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Michael Schlander
Kathrin Stenner
Afschin Gandjour

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About the Authors

Michael Schlander[a-c], Kathrin Stenner[d]
and Afschin Gandjour[d]

[a]Institute for Innovation & Valuation in Health Care, Wiesbaden, Germany,
[b]University of Applied Economics Ludwigshafen, Germany,
[c]University of Heidelberg, Mannheim Medical Faculty, Department of Public Health, Social and Preventive Medicine, Mannheim, Germany,
[d]Frankfurt School of Finance & Management, Frankfurt, Germany

Correspondence:

Professor Michael Schlander, MD, PhD, MBA
Institute for Innovation & Valuation in Health Care (InnoVal[HC])
An der Ringkirche 4, D-65197 Wiesbaden / Germany

Phone: +49 (0) 611 4080 789 12; Facsimile: +49 (0) 611 4080 789 99
E-Mail (1): michael.schlander@innoval-hc.com
E-Mail (2): michael.schlander@medma.uni-heidelberg.de

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Abstract

The objective of the present paper was (1) to review recent studies reporting health care expenditures (budgetary impact) for drugs for rare diseases in Europe, and (2) to contribute to our understanding of the cost drivers of drugs for non-oncological ultra-rare diseases (URDs) by means of an empirical analysis in Germany. **Methods:** A systematic search for relevant studies was conducted in PubMed (1966 – December 2014) and in abstracts in congress proceedings. In addition, annual treatment costs of drugs for non-oncological URDs in Germany were analyzed with respect to five explanatory variables: availability of other treatment indications, availability of alternative treatments for the same indication, oral administration, prevalence of the disease, and evidence for a health benefit. **Results:** A total of seven studies with specific estimates of the budget impact of drugs for rare diseases for a total of nine countries were identified. Annual per-capita spending for orphan drugs ranges from €0.48 in Russia to €16 in France. Only one study on URDs was identified. In Germany, annual treatment costs per patient for drugs for non-oncological URDs varies between €1175 and €726,890. In all regression specifications a significant inverse relationship between availability of alternative treatments for the same indication and annual treatment costs was found. In addition, log prevalence was found to have a significant inverse relationship with log annual treatment cost. **Conclusions:** Despite annual treatment costs in the range of several hundreds of thousands of euros for some of the URD drugs, per-capita spending for URD drugs is relatively small. In this study an inverse relationship between prevalence and annual treatment costs was found specifically for drugs for non-oncological URDs.

IV

Introduction

In the USA, in the EU as well as in Japan, Australia, and some other jurisdictions, legislation has been adopted to encourage the development of treatments for rare or "orphan" diseases. Under this legislation, developers and manufacturers of so-called orphan drugs used to treat orphan diseases benefit from a range of incentives, including reduced or waived licensing fees, extended market exclusivity periods and, in the USA and Japan, tax relief on development costs.

The introduction of regulation for rare disorders has improved the existing market conditions and successfully contributed to the rise of research and development efforts, leading to increasing availability of effective treatments for rare disorders (cf. Luzzatto et al. 2015). From the perspective of the biopharmaceutical industry, orphan medicinal products (OMPs) now are attractive investment opportunities (Meekings et al. 2012; Phillips 2013; Kakkar and Dahiya 2014). At the same time, however, in many cases the use of drugs for rare disorders has been associated with high annual acquisition costs per patient, and "the five most expensive drugs in the world" (Williams 2013) all happen to be medications for ultra-rare disorders (URDs). In fact, as fixed costs of research and development (R&D), which are largely independent from sales volume or, for that matter, number of patients afflicted with a rare disorder, need to be recouped from very small numbers of patients, one should expect an inverse correlation between drug acquisition costs per patient and prevalence of the target condition (e.g., Schlander and Beck 2009).

Thus concerns have been raised that drugs for orphan disorders "may impose substantial increasing costs to the healthcare

system" (McCabe et al. 2005), to the point that these costs may become "unsustainable, even for health services that have met them hitherto" (Luzzatto et al. 2015). If anything, these concerns can only be aggravated by the fact that many of the technologies in question will not meet broadly used benchmarks for cost effectiveness, e.g., incremental costs per quality-adjusted life year (QALY) gained of €50,000 (e.g., Rombach et al. 2013; van Dussen et al. 2014; Schlander et al. 2014a) – providing such data are available at all (cf. Kanters et al. 2013). As a result, recent debate has focused on the appropriateness and usefulness of conventional cost effectiveness analysis as a tool to determine the "value for money" offered by OMPs (Phillips and Hughes 2011; Schlander et al. 2014a). Accordingly, in many jurisdictions OMPs are either exempted from formal health economic analysis (e.g., in the Netherlands), follow specific processes, or receive positive reimbursement decisions despite indications of costs per QALY higher than deemed acceptable in other areas (e.g., Rosenberg-Yunger et al. 2011; Sussex et al. 2013, Cerri et al. 2014; Picavet et al. 2014a).

Increasing rarity of a condition merely represents the end of a continuum. However, any attempts to separate "orphan" and "ultra-orphan" from "normal" conditions are somewhat arbitrary exercises. For policy makers, it has nevertheless been a pragmatic approach to define different categories of diseases and interventions with the aim to provide incentives for drug development in an otherwise unattractive niche. Accordingly, "orphan disorders" have been defined by US and EU legislation. In the USA, these are diseases with a prevalence of fewer than 200,000 affected persons; in the EU, prevalence must be fewer than 5 per 10,000 (or less than 0.05%) of the population.

With an increasing number of drugs becoming available for a wide number of very diverse therapeutic areas, some systems

have felt the need to define subcategories of products with certain characteristics that would justify exemptions or adapted evaluation methods. NICE (formerly, the National Institute for Health and Clinical Excellence, and the National Institute for Clinical Excellence) introduced a definition of ultra-orphan drugs, which applied to drugs with indications for conditions with a prevalence of less than 1 per 50,000 persons initially in 2005, and then subsequently less than 100 patients in England in the recent updated Highly Specialised Technologies (HST) appraisal process in 2013. Similarly, the recent EU Clinical Trials directive (EU Regulation EU No 536/2014) defined ultra-rare diseases as "severe, debilitating and often life-threatening diseases affecting no more than one person in 50 000".

In Australia, the Pharmaceutical Benefits Advisory Committee often considers ultra-rare disease drugs within the context of the Life Saving Drugs Programme (Department of Health 2013). In England and Wales drugs for "ultra-orphan" diseases fall under the Highly Specialised Technology (HST) evaluation process at NICE, or the ultra-orphan processes in the All Wales Scientific Medicines Group (AWMSG) or Scottish Medicines Consortium (SMC) who are charged with Health Technology Assessments (HTAs). HST evaluations are recommendations on the use of new and existing highly specialized medicines and treatments within the English and the Welsh National Health Service. It remains to be seen whether such programs provide sufficient incentives to develop products and reverse possible trends towards an increasing number of companies focusing on more prevalent orphans and fewer in the 'very rare' category.

Against the background delineated above, the objective of the present paper was (1) to review recent studies reporting health care expenditures (budgetary impact) for drugs for orphan diseases in Europe, and (2) to contribute to our understanding

of the cost drivers of drugs for URDs by means of an empirical analysis. This latter should be of interest given the lack of transparency of and very limited research on the pricing of OMPs (Simoens 2011; Michel and Toumi 2012) and, in particular, drugs for URDs.

Specifically, we analyzed URDs in Germany, which represents the largest European market in terms of pharmaceutical production and the second largest European market in terms of pharmaceutical sales (EFPIA 2014). We chose to focus on non-oncological diseases assuming that they are more likely to represent distinct disease entities with typically less off-label use (while acknowledging that this does not need to hold for each disease). Also, the approved indications of cancer treatments seem to be more often broadened over time (Kobayashi and DeLab 2001). Finally, our dependent variable, which is annual treatment costs, does not fit oncology drugs well because the latter are often based on a limited number of cycles or treat to progression.

Methods

(1) Budegatry Impact of Drugs for URDs

We conducted a systematic search for relevant studies in PubMed (1966 – December 2014), using the search algorithm orphan drugs AND (budget impact OR spending). Furthermore, we searched the Value in Health issues of May 2014 and November 2014 for abstracts presented to the International and European Congresses of the International Society for Pharmacoeconomics & Outcomes Research (ISPOR) in Montreal and Amsterdam in 2014, applying the same algorithm.

Local currencies were converted into euros based on the exchange rate on March 13, 2015. To calculate per-capita spending, we used population data of the study year in question from the World Bank.

(2) Drivers of Cost per Patient for Drugs for URDs

Data Sources

Prevalence data: This study included drugs with a marketing authorization and an active orphan drug designation in Europe by the end of 2012. Drugs had to be approved by the EMA in a non-oncological indication. We applied a cut-off prevalence rate of 1:50,000 (0.002%) in the general population. When possible, we used prevalence data gathered by Orphanet. Further details on data sources as well as the identification approach were published in a previous paper (Schlander et al. 2014b). For URD drugs with an indication for more than one URD (i.e., eculizumab and miglustat), we calculated the sum of prevalence rates.

For the indication of carglumic acid, i.e., hyperammonemia, only a few cases have been reported worldwide and the overall incidence is unknown (Genetics Home Reference). For the purpose of our analysis we set the prevalence to 1:2,000,000, representing the lowest prevalence rate in our sample.

Annual treatment costs: The annual treatment dose was calculated for each indication according to the standard treatment plan described in the Summary of Product Characteristics (SPC). No dose adjustment was carried out to account for liver or kidney disease. For treatments extending beyond one

year we calculated the maintenance dose based on the SPC. If a dose range was given (e.g., for carglumic acid), the average dose between the minimum and maximum dose was assumed. For URD drugs with an indication for more than one URD (i.e., eculizumab and miglustat), we calculated a weighted average treatment dose with weights representing prevalence rates.
As a source for prices we used the Drug Index for Germany, which is 'Rote Liste' (2014 data). In case of multiple packaging sizes, the cheapest pack was selected.

Quality of evidence: The variable was coded as "yes" if evidence for a health benefit was available from a randomized controlled trial (RCT). To this end, the PubMed database was searched on November 16, 2014. A special case was eculizumab, which had two indications but evidence only for one URD. In this case we coded the variable as "yes" because the RCT in question was conducted on the URD with the higher prevalence.

Data Analysis

We analyzed annual treatment costs of drugs for non-oncological URDs with respect to five explanatory variables: availability of other treatment indications (yes/no), availability of alternative treatments for the same indication (yes/no), oral administration (yes/no), prevalence of the disease (continuous), and quality of evidence for a health benefit (high/low). Explanatory variables were selected largely based on the study by Picavet et al. (2014b), which will be discussed later. An important exception was disease prevalence which we considered on a continuous scale. Furthermore, we did not include treatment duration as an explanatory variable assuming

continuous treatment for all URD drugs except for miltefosine. We considered p values of <0.05 to be statistically significant.
We used the method of ordinary least squares (OLS) for estimating the unknown parameters in a linear regression model. All independent variables were categorical except for prevalence which was continuous. In order to detect multicollinearity among the explanatory variables we constructed a correlation matrix and two-way contingency tables (the latter only applies to categorical variables) and calculated the variance inflation factors (VIFs) as well.

In addition to conducting a regression analysis based on untransformed variables, we transformed some of the variables in additional analyses. The logarithm of annual treat-ment costs was taken given that histogram, box plot, Q–Q plot, and normal probability plot suggested right skewness of the data (the Shapiro-Wilk test was not significant at p = 0.13). For prevalence rate the Shapiro-Wilk test was not statistically significant either (p value of 0.31), yet again histogram, box plot, Q–Q plot, and normal probability plot suggested right skewness of the data. Therefore, we took the logarithm of the prevalence rate as well. As the aim of our regression was to explain and not to predict annual treatment costs, we purposely did not develop a parsimonious model based on stepwise elimination. All analyses were performed using STATA version 11.0 software (Stata Corporation, College Station, TX).

IV

Results

(1) Budgetary Impcact of Drugs for URDs

Primarily based on the PubMed search described above, using the search algorithm orphan drugs AND (budget impact OR spending), we identified a total of seven studies with specific estimates of the budget impact for a total of nine countries (Table 1). Two estimates related to all European countries and the Eurozone countries, respectively. Five studies determined budget impact based on actual sales and cost data, thus incorporat-ing uptake of drugs implicitly. Two studies (Schey 2011, Schlander 2014b) projected their estimate based on a model which explicitly considered drug uptake. Only one study (Schlander 2014b) focused specifically on ultra-orphan drugs. None of the studies included costs of i) treating side effects; ii) costs of drug-related services such as counseling, monitoring, and testing; iii) savings from a reduction in morbidity; and iv) life extension costs. As Table 1 suggests, estimates vary to a large extent from country to country and even for a single country and are considerably lower for ultra-orphan than for orphan drugs.

Table 1. *Budget impact of (ultra-)orphan drugs in Europe*

Region	Type of drugs	Annual budget impact (€)	% pharma-ceutical expendit ure	Annual per-capita spend-ing (€)*	Year	Type of study	Consider -ation of substitu-tion effects	Con-siderat -ion of uptake	Reference
Belgium	Orphan drugs	62,000,000	5% (hospi-tals only)	5.79	2008	Empir ical	No	NA	Denis 2010
Europe	Ultra-orphan drugs for non-onco-logical diseases	1,113,137,781	0.7%	1.50	2012	Mode ling	No	Yes	Schlander 2014
Eurozone countries plus United Kingdom	Orphan drugs	4,620,000,000	3.3%	11.73	2010	Mode ling	No	Yes	Schey 2011
France	Orphan drugs	460,700,000	1.7%	7.20	2007	Empir ical	No	NA	Orofino 2010
France	Orphan drugs	111,407,800	3.1%	16.05	2012	Empir ical	No	NA	Hutchings 2014
Germany	Orphan drugs	525,000,000	2.1%	6.38	2007	Empir ical	No	NA	Orofino 2010
Italy	Orphan drugs	235,500,000	1.5%	4.03	2007	Empir ical	No	NA	Orofino 2010
Netherla nds	Orphan drugs	260,400,000	4.2%	15.55	2012	Empir ical	No	NA	Kanters 2014
Russia	Orphan drugs	68,464,000	-	0.48	2013	Empir ical	No	NA	Sura 2014
Spain	Orphan drugs	256,000,000	2.0%	5.66	2007	Empir ical	No	NA	Orofino 2010
Sweden	Orphan drugs	122,025,000	2.5%	13.12	2012	Empir ical	No	NA	Hutchings 2014
United Kingdom	Orphan drugs	162,000,000	1.0%	2.64	2007	Empir ical	No	NA	Orofino 2010

*Population size refers to the same year as budget impact.
NA = not applicable

(2) Drivers of Cost per Patient for Drugs for URDs

We found 17 drugs for non-oncological drugs with a marketing authorization and an active orphan drug designation in Europe (Table 2). Annual treatment costs vary between €1175 and €726,890. Mean cost is €235,734.

Table 2. *Drugs for ultra-orphan diseases considered in the analysis (partially adapted from Schlander et al. (2014b))*

Active substance	Indication(s)	Annual treatment cost (€)	Prevalence (per 100,000)	Other treatment indications	Alternative treatments	Oral treatment	Quality of evidence	Reference$
Alglucosidase alfa	Glycogen storage disease type II	246,207	1.5	no	no	no	High	Orphanet Report Series
Amifampridine	Lambert-Eaton myasthenic syndrome	15,748	1.0	no	yes	yes	High	Orphanet Report Series
Betaine anhydrous	Homocystinuria	7,759	0.4	no	yes	Yes	Low	Orphanet Report Series
Budesonide	Graft-versus-host disease	1,175	1.7	yes	yes	yes	High	Jacobsohn 2007
Carglumic acid	Hyperammonaemia	366,606§	0.05	no	no	yes	Low	Genetics Home Reference
Deferasirox	Chronic iron overload	9,364§	0.4	no	yes	yes	High	Orphanet Report Series; Lobo 2011
Eculizumab	Paroxysmal nocturnal haemoglobinuria, atypical haemolytic uremic syndrome	459,708	1.1*	no	no	no	High	Orphanet Report Series; Zimmerhackl 2006
Galsulfase	Mucopolysaccharidosis VI	137,128§	0.2	no	no	no	High	Orphanet Report Series

Active substance	Indication(s)	Annual treatment cost (€)	Prevalence (per 100,000)	Other treatment indications	Alternative treatments	Oral treatment	Quality of evidence	Reference$
Idursulfase	Mucopolysaccharidosis II	542,578§	0.6	no	no	no	High	Orphanet Report Series
Ivacaftor	Cystic fibrosis and the G551D-CFTR mutation	332,472	0.55	no	no	yes	High	Orphanet Report Series; Cystic Fibrosis Foundation 2011
Lomitapide#	364	726,890	0.1	no	no	yes	High	Health Grades
Laronidase	Mucopolysaccharidosis I	331,194§	1.3	no	no	no	High	Orphanet Report Series
Lomitapide#	Homozygous familial hypercholesterolemia	726,890	0.1	no	no	yes	High	Health Grades
Miglustat	Type 1 Gaucher disease, Niemann-Pick type C disease	177,014	1.8*	no	yes	yes	High	Orphanet Report Series
Miltefosine	Visceral and cutaneous leishmaniasis	3,692	0.89	no	yes	no	High	Vfa 2014
Nitisinone	Hereditary tyrosinemia type 1	103,417§	0.05	no	no	yes	Low	Orphanet Report Series
Tafamidis	Transthyretin amyloidosis	227,946	0.5	no	no	yes	High	Coelho 2008
Velaglucer-ase alfa	Type 1 Gaucher disease	318,584§	0.9	no	yes	no	High	Orphanet Report Series

§ assumes a body weight of 35 kg

* combined prevalence for two conditions

approved by European Medicines Agency in 2013

$ refers to prevalence data only.

In the correlation matrix the highest correlation was found between availability of other treatment indications and prevalence (r = 0.65). The chi-squared contingency table analysis showed no significant relationships, indicating absence of multicollinearity. Similarly, all VIFs were below the conventional cutoff of 10.

Table 3. *Regression model using untransformed variables (dependent and independent)*

	Coefficient	Std. Error	t-ratio	p-value
Constant	252,963	92,042.5	2.7483	0.01895
Other indications	120,180	92,553.7	1.2985	0.22068
Alternative treatments	−230,998	104,140	-2.2181	0.04852
Oral treatment	63,631.2	142,647	0.4461	0.66420
Prevalence	−111,357	156,324	-0.7123	0.49108
Quality of evidence	145,598	156,107	0.9327	0.37101

p-values marked in bold are significant at a 0.05 level.

Table 4. *Regression model using log annual treatment costs as the dependent variable*

	Coefficient	Std. Error	t-ratio	p-value
Constant	11.9894	0.52839	22.6904	<0.00001
Other indications	0.19669	1.14884	0.1712	0.86717
Alternative treatments	−2.51025	0.925136	-2.7134	0.02017
Oral treatment	0.940004	1.08352	0.8675	0.40417
Prevalence	−0.31739	0.883374	-0.3593	0.72618
Quality of evidence	0.398531	0.693321	0.5748	0.57698

p-values marked in bold are significant at a 0.05 level.

Table 5. *Regression model using log prevalence and log annual treatment costs*

	Coefficient	Std. Error	t-ratio	p-value
Constant	11.2015	0.575911	19.4500	<0.00001
Other indications	0.0110252	1.43227	0.0077	0.99400
Alternative treatments	−2.37977	0.920428	-2.5855	0.02534
Oral treatment	0.982519	0.947924	1.0365	0.32222
Prevalence	−0.113487	0.0488416	-2.3236	0.04032
Quality of evidence	0.824779	0.503497	1.6381	0.12966

p-values marked in bold are significant at a 0.05 level.

In all regression specifications we found a significant inverse relationship between availability of alternative treatments for the same indication and annual treatment costs (Tables 3 to 5). In addition, log prevalence was found to have a significant inverse relationship with log annual treatment cost (Table 5). According to this log-log specification, a 1% increase in prevalence leads to a 0.1% decrease in annual treatment cost.

Discussion

In principle, there are two competing perspectives - incremental costs per patient and budgetary impact - from which costs of treatment of URDs may be looked at. The budgetary impact often represents the primary concern of policy-makers and payers (cf. Handfield and Feldstein 2013), and it is usually addressed by means of budgetary impact analyses (BIAs). BIAs reflect aggregate spending on an individual or on a group of OMPs, or on the category of URD drugs, and typically are a function of acquisition costs per unit and utilization, i.e., patient numbers and duration of treatment. The notion of

"affordability" is frequently used in the context of BIAs and conceptually implies the existence of a fixed (or at least limited) health care budget (corresponding to the "scarcity" condition of economics).

Empirically, participants in studies measuring public preferences have been found to be reluctant to accept that the decision to cover a program for orphan disorders inevitably leads to the loss of access to effective care of a much larger number of common-disease patients (Dragoijlovic et al. 2015). Rather, a public attitude seems to be prevalent that citizens often prefer reallocating spending from other public programs to health care in order to avoid rationing (e.g., Mossialos and King 1999; Soroka 2007; Dragoijlovic et al. 2015).

Several studies have estimated the budget impact of orphan and ultra-orphan drugs in Europe. Based on our search we identified the studies presented in Table 1. Annual per-capita spending on drugs ranges from €0.48 for orphan drugs in Russia (2013; own calculation based on Sura et al. 2010) to €16 for orphan drugs in France (2012; own calculation based on Hutchings et al. 2014). In terms of total drug budget, expenditures range from 0.7% for ultra-orphan drugs for non-oncological diseases in Europe (Schlander et al. 2014b) to 5% for orphan drugs in Belgium (Denis et al. 2010). Projected future share of spending for orphan drugs ranges – based on the few studies from which such projections were available - from 4% in Sweden (year 2020) to 5% in France (year 2020), translating into annual per-capita expenditures between €25 (or €2.10 per person month) in Sweden (2020) to €30 (or €2.48 per person month) in France (2020) (own calculation based on Hutchings et al. (2014)). Two studies predicted that future spending on orphan drugs should reach a plateau at 4% to 5% of total pharmaceutical expenditure

by the year 2020 (Schey et al. 2011; Hutchings et al. 2014), thereafter growing at a rate not faster than the total market. This effect is expected to be largely driven by the anticipated expiry of market exclusivity for many OMPs.

Only one study specifically addressed ultra-orphan drugs: it predicted that spending for drugs for non-oncological URDs might reach 1.4 percent of total European pharmaceutical expenditures by 2021 assuming a 1.1 annual growth of total pharmaceutical expenditures in Europe (Schlander et al. 2014b). The authors concluded that their analyses did not support concerns about an uncontrolled growth in expenditures for URD drugs. Nevertheless they recommended "continuously monitoring the budget impact in order to provide an input into rational policy making." If projected spending in Europe for non-oncological URD drugs was related to current population figures, the data cited would translate into €4.04 per person year or €0.34 per person month. The question, of course, arises whether this is an unreasonably high amount given the relatively small number of patients benefitting – or is it a modest and justified social transfer ensuring that patients unfortunate enough to suffer from an ultra-rare disorder are not abandoned and left behind? For example, the authors of a recent BIA of a new cystic fibrosis therapy in the United States – at an annual acquisition cost of US-$200,000 per patient treated – calculated that the per member per month increase in premiums of a hypothetical managed care plan to cover this new expense would amount to 5 cent. On this basis, these authors concluded "that new therapies for rare conditions […] can have a substantial impact on the overall budget of a health plan even though only a small number of patients are treated" (Schultz and Malone 2014).

One approach to empirically address this issue might be to systematically measure the social willingness-to-pay or, in the case of a national health scheme, the willingness to be taxed to cover the population by the health scheme. Methods to measure social preferences for – as a proxy for social value of – access to health care programs are well established (e.g., Ryan et al. 2001; Murphy and Ackermann 2014; Richardson et al. 2014). Their use has been advocated recently by health economists and HTA experts on grounds of normative considerations and an in-depth review of the broader literature on "empirical ethics" (Richardson and McKie 2005, 2007; Schlander et al. 2014a).

As unit costs are one of the variables determining the budgetary impact of an OMP, understanding the drivers of unit costs will be of interest even in the context of a social value framework relying on "social" (i.e., non-selfish) preferences beyond individual utility maximization. Furthermore, costs per average patient treated is of primary interest (a) when traditional cost-benefit or cost-effectiveness assessments are intended or (b) when judgments are to made concerning the affordability of out-of-pocket payments from a patient's or household's perspective. Deliberately refraining from normative considerations, we focused on variables potentially explaining higher costs of OMPs based on a sample of German URD drug prices. We intended to describe empirically identifiable variables, hereby hoping to contribute to future informed debate about reasonable URD drug price regulation. We explicitly do not intend to derive predictions or prescriptive statements.

A few prior studies analyzed the factors which explain prices of drugs for orphan and ultra-orphan diseases (UODs) (Simoens 2011; Schlander et al. 2014a, Picavet et al. 2014b). By far the most comprehensive and sophisticated analysis was published just

recently, by Picavet and colleagues (2014b). Using data on annual treatment costs of 59 orphan drugs from six European countries (Belgium, The Netherlands, Czech Republic, France, Italy, and the United Kingdom), the study identified three predictors of lower annual treatment costs: availability of other treatment indications ("repurposed orphan drugs") (yes/no), oral administration (yes/no), and availability of alternative treatments for the same indication (yes/no). Furthermore, four predictors were found to be associated with higher annual treatment costs: availability of multiple orphan indications as a proxy for the size of the "potential treatment population" or prevalence, improvement in survival (yes/no), improvement in quality of life (yes/no), and treatment duration of six months and more (yes/no). In addition, the study attempted to determine the impact of non-oncological diseases and URDs on annual treatment costs but found no significant relationship.

The perhaps most surprising finding was the lack of an inverse relationship between availability of multiple orphan indications and annual treatment cost. The authors justified this finding by arguing that orphan drug prices are determined based on the prevalence of the first indication and that launch prices for the first indication are unlikely to be reviewed following approval in other indications. This argumentation then presupposes that the relationship between prevalence and costs depends on whether the orphan drug has been approved for two or more indications or not. The relationship between prevalence and annual treatment costs is usually considered to be inverse based on the assumption of largely fixed R&D costs (i.e., costs are assumed to be independent from sales volume) (Schlander et al. 2014b). From reading the literature, prevalence is therefore usually held to be the most important predictor. This relationship between prevalence and annual treatment costs has

also been confirmed empirically in univariate analyses (Messori et al. 2010; Simoens 2011). As the trend in the six countries analyzed by Picavet and colleagues (2014b) was positive for URDs vs. no URDs it cannot be excluded that prevalence as a continuous variable (as opposed to the dichotomous indicator of URD used by Picavet et al. 2014b) would have yielded a significant result. Furthermore, as the study by Picavet et al. (2014b) did not include interaction terms, it is not clear whether the above-mentioned seven significant predictors are transferable to URDs and non-oncological diseases.

In contrast to the study by Picavet et al. (2014b), which – as stated - did not include prevalence as a continuous variable, we find that lower prevalence is associated with higher annual treatment costs in a log-log specification. Thus, we are able to confirm prior analyses and intuition (Schlander and Beck 2009; Messori et al. 2010, Simoens 2011, Schlander et al. 2014a, 2014b). In line with Picavet et al. (2014b) we show a reduction in prices when alternative treatments are available for the same indication. While we do not find additional significant relationships, we cannot exclude that a larger sample would have had more power to detect these.

Despite its plausible results our study suffers from a few limitations. First, prevalence estimates for UODs show large uncertainty. Furthermore, a considerable number of cases may not be detected. For example, in Germany less than 200 patients with type 1 Gaucher disease were treated in 2009 (Schwabe 2011). Second, we did not adjust prices for the size of health benefits as reliable information was difficult to gather from the litera-ture. Third, we did not consider whether RCTs met certain quality criteria such as double blinding or allocation concealment. And forth, there exists a controversy around the

need to require data from RCTs in order to demonstrate the efficacy of drugs for URDs. On the one hand, it may be difficult to conduct an RCT due to an insufficient number of cases (Behera et al. 2007). On the other hand, it may be permissible to raise the significance level, e.g., from 5% to 10%.

The data included in this study do not allow calculating cost-effectiveness ratios; yet, the mean annual treatment cost of €235,734 suggests that health gains in the order of several (quality-adjusted) life years were needed for drugs to be considered cost-effective by conventional standards. From the standard utilitarian perspective underlying the logic of cost effectiveness, assuming that the goal of collectively financed health schemes is to maxim-ize population health gains (valued on the basis of individual, selfish preferences) within the available resource constraints, drugs for URDs would therefore hardly receive priority (e.g., McCabe et al. 2005; Phillips and Hughes 2011; Drummond and Towse 2014; Juth 2014).

Rights-based reasoning (e.g., Hyry et al. 2013) as well as the empirical ethics literature (e.g., Richardson and McKie 2005, 2007; Schlander et al. 2014a) suggest that this approach may be in serious conflict with prevailing social norms and preferences. In this context, we believe it is worth pointing out that on a per-capita basis spending for orphan drugs is generally low as found by our literature search (Table 1), currently running at €1.50 for non-oncological URD drugs in Europe (projected to rise to €4.04 in 2021 assuming un-changed population size) and a current maximum of €16 per year for orphan drugs in France (projected to plateau at €30 in 2020) (based on Hutchings et al. (2014)).

Ultimately, this conflict can be traced back to fundamental value judgments, and for this reason, it is not quite clear which of the two perspectives – incremental costs per patient or budgetary impact – ought to be given priority. While standard health economic evaluations rely on a utilitarian framework, stronger emphasis on social value judgments might lead to a greater role for budget impact and social willingness to pay as an expression of sharing resources – an emerging paradigm that will deserve (and require) further in-depth analysis, deliberation and empirical research.

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