Outrageous prices of orphan drugs: a call for collaboration

Lucio Luzzatto, Hanna I Hyry*, Arrigo Schieppati, Enrico Costa, Steven Simoens, Franz Schaefer, Jonathan C P Roos, Giampaolo Merlini, Helena Kääriäinen, Silvio Garattini, Carla E Hollak, Giuseppe Remuzzi, on behalf of the Second Workshop on Orphan Drugs participants*

Few instances of a single act of legislation have shifted industrial policy in the pharmaceutical industry like the Orphan Drugs Act did when it was signed in the USA in 1983. The Act was written to facilitate the development of drugs for rare diseases and health conditions,[1] and the incentives provided by the Act, such as 7 year exclusivity, tax credits of up to 50% of research and development costs, and access to research and development grants, resulted in the US Food and Drug Administration[2] (FDA) approving 575 drugs and biological products for rare diseases between 1983 and 2017—a real success. In 2000, the European Commission passed similar legislation for orphan medicinal products (OMPs). As a matter of fact, the diseases, not the drugs, are the orphans because all drugs are very expensive,[3] having marrying this success story (table).

Although we are dealing with rare diseases, the increasing number of new OMPs introduced each year is beginning to threaten the sustainability of health-care systems.[5,6] The socioeconomic, ethical, and legal implications of this state of affairs have been analysed extensively.[7] We have previously discussed these implications,[8] and here we concentrate on possible corrective actions. Although the focus here is on OMPs, our recommendations are applicable to other drugs.

The landscape

More than 7000 rare diseases exist, according to official counts.[9,10] However, the number depends on definitions. Cancer, although one of the most common causes of death as a whole, is a good example. Many types of cancer already qualify as rare diseases (eg, osteosarcoma) or even ultra-rare diseases (eg, uveal melanoma).[11,12] By molecular analysis, vast heterogeneity has been detected in all common cancers; many subtypes (eg, adenocarcinoma of the lung with an *ALK* rearrangement[13]) are therefore rare diseases. So-called orphanisation of common disorders, which is a direct result of the genomics era, enhances the scope for precision medicine and is expected to expand the scope further. At present, 40% of drugs with OMP status are approved for specific types of cancer.[14]

Free market competition is distorted in the case of OMPs. First, often only one drug is available, giving rise to a monopoly situation. Second, in some cases, several OMPs are available for the same disease; for example, three drugs are licensed for treatment of Gaucher's disease (imiglucerase, velaglucerase alfa, and taliglucerase alfa).[15] No evidence favours any one product over the other, and each drug costs about US$200 000 per patient per year. To an outside observer, this might look like a cartel.

Value, cost, and pricing of drugs

Drug pricing is generally reminiscent of consumer goods pricing, where the practice is often to set a price as high as the market will allow. However, it is absurd to regard a patient with a serious and life-long disease as a consumer pondering, for example, what car to buy. Working out the value of a drug and the production cost would seem more appropriate; these two approaches are not in conflict with each other. In some cases, an OMP has been shown to be of high benefit to patients before licensing; but in other cases, OMPs have been approved on the basis of surrogate endpoints. One attempt to assess the value of a drug has been the quality-adjusted life-years threshold, adopted in the UK by the National Institute for Health and Care Excellence.[16,17] This approach is innovative but has limitations. In the European Union (EU), the adaptive pathway approach has been explored but not (yet) adopted.[18] Given the multitude of rare diseases with disparate aetiologies and pathophysiologies, the varying

	Disorder	Affected population	Estimated price (US$)	Manufacturer
Eculizumab (Soliris)	Paroxysmal nocturnal haemoglobinuria; atypical haemolytic-uremic syndrome	2000	$409 500	Alexion Pharmaceuticals
Idursulfase (Elaprase)	Mucopolysaccharidosis II	2000	$375 000	Shire
Galsulfase (Naglazyme)	Mucopolysaccharidosis VI	1100	$365 000	BioMarin Pharmaceuticals
Alglucosidase alpha (Myozyme)	Pompe disease	900	$300 000	Genzyme, BioMarin
Rilonacept (Arkalyst)	Muckle-Wells disease	2000	$250 000	Regeneron
Algasidase beta (Fabrazyme)	Fabry disease	2200	$200 000	Genzyme
Imiglucerase (Cerezyme)	Imiglucerase (Cerezyme)	5200	$200 000	Genzyme
Laronidase (Aldurazyme)	Mucopolysaccharidosis I	600	$200 000	Genzyme

Drug names are followed by brand names in parenthesis. Affected population sizes are estimates. Source: M Harper (2010).[4]

Table: **The most expensive drugs**

Lancet 2018; 392: 791–94

Published Online July 20, 2018 http://dx.doi.org/10.1016/S0140-6736(18)31069-9

*Contributed equally

Muhimbili University of Health and Allied Sciences, Dar-es-Salaam, Tanzania (Prof L Luzzatto MD); **Department of Medicine, University of Cambridge, Cambridge, UK** (H I Hyry MA, J C P Roos PhD); **Rare Disease Unit, Azienda Socio-Sanitaria Territoriale Papa Giovanni XXIII, Bergamo, Italy** (A Schieppati MD); **Pharmacy Service, Ospedale Policlinico "GB Rossi", Azienda Ospedaliera Universitaria Integrata, Verona, Italy** (E Costa Pharm D); **KU Leuven Department of Pharmaceutical and Pharmacological Sciences, Leuven, Belgium** (Prof S Simoens PhD); **Pediatric Nephrology Division, Heidelberg University Center for Pediatrics and Adolescent Medicine, Heidelberg, Germany** (Prof F Schaefer); **Department of Molecular Medicine, University of Pavia, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy** (Prof G Merlini MD); **Genomics and Biomarkers Unit, National Institute for Health and Welfare, Helsinki, Finland** (Prof H Kääriäinen MD); **IRCCS-Istituto di Ricerche Farmacologiche Mario Negri, Milano, Italy** (Prof S Garattini MD); **IRCCS-Istituto di Ricerche Farmacologiche Mario Negri, Milano, Italy** (Prof S Garattini); **Department of Endocrinology and Metabolism, Academic Medical Center, Amsterdam, Netherlands** (Prof C E Hollak MD); **IRCCS-Istituto di Ricerche Farmacologiche Mario Negri, Bergamo, Italy** (Prof G Remuzzi MD); **Unit of Nephrology and Dialysis, Azienda Socio-Sanitaria Territoriale Papa Giovanni XXIII, Bergamo, Italy** (Prof G Remuzzi); **and Department of Biomedical and Clinical Sciences, University of Milan, Milan, Italy** (Prof G Remuzzi)

Correspondence to:
Prof Giuseppe Remuzzi,
IRCCS-Istituto di Ricerche
Farmacologiche Mario Negri,
24126 Bergamo, Italy
giuseppe.remuzzi@marionegri.it

***Panel 1*: Criteria for assessing the value of a new drug**

Disease-specific factors
- Incidence or prevalence
- State of knowledge with respect to aetiology, pathogenesis, and pathophysiology
- Clinical severity

Costs to manufacturer
- Previous research and development
- Production costs in relation to manufacturing complexity
- Costs of previous failures, if any
- Profit margins

Benefits to patient
- Life saving
- Life changing
- Effect on quality of life
- Alternative therapies or unmet need
- Certainty or uncertainty about disease modification

modalities and degrees of efficacy of OMPS is not surprising. The best tools to assess value in real life are robust patient registries designed to collect reliable longitudinal data from doctors, independently of industry. Registries are not meant to replace appropriate post-licensing trials; instead, through transparent collaboration from an early stage between patients, doctors, and governments (including health technology assessment bodies), registry data can define the real value of a drug and its appropriate use. In a landmark departure from previous practice in 2014, the US Senate requested information on developmental costs and numerous other details for sofosbuvir, a drug for radical treatment of hepatitis C virus infection.[19] Individual EU member state governments have since increasingly been requesting that industry disclose information about costs incurred during drug development that justify drug prices, but without legal obligations, these requests have largely been evaded.

Production costs include raw materials, chemical technology or biotechnology for production, quality controls, research and development investments, and a reasonable margin of profit.[20] One must also consider that many drugs never reach the market. However, research and development costs might be reduced when research underpinning the discovery of a new drug is largely done by academics, mostly with public funding.[21]

The case of hydroxyurea is an important and current example of what could happen when an old drug is repurposed. First synthesised in 1869, hydroxyurea has been used for decades in patients with myeloproliferative disorders and is now also indicated for sickle-cell disease.[22,23] In the 2017 issue of the British National Formulary, one type of hydroxyurea for myeloproliferative disorders is listed at £0·24 per g, and another type of hydroxyurea for sickle-cell disease is listed at £16·7 per g. Common sense suggests that something must be wrong here.

Stakeholder involvement

Patient empowerment has been a positive development in contemporary medicine, particularly with respect to patients being more fully informed about their diseases and about therapeutic options. Understandably, patients with rare diseases often feel neglected, despite the fact that they might actively have contributed to drug development. This was the case with ivacaftor, the trials for which the Cystic Fibrosis Foundation recruited patients and invested in financially.[24]

The need for change

The spiralling costs of drugs have raised concerns in health services worldwide,[25] and corrective measures have been introduced or attempted. These measures include restrictions on indications, risk sharing, performance-related payments, and monitoring appropriate use. All of these attempts must have some merit because they have helped limit pharmaceutical expenditure. However, they only scratch the surface of the problem.

Given the success of orphan drug legislation, we are convinced that incentives should continue (and perhaps new incentives should be added[26]) lest OMPs are no longer developed by the pharmaceutical industry. We must do all we can to encourage innovation rather than stifle it. We must also reconcile finite health budgets with optimal treatment, which is not accessible to all patients at present.[27] We think the price proposed by the industry must be subject to scrutiny and regulation (panel 1). In *The Price of Inequality*, Joseph Stiglitz[28] stated that "drug prices are so much higher than the cost of production that it pays drug companies…to now spend more on marketing than on research".

Prices should be adapted to the maturity of the product. As long as the drug needs further investigation, early market access should be associated not only with a robust evaluation system but with a reduced price. The price can be adjusted subsequently, after use has been optimised. When a drug becomes approved for another disease, the price should be reduced as the market for that drug increases, especially when an OMP finds an indication in a non-rare disease.

The European Medicines Agency has not yet set or even negotiated prices because EU member states have preferred to retain their sovereignty in this matter. Member states might have valid reasons for this, but it means that Europe has relinquished its ability to take advantage of the fact that, with 500 million inhabitants, it is now the single largest customer for any new drug. Some European countries have teamed up for OMP price negotiations, and the industry has shown interest in this move.[29,30] However, the EU is now largely ceding the

Panel 2: Recommendations

1 Price negotiation should take place at the European level, not at the member state level.
2 Pricing should be based on two main criteria: (1) the cost of research and development plus production; and (2) the value of the drug for patient life and quality of life.
3 Pricing should allow for profit. Since profits depend on the size of the patient population, prices per patient should be allowed to increase when there are fewer patients. European legislation on OMPs should include new rules, which might include effectiveness-related payments and should be monitored by the Antitrust Authority.

opportunity to negotiate drug prices from a position of strength. Even a single visible price reduction obtained through this approach would go a long way toward persuading member states that sovereignty is not advantageous in this context.

We feel that there is a need for new legislation. We have no mandate from official bodies, and our status is that of concerned professionals. On this basis, we have three key recommendations for pricing (panel 2). Following these recommendations would be a logical way to redress the balance between the profit that industry naturally expects and the costs that health services can bear. It is not in the industry's interest for the procurement of OMPs to be suspended by health services, much less that they collapse. Most importantly, it is a moral duty for governments and professionals to reconcile expensive research leading to novel treatments with our ability to actually deliver these treatments to affected patients.

Contributors
This paper reflects the discussion that took place during the 2nd International Workshop on Orphan Drugs at the Clinical Research Center for Rare Diseases, IRCCS - Mario Negri Institute for Pharmacological Research in Ranica, Italy, on Sept 8, 2015. The list of participants in the workshop is reported in the appendix. We thank all the participants for their contributions to the discussion. LL drafted the Viewpoint with contributions from HH, EC, AS, and GR. All authors critically revised the Viewpoiont for intellectual content and approved the final version.

Declaration of interests
SS declares research support from the Belgian Health Care Knowledge Centre, the King Baudouin Foundation, Fonds Wetenschappelijk Onderzoek, KU Leuven, and University Hospitals Leuven, outside the submitted work. FS declares grants from Alexion and personal fees from Otsuka, outside the submitted work. GM serves on the advisory board of Pfizer and Janssen. HK is the Finnish representative in the EU Commission board of member states for European Reference Networks. CEH declares that the Sphinx research group at the Academic Medical Center is involved in pre-marketing clinical trials funded by Sanofi-Genzyme, Protalix, and Idorsia. LL, HIH, JCPR, AS, EC, SG, and GR declare no competing interests.

Acknowledgments
We thank the Menarini Foundation for an unrestricted grant.

References

1 US Food and Drug Administration,Orphan Drug Act, Pub L. No. 97-414, 96 Stat. 2049. http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/HowtoapplyforOrphanProductDesignation/ucm364750.htm (accessed March 1, 2018).
2 Office of Orphan Products Development. List of orphan designations and approvals http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/default.htm (accessed March 1, 2018).
3 Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products (consolidated version .7/8/2009). http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2000:018:0001:0005:en:PDF (accessed March 1, 2018).
4 Harper M. The world most expensive drugs. Feb 22, 2010. https://www.forbes.com/2010/02/19/expensive-drugs-cost-business-healthcare-rare-diseases.html#2fb30c285e10 (March 1, 2018).
5 America's Health Insurance Plans. Orphan Drug Utilization and Pricing pattern (2012–2014). https://www.ahip.org/wpcontent/uploads/2016/10/OrphanDrug_DataBrief_10.21.16.pdf (accessed March 1, 2018).
6 Henrard S, Arickx F. Negotiating prices of drugs for rare diseases. *Bull World Health Organ* 2016; **94:** 779–81.
7 Hughes-Wilson W, Palma A, Schuurman A, Simoens S. Paying for the orphan drug system: break or bend? Is it time for a new evaluation system for payers in Europe to take account of new rare disease treatments? *Orphanet J Rare Dis* 2012; **7:** 74.
8 Luzzatto L, Hollak CE, Cox TM, et al. Rare diseases and effective treatments: are we delivering? *Lancet* 2015; **385:** 750–52.
9 Orphanet. About rare diseases. http://www.orpha.net/consor/cgi-bin/Education_AboutRareDiseases.php?lng=EN (accessed March 1, 2018).
10 Rare list. Global genes. https://globalgenes.org/rarelist/ (accessed March 1, 2018).
11 Boyd N, Dancey JE, Gilks CB, Huntsman DG. Rare cancers: a sea of opportunity. *Lancet Oncol* 2016; **17:** e52–61.
12 Gatta G, Capocaccia R, Trama A, Martínez-García C, RARECARE Working Group. The burden of rare cancers in Europe. *Adv Exp Med Biol* 2010; **686:** 285–303.
13 Cooper WA, O'Toole S, Boyer M, Horvath L, Mahar A. What's new in non-small cell lung cancer for pathologists: the importance of accurate subtyping, EGFR mutations and ALK rearrangements. *Pathology* 2011; **43:** 103–15.
14 European Medicines Agency. Orphan Medicine figures. http://www.ema.europa.eu/docs/en_GB/document_library/Other/2015/04/WC500185766.pdf (accessed March 1, 2018).
15 Van Rossum A, Holsopple M. Enzyme replacement or substrate reduction? A review of Gaucher disease treatment options. *Hosp Pharm* 2016; **51:** 553–63.
16 National Institute for Health and Care Excellence. Guide to the methods of technology appraisal 2013. https://www.nice.org.uk/process/pmg9/chapter/foreword (accessed March 1, 2018).
17 Hyry HI, Stern AD, Cox TM, Roos JC. Limits on use of health economic assessments for rare diseases. *QJM* 2014; **107:** 241–45.
18 European Medicine Agency. Final report on adaptive pathways pilot. http://www.ema.europa.eu/docs/en_GB/document_library/Report/2016/08/WC500211526.pdf (accessed March 1, 2018).
19 Wyden R, Grassley CE. United States Senate Committee on finance. July 11, 2014. http://www.finance.senate.gov/imo/media/doc/Wyden-Grassley%20Document%20Request%20to%20Gilead%207-11-141.pdf (accessed March 1, 2018).
20 Sarpatwari A, Avorn J, Kesselheim AS. State initiatives to control medication costs—can transparency legislation help? *N Engl J Med* 2016; **374:** 2301–04.
21 Avorn J. The $2·6 billion pill—methodologic and policy considerations. *N Engl J Med* 2015; **372:** 1877–79.
22 Platt OS. Hydroxyurea for the treatment of sickle cell anemia. *N Engl J Med* 2008; **358:** 1362–69.
23 Orphan designation. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/orphans/2009/11/human_orphan_000424.jsp&mid=WC0b01ac058001d12b (accessed March 1, 2018).

See Online for appendix

24 Rowe SM, Borowitz DS, Burns JL, et al. Progress in cystic fibrosis and the CF Therapeutics Development Network. *Thorax* 2012; **67:** 882–90.

25 Boseley S. Health secretary urged to tear up patent on breast cancer drug. *The Guardian*, Oct 25, 2015.

26 Committee on Petitions. Opinion of the Committee on Petitions for the Committee on the Environment. Public Health and Food Safety on the EU options for improving access to medicines. (2016/2057(INI)). http://www.europarl.europa.eu/sides/getDoc.do?type=COMPARL&reference=PE-582.217&format=PDF&language=EN&secondRef=02 (accessed March 1, 2018).

27 Kole A, Faurisson F. Rare diseases social epidemiology: analysis of inequalities. *Adv Exp Med Biol* 2010; **686:** 223–50.

28 Stiglitz JE. The price of inequality: how today's divided society endangers our future. New York, NY: Norton & co, 2013.

29 Bartunek R-J. Belgium, Netherlands plan joint purchase of rare disease drugs. http://www.reuters.com/article/us-belgium-netherlands-healthcare-idUSKBN0NC11Z20150421 (accessed March 1, 2018).

30 Communiqué de presse. 24 Septembre 2015. The Grand Duchy of Luxemburg joins Belgium-Netherlands Initiative on Orphan Drugs. http://www.deblock.belgium.be/fr/grand-duchy-luxemburg-joins-belgium-netherlands-initiative-orphan-drugs (accessed March 1, 2018).