The Viewpoint by Luzzatto and colleagues' on drug pricing addresses a very crucial issue because an increasing number of orphan drugs have been marketed in the past decade, and genetic treatments costing more than €300 000 are being made available. Among the determinants of drug pricing reported in the Viewpoint, benefit to the patient is the main factor that is typically examined in cost-effectiveness analyses; disease-specific factors are already recognised to influence drug prices because an inverse association exists between treatment cost and disease prevalence.\textsuperscript{2,4} Needless to say, patent expiration and price competition are also involved in the pricing process.

In our view, the main point of controversy is the role that production costs should play in the price of the new agent.\textsuperscript{1} In decisions regarding the price of Sovaldi,\textsuperscript{2} the role of production costs was emphasised in 2014 by two American senators of the opinion that knowing the production costs could be useful information for determining a fair price for the drug. We are of the opinion that production costs essentially have a political nature rather than a scientific one. Importantly, production costs have the disadvantage that information regarding the reasonable profit recognisable to the manufacturer (as well as on the ratio between research costs vs promotion costs and the balance between research on successful drugs vs research on unsuccessful ones) is lacking. Additionally, the patients’ interests would regrettably conflict with those of the manufacturer’s shareholders.

In conclusion, accounting for production costs in drug pricing is a poorly standardisable process that remains outside the boundaries of evidence-based medicine and previous health technology assessments. Additionally, discretion would be unnecessarily increased by adopting an approach based on production costs.

We declare no competing interests.

*Andrea Messori, Francesco Attanasio, Sabrina Trippoli, Roberto Banfi andrea.messori@regione.toscana.it
Sector of Pharmaceuticals, Regional Health Service, Regione Toscana, 50135 Firenze, Italy

2 Rawson NS. Health technology assessment of new drugs for rare disorders in Canada: impact of disease prevalence and cost. Orphanet J Rare Dis 2017; 12: 59

Luzzatto and colleagues\textsuperscript{1} give three recommendations for pricing orphan drugs. We will focus on the first recommendation (European price negotiation) and on the first part of the second (cost-based pricing).

Negotiations at the European level are not indispensable for the public buyers to get enough market power. Even for orphan drugs, the market size of most European national insurers allows them to exert buyer market power. Most importantly, it could be inappropriate to get a single European price: differential pricing applied in the EU could increase access in all countries and provide stronger incentives for research and development.\textsuperscript{3}

Proposing that pricing should be based on the cost of research and development, production, and profit, could be misleading for research and development incentives and is in contrast with aligning price with the value of the drug for patient life and quality of life. The regulation of public monopolies has long shown that a cost-plus reimbursement system rewards and incentivises inefficient investments; price regulation exclusively based on research and development costs (global and joint) could result in an incentive to overinvest on research and development (Averch Johnson effect).\textsuperscript{1,4}

Moreover, under maximum cost per quality-adjusted life-year thresholds, prices should be the result of decentralised negotiation and market power of industry and buyer, and depend on two references: research and development and production costs, and society’s maximum willingness to pay.\textsuperscript{2}

The price paid for any drug is a signal to the market regarding research and development of new drugs. This signal is crucial, particularly when it comes to drugs mostly authorised with considerable uncertainty regarding their efficacy and safety.

We declare no competing interests.

Jaume Puig-Junoy,* Carlos Campillo-Artero
Carlos.campillo@upf.edu
Department of Economics and Business (JP-J), and Center for Research in Health and Economics (CC-A) Pompeu Fabra University, 08005 Barcelona, Spain, and Balearic Health Service, Palma de Mallorca, Spain (CC-A)

2 Danzon PM. Regulation of price and reimbursement for pharmaceuticals. In: Danzon PM, Richardson S, eds. The Oxford handbook of the economics of the biopharmaceutical industry. Oxford: Oxford University Press; 2012: 266–301

**Authors’ reply**

We agree with Francesca Cainelli and Sandro Vento that patients with orphan diseases, regardless of location, ought to receive the best treatment available. We share their appeal on behalf of low-income and