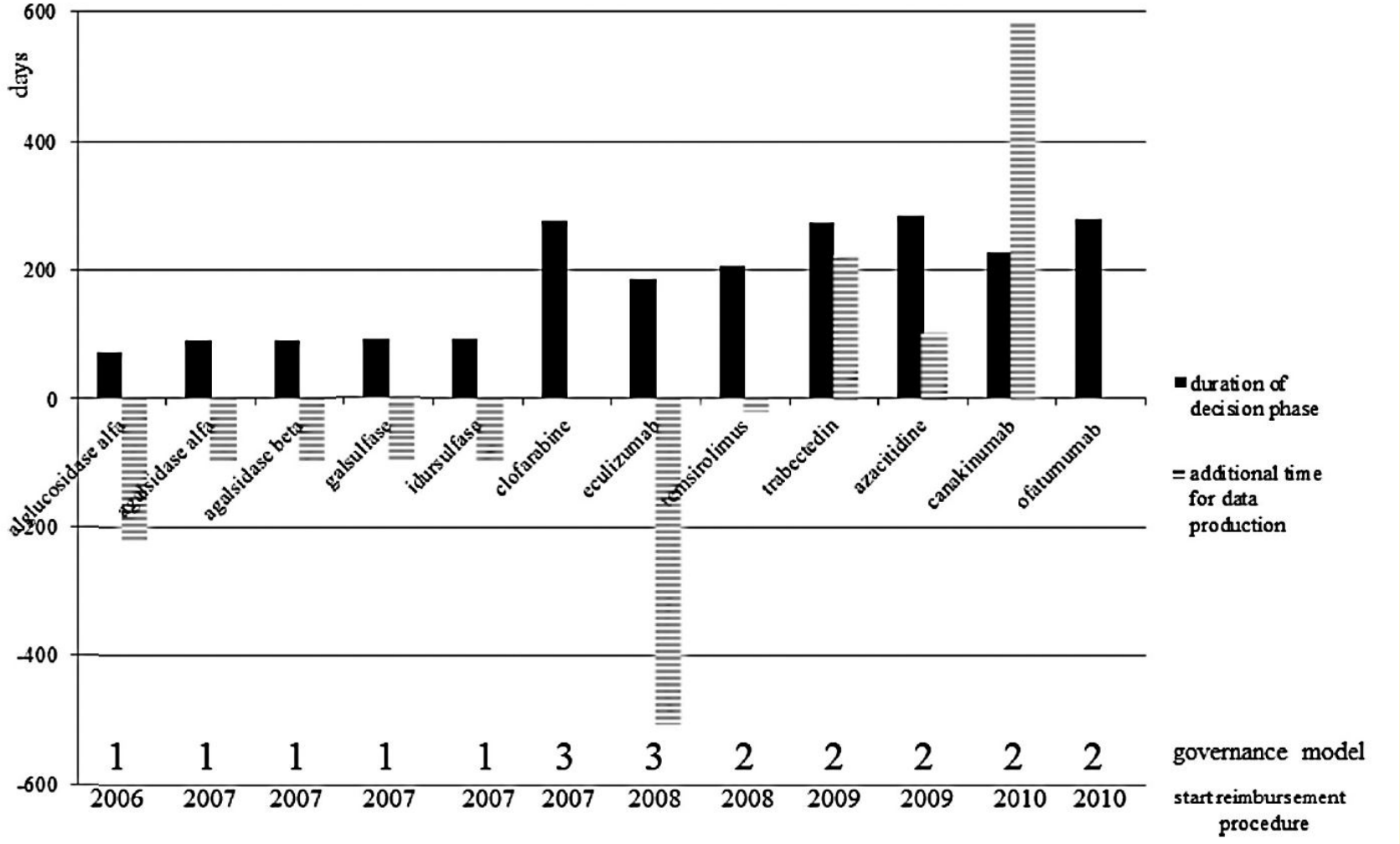
T=0	stofnaam	merknaam	ziekte	bedrijf	arts-onderzoekers
	laronidase	Aldurazyme	MPS I	Genzyme	UMCU, Erasmus MC, AMC
26-02-'07	alglucosidase alfa	Myozyme	ziekte van Pompe	Genzyme	Erasmus MC
25-06-'07	agalsidase alfa	Replagal	ziekte van Fabry	Shire (vroeger TKT Europe AB)	AMC
25-06-'07	agalsidase beta	Fabrazyme	ziekte van Fabry	Genzyme	AMC
25-06-'07	galsulfase	Naglazyme	MPS VI	Biomarin	Erasmus MC
25-06-'07	idursulfase	Elaprase	MPS II	Shire	Erasmus MC
07-01-'08	clofarabine	Evoltra	ALL bij kinderen	Genzyme (Bioenvision)	Erasmus MC
16-06-'08	eculizumab	Soliris	PNH	Alexion	UMC Nijmegen
15-12-'08	temsirolimus*	Torisel	gemetastaseerd niercelcarcinoom	Wyeth	onbekend
15-12-'09	azacitidine*	Vidaza	myelodysplastisch syndroom (MDS)	Celgene	onbekend
15-07-'10	trabectedin	Yondelis	weke delen sarcoom	PharmaMar	LUMC
in aanvraag	canakinumab	Ilaris	caps bij volwassenen en kinderen vanaf 4 jaar	Novartis Europharm Ltd.	
in aanvraag	histamine dihydrochloride	Ceplene	acute myeloide leukemie AML	EpiCept GmbH	
aanvraag afgewezen	icatibant - acetate	Firazyr	acuut angio-oedeem	Shire (Jerini AG)	AMC
aanvraag afgewezen	plerixafor	Mozobil	progenitorcellen voorafgaand aan stamceltransplantatie	Genzyme	

Criteria and consequences

Invulling criteria	Gevolg
Geen dossier ingediend op T=4 Onvoldoende data in dossier Kostendrempel niet gehaald	Geen beoordeling CFH en negatief advies richting NZa
Kostendrempel wel gehaald maar therapeutische minderwaarde	Negatief advies richting Nza (waarschijnlijk niet besproken door RvB van het CVZ)
Kostendrempel gehaald, therapeutische meerwaarde maar onvoldoende onderbouwde doelmatigheid of onvoldoende doelmatigheid	Negatief advies richting Nza (waarschijnlijk niet besproken door RvB van het CVZ)
Kostendrempel gehaald, therapeutische meerwaarde, voldoende onderbouwde doelmatigheidsdata, maar onzekerheid over doelmatigheid	Discussie in RvB en waarschijnlijk advies van Advies Commissie Pakket
Kostendrempel gehaald, therapeutische meerwaarde, voldoende onderbouwde doelmatigheidsdata, voldoende doelmatigheid	Positief advies richting Nza (waarschijnlijk niet besproken door RvB van het CVZ)

CVZ (2010) Procedure herbeoordeling intramurale geneesmiddelen. CVZ, Diemen.

Efficiency of re-evaluation process



Despite fine-tuning…

- Quality of cost-effectiveness research?

- Perspectives on cost-effectiveness
  - McCabe: disease burden, spin-off, no alternatives; no positive public preference → utilitarian approach: ‘the greatest good for the greatest number’
  - Hughes en Drummond: rights-based approach: ‘individuals in society have right on minimal level of health’

- Political and ethical considerations enter the debate

Conclusions

- ‘Conditional’ promises flexibility and opportunities
- Regulating uncertainties + emphasizing obligations
- But: uneven division of risks? Suboptimal pathway?

- Future conditional/early-access schemes should take time to learn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Thank your for your attention!
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