Deutsche Gesellschaft
für Innere Medizin e.V. ®

Opinion-Leader-Meeting

Seltene Erkrankungen –
Defizite, Chancen, Perspektiven
„Keine Krankheit ist zu selten“
18. /19. Januar 2019
Schloss Reinhartshausen,
Eltville-Erbach

Orphan Drugs – Chancen und Herausforderungen aus Sicht der AkdÄ

Wolf-Dieter Ludwig
Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ)

„Orphan Drugs“ (OD) – *Historie*

- **Verordnung (EG) Nr. 847/2000 der EC vom 27.4.2000**
- **Prävalenz:** nicht mehr als 5 von 10.000 Personen betroffen
- **Wirtschaftlichkeitkriterium: …** „ohne Anreize vermutlich nicht genügend Gewinn bringen“
- **Patienten mit seltenen Leiden haben denselben Anspruch auf Qualität, Unbedenklichkeit und Wirksamkeit von OD wie andere Patienten**
- Definitionen: u.a. **„erheblicher Nutzen“ („significant benefit“)**; **„klinisch überlegen“**: AM im Vergleich zu einem zugelassenen AM für seltene Leiden **nachweislich zusätzlich einen oder mehrere erhebliche therapeutische Vorteile**:
  - größere Wirksamkeit
  - größere Sicherheit bei einem erheblichen Teil der Zielpopulation(en)
  - bedeutenden Beitrag zur Diagnose oder Behandlung von Patienten

EvaluatePharma®

Orphan Drug Report 2018

Rare disease patient populations are defined in law as:

- **USA:** <200,000 patients (<6.37 in 10,000, based on US population of 314m)
- **EU:** <5 in 10,000 (<250,000 patients, based on EU population of 514m)
- **Japan:** <50,000 patients (<4 in 10,000 based on Japan population of 128m)

Financial incentives by law include:

Orphan drug exclusivity

During the period of marketing exclusivity, the regulatory bodies are barred from approving the same product for the same orphan indication. A product holding several separate orphan designations for different indications can have several separate market exclusivities, which can run concurrently.

- **USA:** Seven years of marketing exclusivity from approval.
- **EU:** Ten years of marketing exclusivity from approval.
- **Japan:** Ten years registration validity period (also known as re-examination period).

Reduced R&D costs

- **USA:** 50% Tax Credit on R&D Cost (owing to new tax legislation, is expected to decrease to 25%).
- **USA:** R&D Grants for Phase I to Phase III Clinical Trials.
- **USA:** User fees waived (FFDCA Section 526: Company WW Revenues <$50m).
- **EU:** EMA protocol assistance at a reduced cost.
- **EU:** Administrative and procedural assistance at a reduced fee for small and medium sized enterprises.
- **EU:** The EMA does not offer research grants but funding is available for the European Commission (EC) and other sources, such as Horizon 2020 and E-Rare.
- **Japan:** Orphan products can be subsidised through the National Institute of Biomedical Innovation (NIBIO).
- **Japan:** Guidance and consultations from the Pharmaceuticals and Medical Devices Agency (PMDA) at a lower user fee.
- **Japan:** 12% of study expenses incurred during the NIBIO payment period can be reported as a tax credit.

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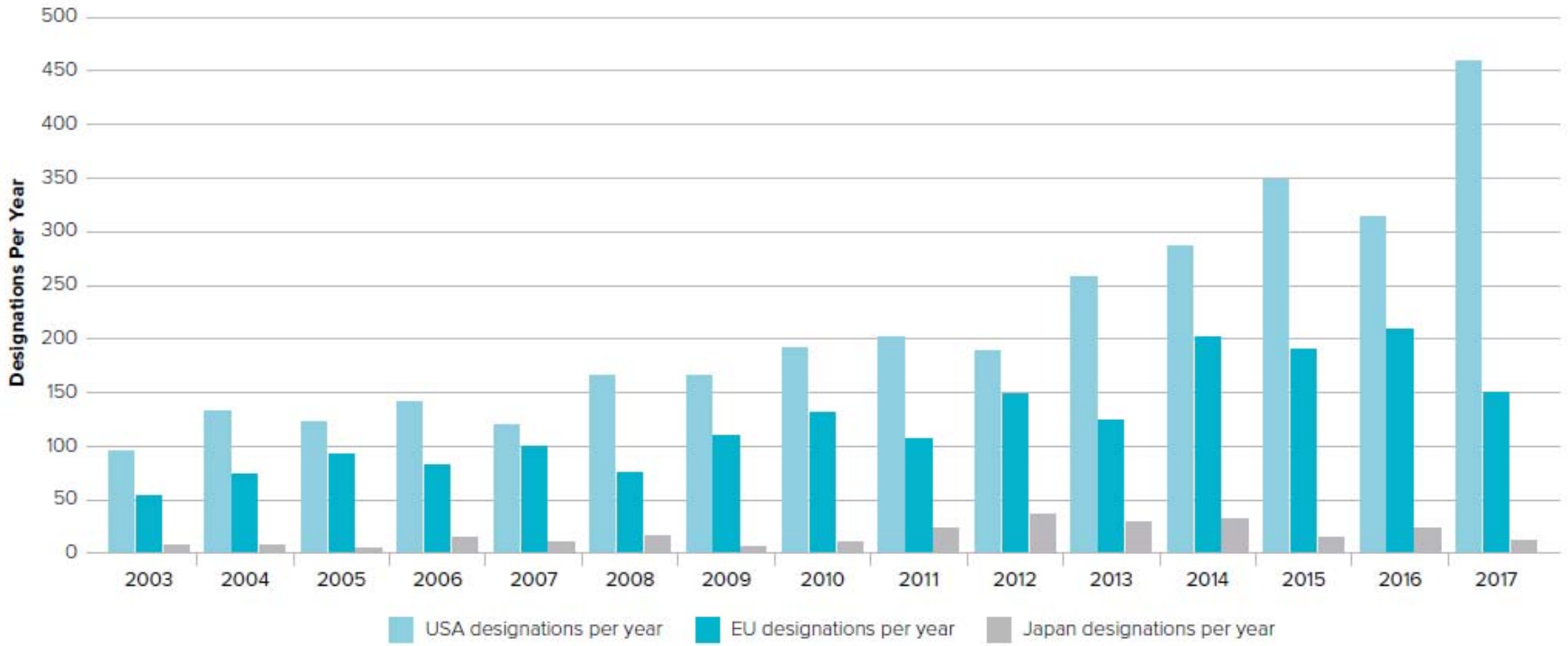
Orphan Drug Report 2018

USA, EU & Japan Orphan Designations per Year (2003-2017)

Source: EvaluatePharma® May 2018



Challenges

Council Conclusions June 2016

"The incentives in orphan legislation need to be proportionate to the goal of encouraging innovation, improving patients' access to innovative medicines with therapeutic added value and budgetary impact, and it should be avoided that circumstances are created that might encourage inappropriate market behaviour of some manufacturers and/or hamper the emergence of new or generic medicinal products and in this way potentially limit patients' access to new medicines for unmet medical needs and that can affect the sustainability of health systems (…)"

Health and Food Safety

[adapted from Kaja Kantorska, 2017]

Challenges

High prices

Is Art. 8(2) implemented well?

Only 1% of rare diseases covered by OMP authorised in the EU

Almost no applications based on "insufficient return on investment"

?

Health and Food Safety

[adapted from Kaja Kantorska, 2017]

BMJ Open

Failures to further developing orphan medicinal products after designation granted in Europe: an analysis of marketing authorisation failures and abandoned drugs

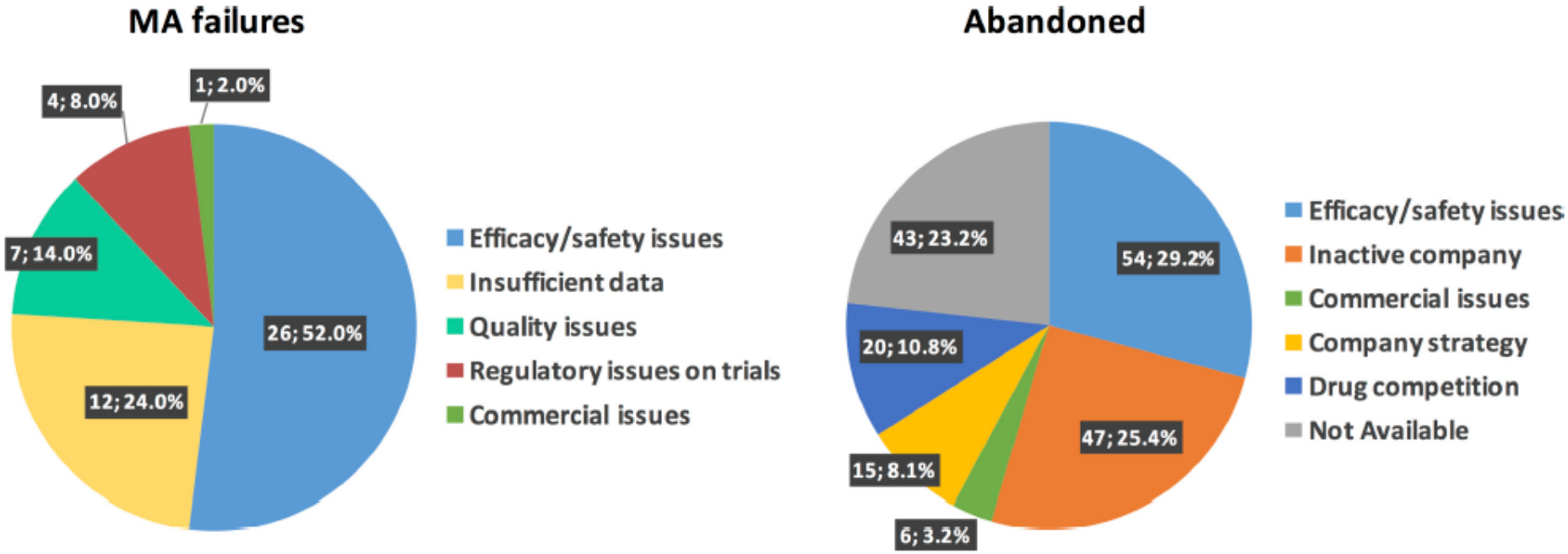


Figure 3 Reasons for failures of abandoned drugs (left) and marketing authorisation (MA) failures (right).

Conclusions This analysis shows that failures occurred in 27.8% of all designations granted in Europe, the main reasons being safety and efficacy issues. Moreover, the stage of development reached by drugs represents a specific risk factor for failures.

Marketing authorisation of orphan medicines in Europe from 2000 to 2013

Matthias P. Hofer[1], Hanna Hedman[1,‡], Maria Mavris[1], Franz Koenig[2], Thorsten Vetter[1], Martin Posch[2], Spiros Vamvakas[1], Jan Regnstrom[1] and Stiina Aarum[1]

Evidenz zum Zeitpunkt der Marktzulassung

TABLE 3

Level of evidence for marketing authorisation for orphan medicines

Prevalence (per 10 000)	Positive MAA	RCT	Bibliographic	Statistical significance	Surrogate primary endpoint	Conditional MA	Exceptional MA
Less than 0.5	32	18 (56%)	4 (13%)	18 (56%)	18 (56%)	3 (9%)	15 (47%)
0.5–1.0	15	7 (47%)	2 (13%)	6 (40%)	10 (67%)	1 (7%)	6 (40%)
1.0–2.0	26	19 (73%)	1 (4%)	19 (73%)	18 (69%)	4 (15%)	4 (15%)
2.0–3.0	14	13 (93%)	1 (7%)	11 (79%)	7 (50%)	2 (14%)	2 (14%)
3.0–5.0	17	13 (73%)	0	13 (76%)	11 (65%)	3 (18%)	1 (6%)
Total	**104**	**70 (67%)**	**8 (8%)**	**67 (64%)**	**64 (62%)**	**13 (13%)**	**28 (27%)**

Drug Discovery Today • Volume 23, Number 2 • February 2018

Characteristics of Clinical Trials to Support Approval of Orphan vs Nonorphan Drugs for Cancer

Aaron S. Kesselheim, MD, JD, MPH
Jessica A. Myers, PhD
Jerry Avorn, MD

JAMA. 2011;305(22):2320-2326

Table 2. Characteristics of Pivotal Preapproval Trials of Orphan and Nonorphan Cancer Drugs

N= 15 OD, N=12 NOD
2004-2010

Characteristics	No. (%)[a] Orphan Drug Pivotal Trials (n = 23)	No. (%)[a] Nonorphan Drug Pivotal Trials (n = 15)	*P* Value
Enrollees, median (interquartile range)	96 (66-152)	290 (185-394)	<.001
Randomized, multigroup	7 (30)	12 (80)	.007
Comparator			
Active	4 (17)	7 (47)	.007
Supportive care	2 (9)	1 (7)	
Placebo	1 (4)	4 (27)	
None	16 (70)	3 (20)	
Blinding			
Double-blind	1 (4)	5 (33)	.04
Single-blind	1 (4)	0	
Open-label	21 (91)	10 (67)	
Primary trial end point reported[b]			
Disease response[c]	17 (68)	4 (27)	.04
Disease progression[d]	4 (16)	6 (40)	
Overall survival	2 (8)	4 (27)	
Other	2 (8)	1 (7)	

Conclusion Compared with pivotal trials used to approve nonorphan cancer drugs, pivotal trials for recently approved orphan drugs for cancer were more likely to be smaller and to use nonrandomized, unblinded trial designs and surrogate end points to assess efficacy.

JAMA. 2011;305(22):2320-2326

Characteristics of Clinical Trials to Support Approval of Orphan vs Nonorphan Drugs for Cancer

The Orphan Drug Act is widely regarded as a watershed piece of legislation that has helped spur the development of numerous useful drugs for rare medical conditions. However, given the limited evidentiary basis on which orphan cancer drugs are approved, the act may need to be amended so that its resources can be more selectively guided to first-in-class drugs or those that treat a condition for which no other treatments are available, and to ensure that orphan products are rigorously evaluated and closely followed up once they are approved.

JAMA. 2011;305(22):2320-2326

ARZNEIMITTEL

Ein Verzicht auf die frühe Nutzenbewertung bei Mitteln gegen seltene Erkrankungen stößt auf heftige Kritik (DÄ 42/2010: „Arzneimittelmarktneuordnungsgesetz: Zu guter Letzt ist alles selten“ von Jürgen Windeler, Klaus Koch, Stefan Lange und Wolf-Dieter Ludwig).

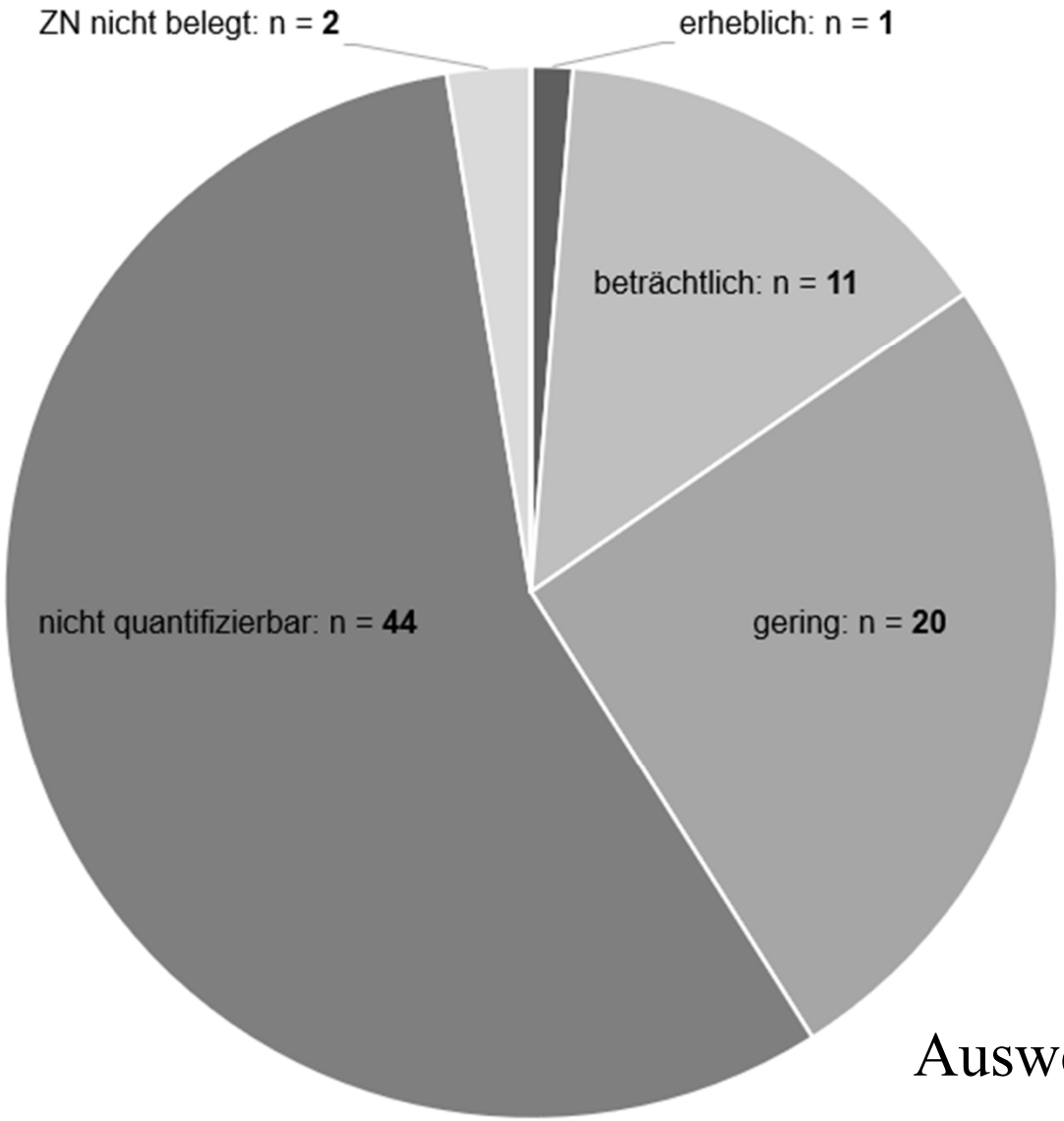
Jedes Maß verloren?

Die Autoren wollen offensichtlich für die Nutzenbewertung andere Regeln als die EU anlegen, sonst bedürfte es keiner doppelten Nutzenbewertung. Denn wie sonst sollen IQWiG und G-BA im Rahmen der (frühen) Nutzenbewertung von Orphan Drugs zu anderen Ergebnissen kommen als die EU-Kommission?

**„Was in Europa als Zusatznutzen gilt,
muss auch auf nationaler Ebene ein Zusatznutzen bleiben“.**

Prof. Dr. Barbara Sickmüller,
Stellv. Hauptgeschäftsführerin des Bundesverbands der Pharmazeutischen Industrie e.V. (BPI),
10117 Berlin

Ergebnisse der frühen Nutzenbewertung bei **Orphan Drugs**



Auswertung AkdÄ

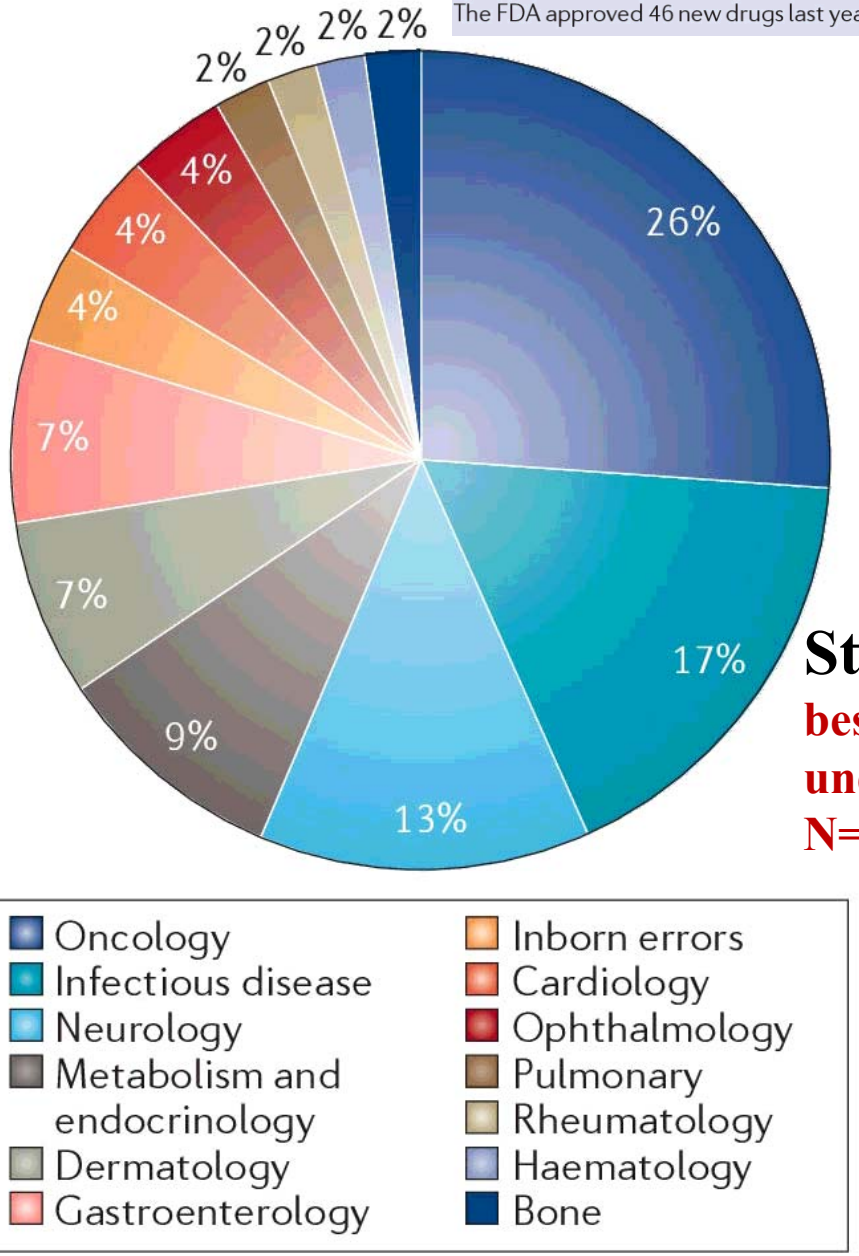
21.12.2018

2017 FDA drug approvals

The FDA approved 46 new drugs last year, the highest total in more than two decades.

Zulassungen nach Anwendungsgebiet FDA 2017

N=46



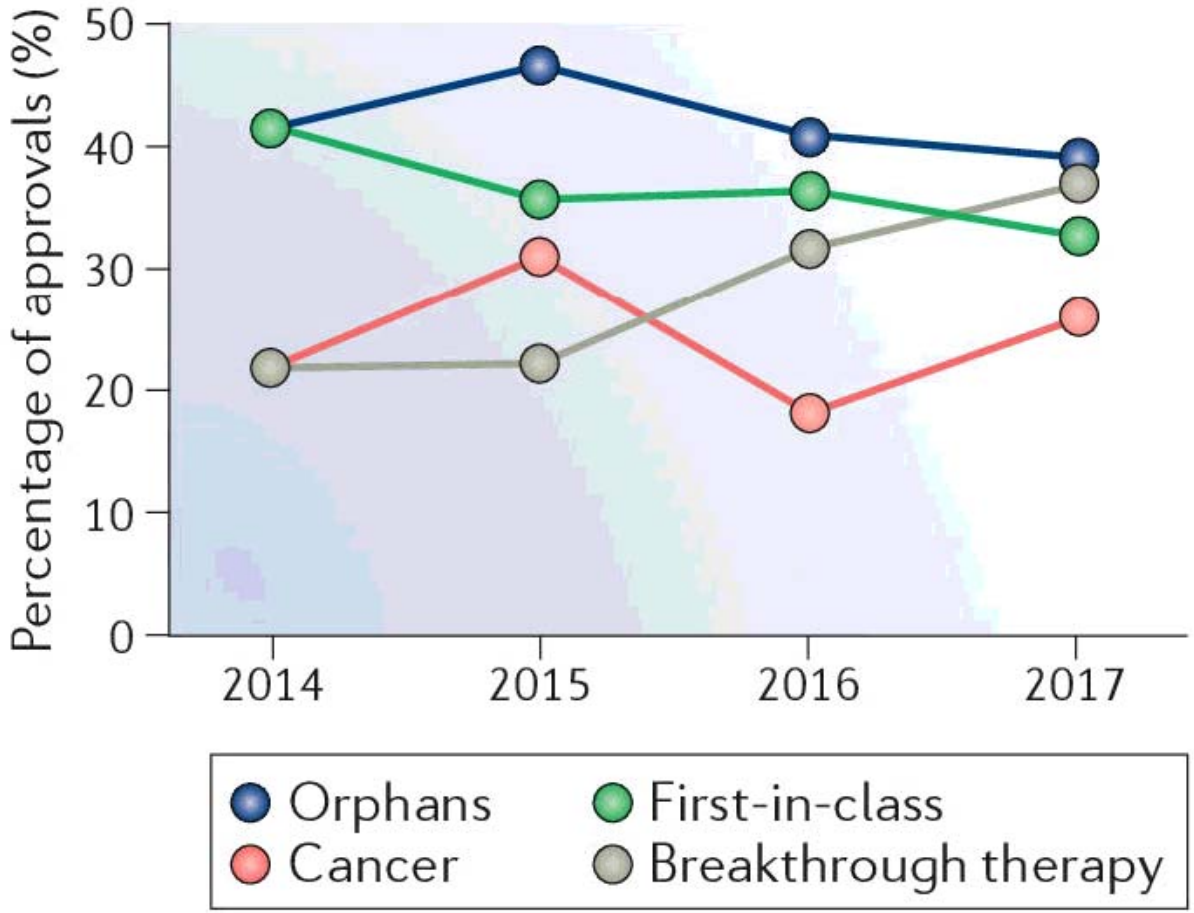
Standard N=12

beschleunigte Zulassung und/oder „Orphan Drugs“

N=34

> There is almost a herd mentality right now to move towards oncology, immunotherapies and the rare disease drugs

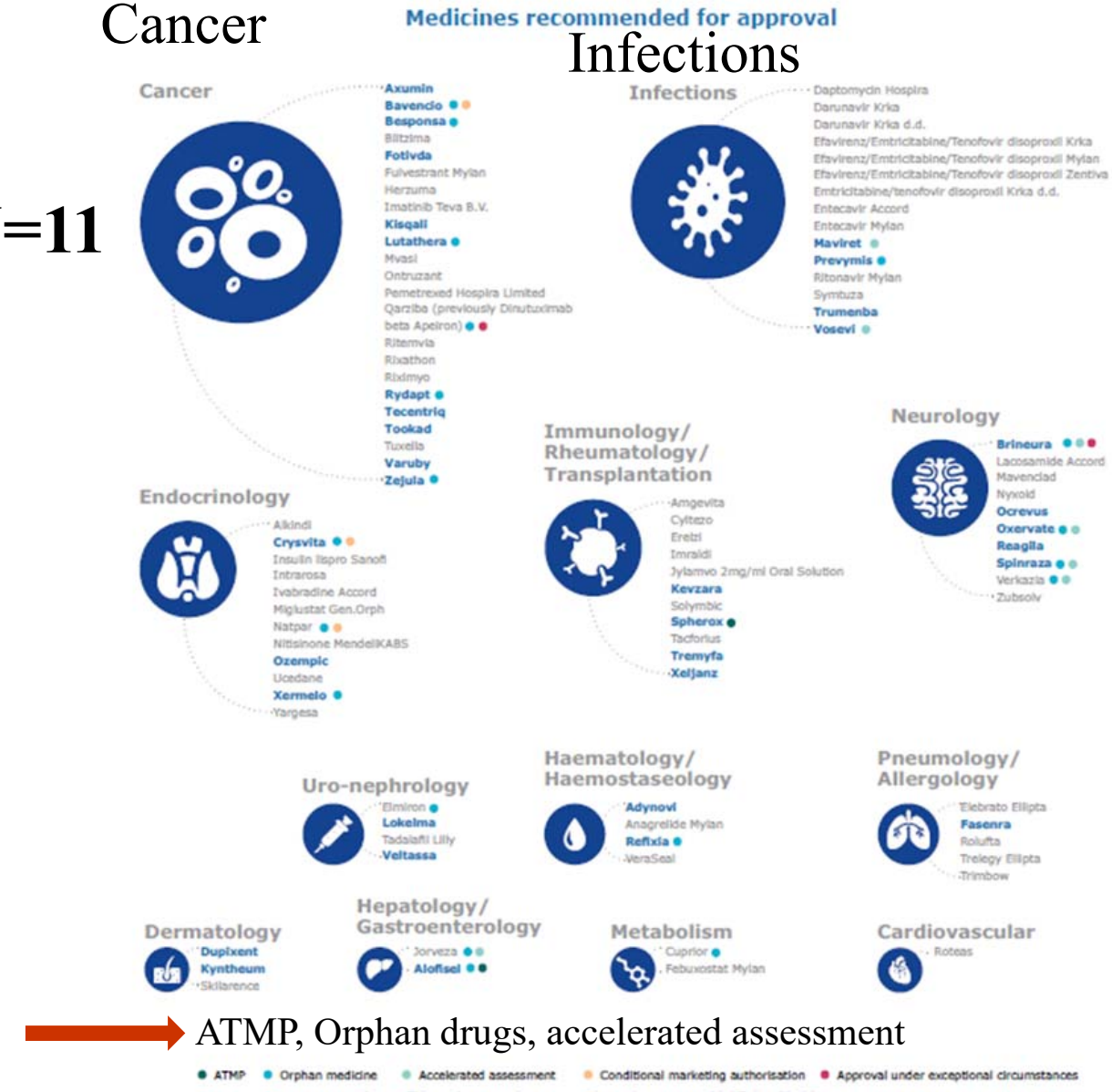
> First-in-class drugs have been becoming less common in recent years



Cancer

Infections

N=11

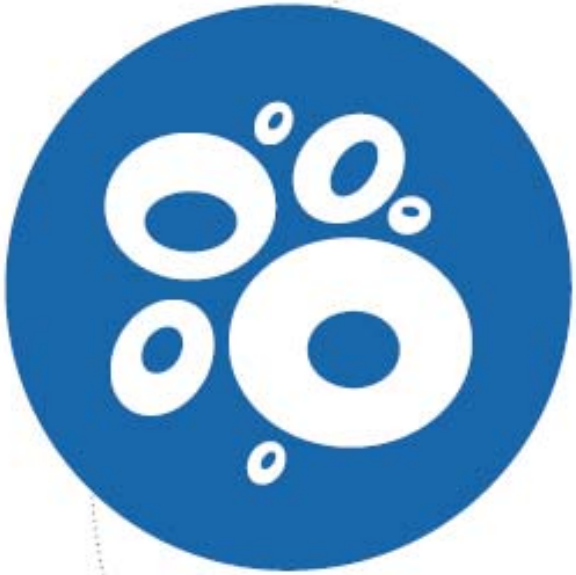


ATMP, Orphan drugs, accelerated assessment

Authorisation of new medicines in 2017

EMA, March 2018

Cancer



Axumin
Bavencio
Besponsa
Blitzima
Fotivda
Fulvestrant Mylan
Herzuma
Imatinib Teva B.V.
Kisqali
Lutathera
Mvasi
Ontruzant
Pemetrexed Hospira Limited
Qarziba (previously Dinutuximab beta Apeiron)
Ritemvia
Rixathon
Riximyo
Rydapt
Tecentriq
Tookad
Tuxella
Varuby
Zejula

POLICY FORUM

Biomarker-Defined Subsets of Common Diseases: Policy and Economic Implications of Orphan Drug Act Coverage

Aaron S. Kesselheim[1]*, Carolyn L. Treasure[1], Steven Joffe[2,3]

PLOS Medicine | DOI:10.1371/journal.pmed.1002190 January 3, 2017

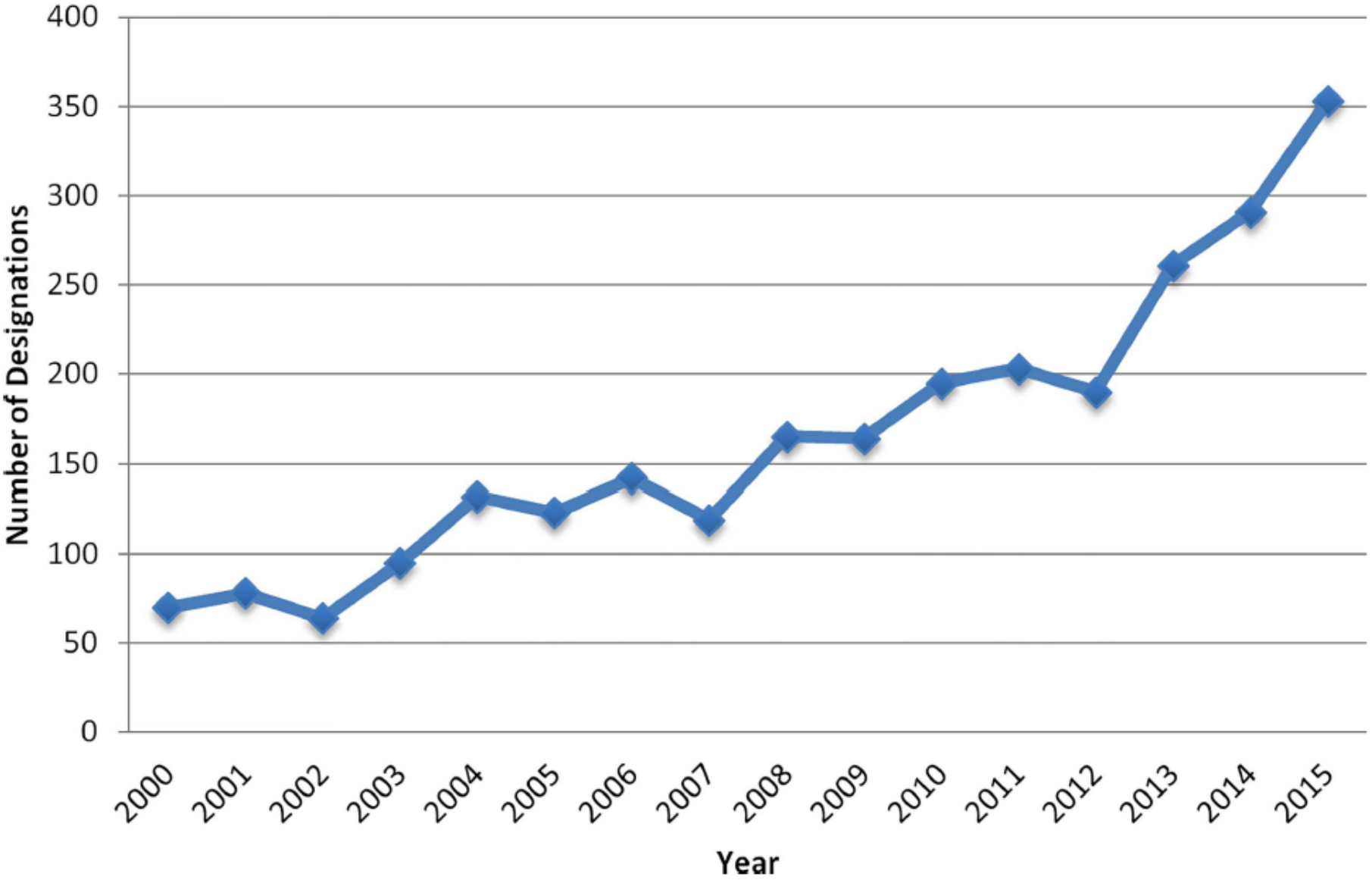


Fig 1. Orphan drug designations per year.

Table 1. Approvals of New Orphan-Designated Drugs Indicated for Biomarker-Defined Subsets of More Common Diseases, 2009–2015

Orphan-Designated Drug (Brand Name)	Approved Indication	Other Special FDA Designation	Subsequent FDA-Approved Indications	Patients Receiving Drug in Pivotal Trial (s), *n* (Phase)	Surrogate Endpoint of Pivotal Trial (s)	Estimated Cost Per Month (2014 US $ Thousand)	2014 Net Revenue from U.S. Sales (US $ Million)
Cabozantinib (Cometriq)	Medullary thyroid carcinoma with activating RET point mutation M918T	P, F	–	219 (Phase III)	PFS	10,229	40.1
Ponatinib (Iclusig)	CML with T315I mutation	A, P, F	–	449 (Phase II)	Cytogenic response	9,387	55.7
Ivacaftor (Kalydeco)	Cystic fibrosis mutation Gly551Asp	P, F	Y	212* (Phase III)	Improved FEV1	–**	463
Afatinib (Gilotrif)	EGFR mutated NSCLC (EGFR exon 19 deletions or exon 21 L858R substitution)	P, F	Y	230 (Phase III)	PFS	6,170	–
Dabrafenib (Tafinlar)	BRAF V600E mutated metastatic melanoma	F	Y	187 (Phase III)	PFS	9,564	87.6
Idelalisib (Zydelig)	CLL with p53 mutation; PI3K inhibitor	A, P, F	Y	110 (Phase III)	PFS	8,015	23
Crizotinib (Xalkori)	Alk+ NSCLC, Alk and ROS inhibitor	A, P, F	Y	172 (Phase III)	PFS	11,589	438
Ceritinib (Zykadia)	Alk+ NSCLC, specific ALK mutations	A, P	–	163 (Phase III)	Objective response rate	13,672	31
Vemurafenib (Zelboraf)	BRAFV600E mutated unresectable or metastatic melanoma	P, F	Y	337 (Phase III)	PFS	11,332	69.2
Alectinib (Alecensa)	Alk+ NSCLC, specific ALK mutations	A, P	–†	225* (Phase III)	Objective Response Rate	–**	–‡
Cobimetinib (Cotellic)	BRAF V600E or V600K mutated unresectable or metastatic melanoma used with vemurafenib	P, F	–†	247 (Phase III)	PFS	7,475	–‡
Lumacaftor/ ivacaftor (Orkambi)	F508del mutation in cystic fibrosis	P, F	–	737 (Phase III)	Improved FEV1	–**	–‡
Osimertinib (Tagrisso)	EGFR T790M mutation-positive NSCLC	A, P, F	–†	411* (Phase III)	Tumor response rate, PFS	12,735	–‡

POLICY FORUM

Biomarker-Defined Subsets of Common Diseases: Policy and Economic Implications of Orphan Drug Act Coverage

Aaron S. Kesselheim[1]*, Carolyn L. Treasure[1], Steven Joffe[2,3]

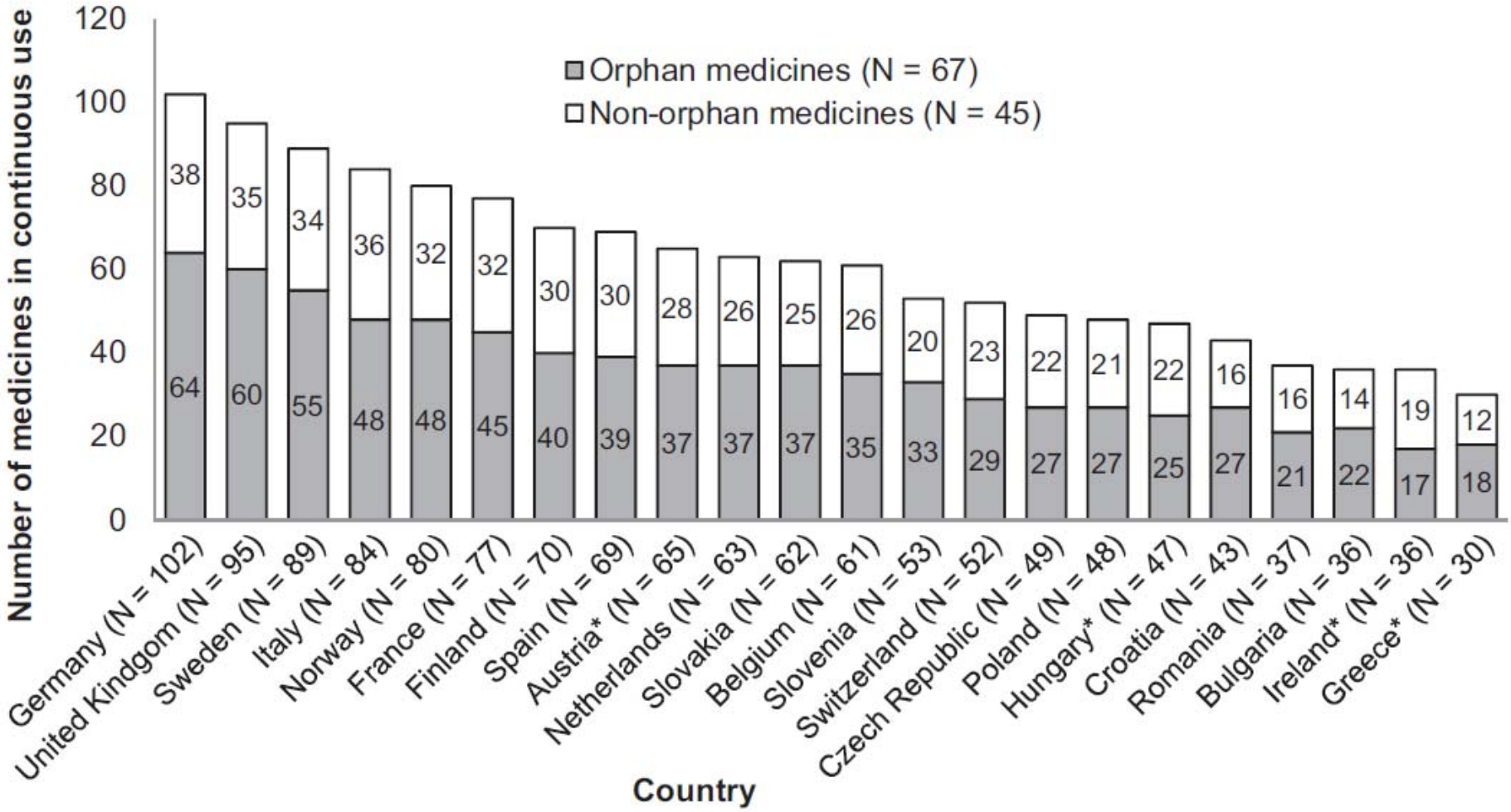
Summary Points

- The Orphan Drug Act of 1983 was intended to incentivize the development of pharmaceutical products for rare diseases by providing manufacturers with the opportunity to earn grants, tax credits, fee waivers, and seven years of post-approval market exclusivity for the approved indication.
- Over the past decade, the number of orphan drug designations has roughly doubled, with a simultaneous increase in those that target biomarker-defined subsets of common diseases.
- Among all orphan-designated drugs approved in 2009–2015 indicated for biomarker-defined disease subsets, we examined the circumstances surrounding the drug's discovery and development, secondary approvals, off-label uses, subsequent revenues, and the reported monthly cost.
- Orphan-designated drugs to treat biomarker-defined subsets of common conditions have a number of characteristics that make them ill-suited to the orphan drug designation, including short development times and rapid expansion of off-label indications after approval. Application of the Orphan Drug Act in these cases risks wasting resources that might be better focused on truly rare conditions.

PLOS Medicine | DOI:10.1371/journal.pmed.1002190 January 3, 2017

Patient Access to Medicines for Rare Diseases in European Countries

*Andreja Detiček, MPharm, Igor Locatelli, MPharm, PhD, Mitja Kos, MPharm, PhD**



Patient Access to Medicines for Rare Diseases in European Countries N=22 Zeitraum: 2005-2014

Active substance	ATC code	Year of marketing authorization	Indication	Orphan designation
Sildenafil	G04BE03	2005	Pulmonary hypertension	Yes
Bevacizumab*	L01XC07	2005	Nonsmall-cell lung carcinoma; renal cell carcinoma; colorectal, ovarian, and breast neoplasms	No
Erlotinib	L01XE03	2005	Nonsmall-cell lung carcinoma, pancreatic neoplasms	No
Somatropin*	H01AC01	2006	Prader-Willi syndrome, pituitary dwarfism, Turner syndrome	No
Sunitinib	L01XE04	2006	Neuroendocrine tumours, Gastrointestinal stromal tumours, Renal cell carcinoma	No
Dasatinib	L01XE06	2006	Chronic myelogenous leukemia (BCR-ABL positive), precursor cell lymphoblastic leukemia-lymphoma	Yes
Deferasirox	V03AC03	2006	Beta-thalassemia, iron overload	Yes
Trabectedin*	L01CX01	2007	Ovarian neoplasms, sarcoma	Yes
Nilotinib	L01XE08	2007	Chronic myelogenous leukemia (BCR-ABL positive)	Yes
Ambrisentan	C02KX02	2008	Pulmonary hypertension	Yes
Azacitidine*	L01BC07	2008	Myelodysplastic syndromes	Yes
Everolimus	L01XE10	2009	Renal cell carcinoma, pancreatic neoplasms, breast neoplasms	No
Tocilizumab	L04AC07	2009	(Juvenile) rheumatoid arthritis	No
Eltrombopag	B02BX05	2010	Idiopathic thrombocytopenic purpura	No
Pazopanib	L01XE11	2010	Renal cell carcinoma	No

VALUE IN HEALTH 21 (2018) 553–560

Stete Gewinne mit seltenen Krankheiten

«Orphan-Drugs» bringen Pharmaindustrie und Patienten Hoffnung zurück

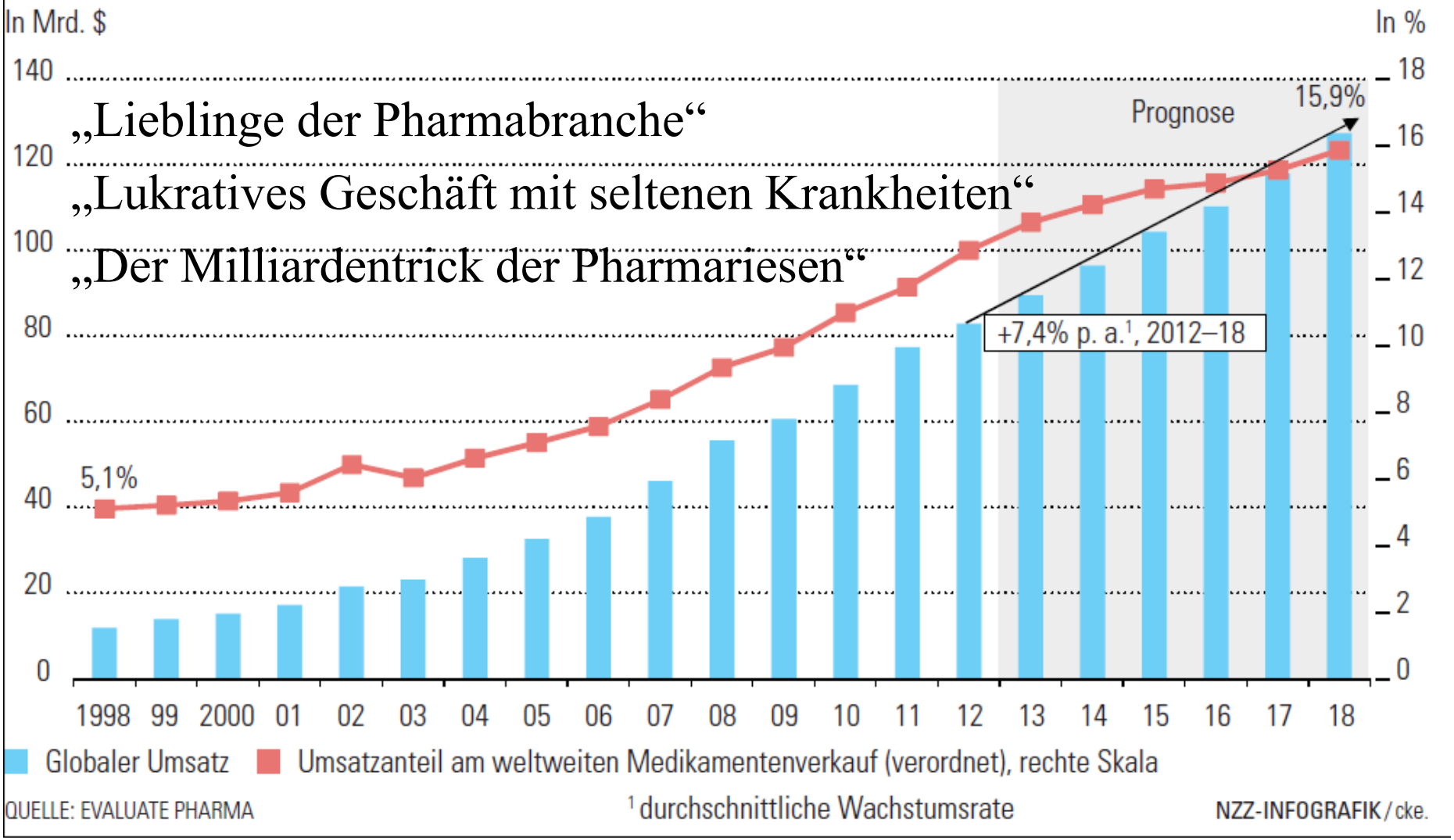
Orphan-Drugs mit stabilem Umsatzwachstum

05.08.2013

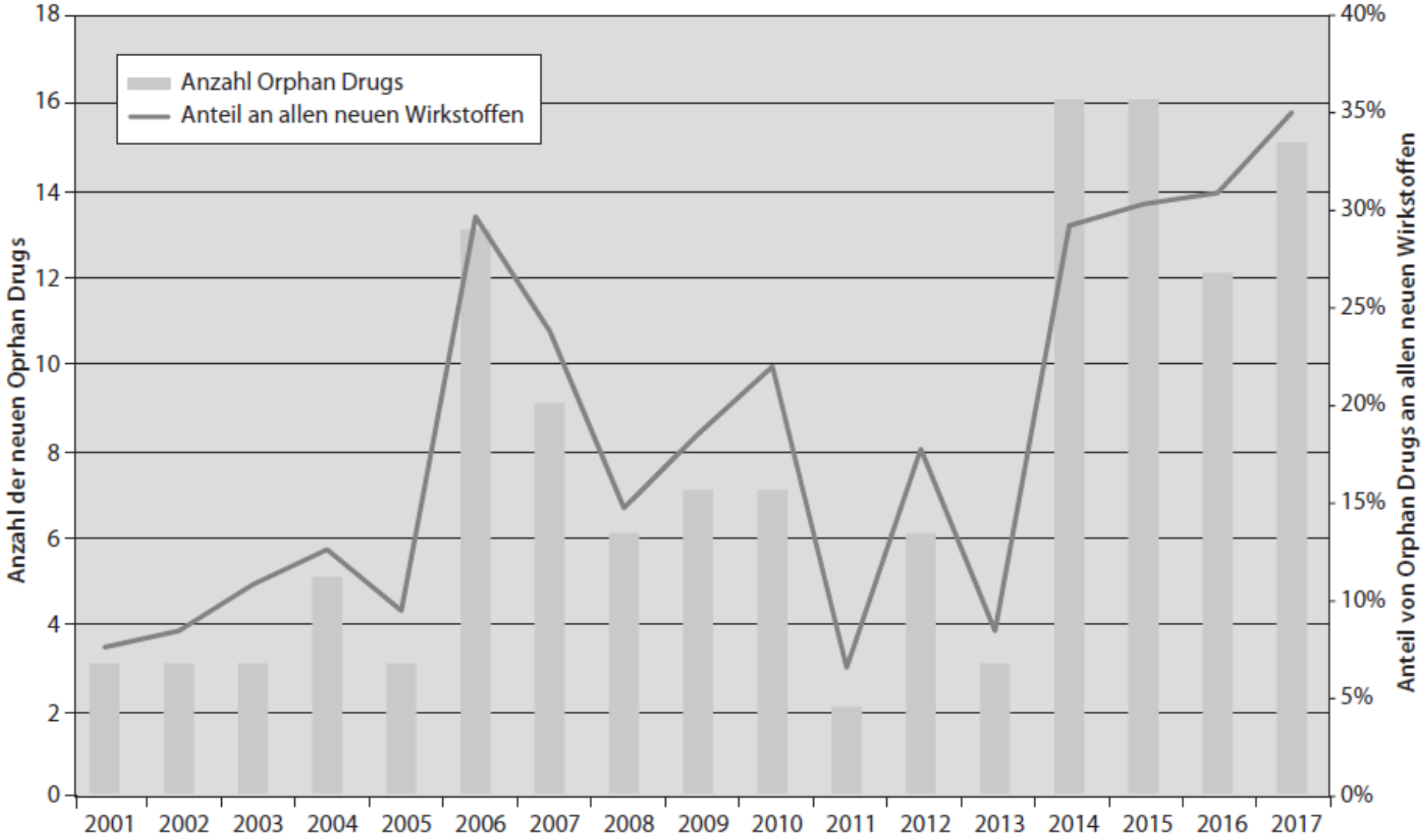
„Lieblinge der Pharmabranche“

„Lukratives Geschäft mit seltenen Krankheiten“

„Der Milliardentrick der Pharmariesen“

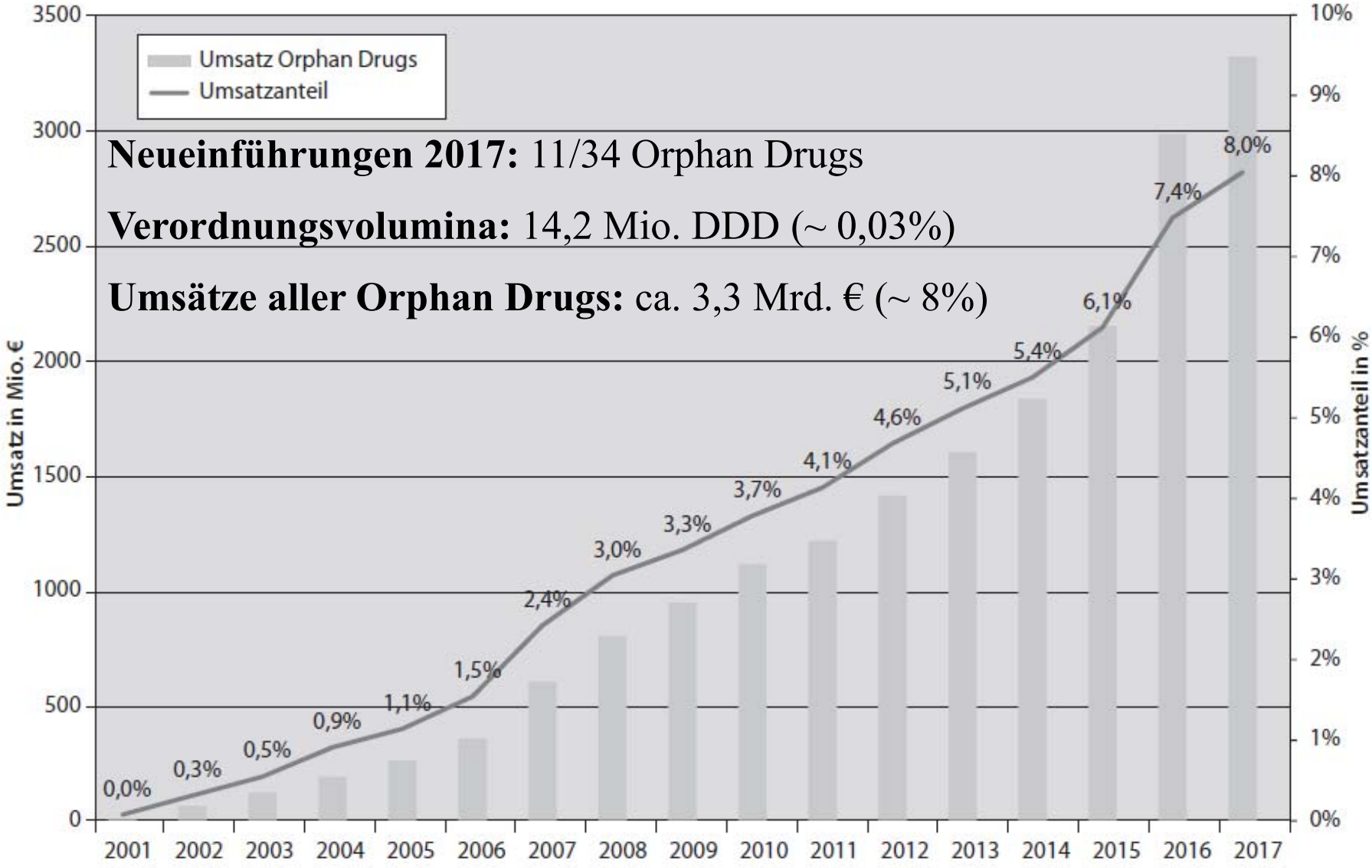



Ulrich Schwabe · Dieter Paffrath
Wolf-Dieter Ludwig · Jürgen Klauber
Hrsg.
Arzneiverordnungs-Report 2018
EXTRAS ONLINE
Springer



198 Verfahren zu Orphan Drugs
179 Orphan Drugs (117 OD mit OD-Status)

Ulrich Schwabe, Dieter Paffrath, Wolf-Dieter Ludwig, Jürgen Klauber (Hrsg.)
Arzneiverordnungs-Report 2018



Ulrich Schwabe, Dieter Paffrath, Wolf-Dieter Ludwig, Jürgen Klauber (Hrsg.)
Arzneiverordnungs-Report 2018

EvaluatePharma®

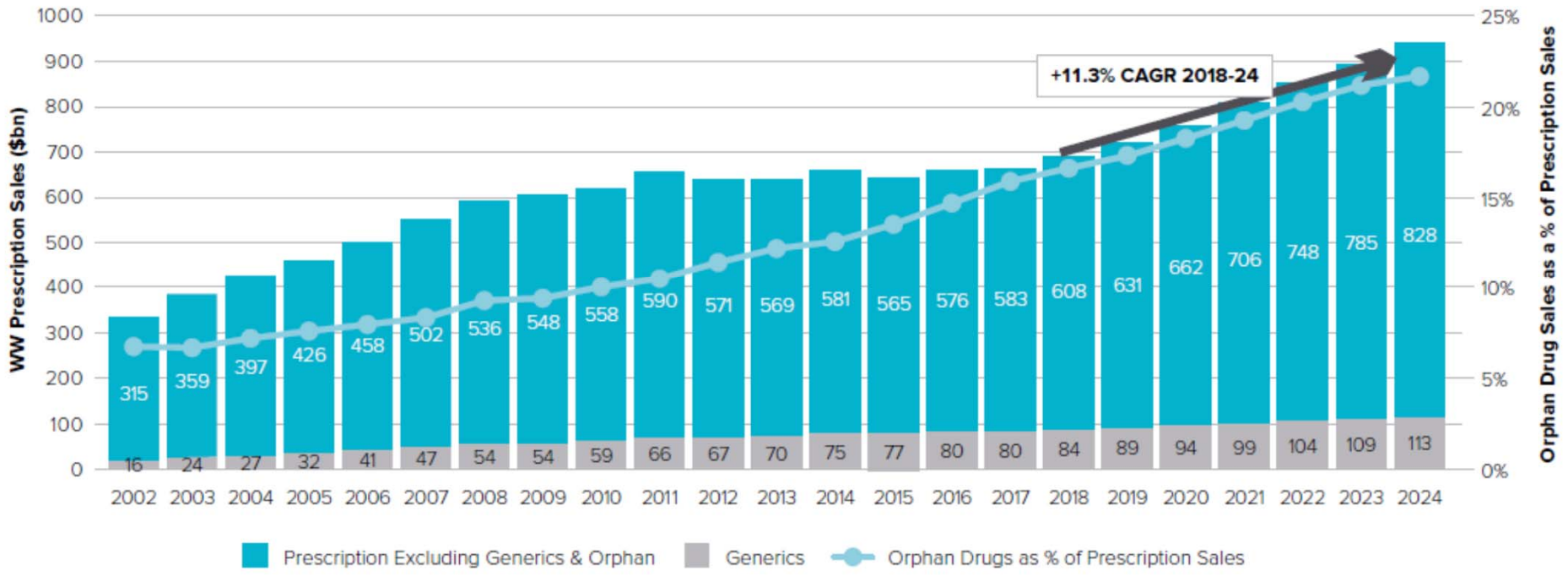
Orphan Drug Report 2018

Analysis Highlights

- Worldwide orphan drug sales are forecast to grow at a CAGR of 11.3% from 2018 to 2024, double the rate forecast for the non-orphan drug market.
- By 2024, orphan drugs are expected to capture a fifth of worldwide prescription sales and to reach $262bn.

Worldwide Orphan Drug Sales & Share of Prescription Drug Market (2002-2024)

Source: EvaluatePharma® May 2018



EvaluatePharma®

Orphan Drug Report 2018

Worldwide Top 20 Selling Orphan Drugs in 2024

Source: EvaluatePharma® May 2018

Rank	Product	Generic name	Company	Phase (current)	Mechanism of action	WW product sales ($bn)		
						2017	2024	CAGR
1.	**Keytruda**	pembrolizumab	Merck & Co/ Otsuka Holdings	Marketed	Programmed cell death protein 1 (PD1) antibody	3.8	**12.7**	+19%
2.	**Revlimid**	lenalidomide	Celgene/BeiGene	Marketed	Immunomodulator	8.2	**11.9**	+6%
3.	**Opdivo**	nivolumab	Bristol-Myers Squibb/Ono Pharmaceutical	Marketed	Programmed cell death protein 1 (PD1) antibody	5.7	**11.2**	+10%
4.	**Imbruvica**	ibrutinib	AbbVie/Johnson & Johnson	Marketed	Bruton's tyrosine kinase (BTK) inhibitor	3.2	**9.6**	+17%
5.	**Darzalex**	daratumumab	Johnson & Johnson	Marketed	Lymphocyte differentiation antigen CD38 antibody	1.2	**6.0**	+25%
6.	**Soliris**	eculizumab	Alexion Pharmaceuticals	Marketed	Complement factor C5 antibody	3.1	**5.2**	+7%
7.	**Hemlibra**	emicizumab	Roche/Chugai Pharmaceutical	Marketed	Coagulation factor IXa antibody; Coagulation factor X antibody	0.0	**4.4**	+183%
8.	**Jakafi**	ruxolitinib phosphate	Incyte/Novartis	Marketed	Janus kinase 1 (JAK1) inhibitor; Janus kinase 2 (JAK2) inhibitor	1.9	**3.9**	+11%
9.	**Venclexta**	venetoclax	AbbVie/Roche	Marketed	B-cell lymphoma 2 (BCL-2) inhibitor	0.1	**2.8**	+54%
10.	**Epidiolex**	cannabidiol	GW Pharmaceuticals	Filed	Cannabinoid (CB) receptor agonist	-	**2.3**	n/a

16/20 für onkologische/hämatologische Indikationen

Deutscher Ethikrat

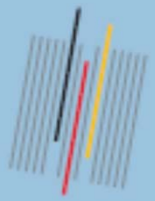
Berlin, 23. November 2018

Herausforderungen im Umgang mit seltenen Erkrankungen

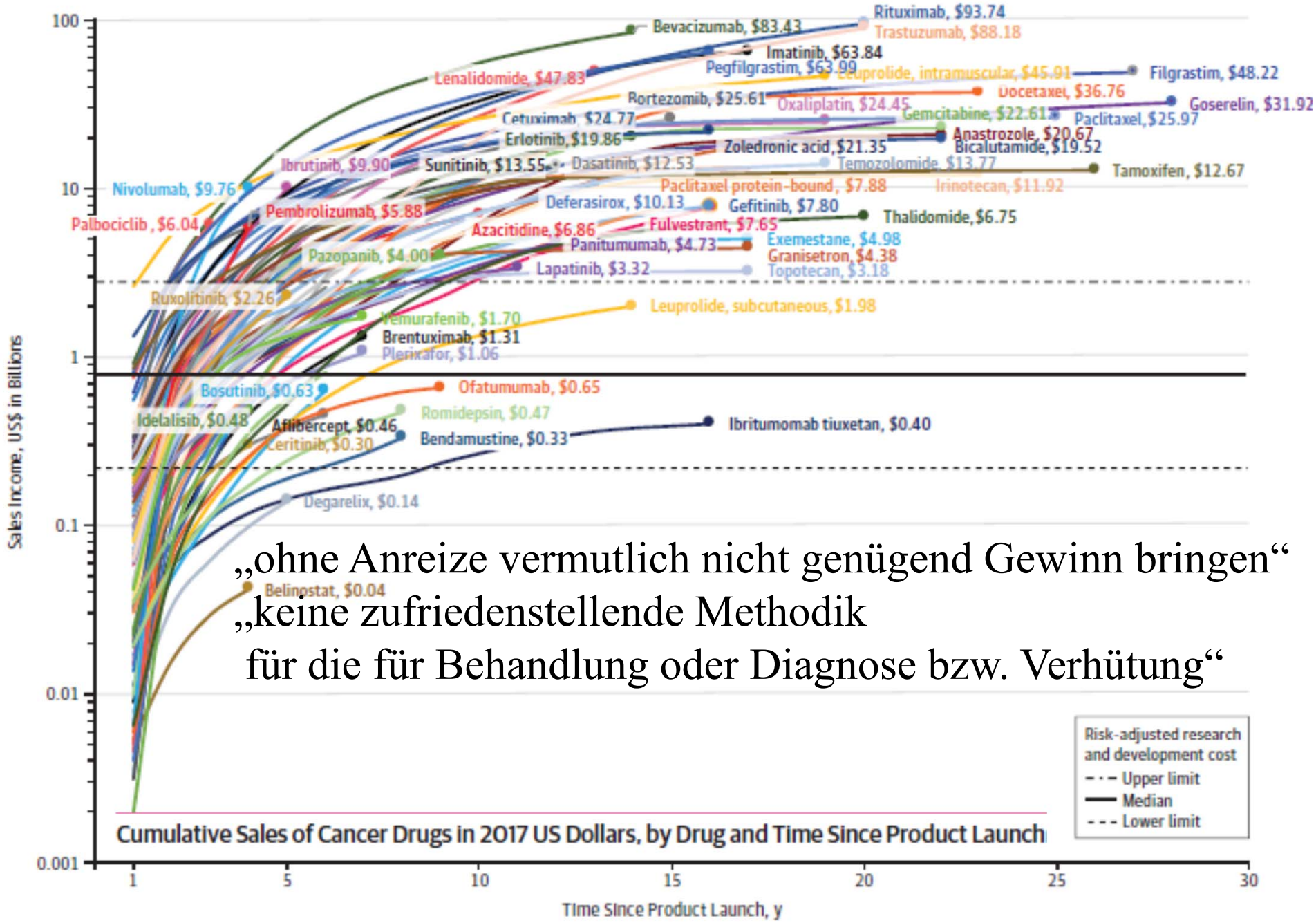
AD-HOC-EMPFEHLUNG

Arzneimittel für seltene Erkrankungen: Hoffnung auf Therapie

Deutscher Ethikrat



Da inzwischen jede vierte deutsche Marktneueinführung mit neuen Wirkstoffen ein Orphan-Arzneimittel ist,[23] erscheint es zunehmend wichtig, Patienten vor unzureichend geprüften Wirkstoffen besser zu schützen und mit der Zulassung eindeutige Auflagen zu verbinden, denn Patienten mit seltenen Erkrankungen haben denselben Anspruch auf Qualität, Unbedenklichkeit und Wirksamkeit von Arzneimitteln wie andere Patienten.[24] Überdies ist bedenklich, dass auch nicht von seltenen Erkrankungen betroffene Patienten im Rahmen der Therapiefreiheit solche unzureichend geprüften Wirkstoffe verschrieben bekommen können.[25]



„ohne Anreize vermutlich nicht genügend Gewinn bringen“

„keine zufriedenstellende Methodik
für die für Behandlung oder Diagnose bzw. Verhütung“

JAMA Network Open. 2019;2(1):e186875. doi:10.1001/jamanetworkopen.2018.6875

Priorities Dutch EU Presidency 2016

- **Key theme:**

  Strengthening checks-and-balances in the pharmaceutical system

- Improve voluntary cooperation and exchange of information on pricing and reimbursement between Member States
- Support timely access to new, essential medicines by clarifying conditions and exit options
- **Initiate debate on unintended effects of current incentives in EU pharmaceutical legislation and their impact on innovation and costs**
- Strategic debate on cooperation on future challenges and directions for pharmaceutical policy in the EU

EU orphan and paediatric regulation

State of play since October MB meeting:

Public and targeted consultations to be held until the end of this year. Targets:

- National public authorities, sponsors of orphan medicines, developers of generic or biosimilar orphan medicinal products, academic experts and patient & consumer (consultations are now closed)
- citizens and healthcare professionals (deadline 4th of January)

All members of the COMP, PDCO and CAT have received an invitation to complete the survey themselves, but have also been asked to forward the invitation to other representatives of relevant national authorities in their home countries.

The evaluation shall be completed in the 3rd quarter of 2019 in the form of a Commission Staff Working Document