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# Making rareness count: testing and pricing orphan drugs

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## ABSTRACT

This paper examines the testing and the pricing of orphan drugs, e.g. drugs for patients suffering from rare diseases. Due to the small size of these populations, orphan molecules question established evidentiary practices, namely randomized controlled trials (RCT) and health technology assessments (HTA), driven by numbers and statistical reasoning. Drawing on the notions of “statactivism” (Bruno et al. 2014) and “evidence-based activism” (Rabeharisoa et al. 2014), this paper shows how stakeholders in the field of rare diseases come to test a variety of solutions, ranging from adapting RCT and HTA on the fringe, advocating for exceptional procedures, to recomposing RCT and HTA from within. These initiatives offer new insights into the pricing of orphan drugs as a testing device of who is accountable for the evaluation of these molecules, and of how rare diseases are made to count for society at large.

## KEYWORDS

Rare diseases; Patient organizations; Evidence-based activism; Drug pricing; Valuation; Market regulation

# Introduction

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This paper draws on a research project on the testing and the pricing of orphan drugs, e.g. drugs targeted to patients suffering from rare diseases. Because of the small size of these populations, orphan drugs could not pass the gold standard clinical trials that regulate the marketing of drugs, and were considered economically non viable by the industry. It took multiple negotiations between patient organizations, European regulatory bodies, national authorities, and the pharmaceutical and biotech industry, before markets for orphan drugs started to emerge about two decades ago. Orphan drugs thus are interesting entities “to think with”: they offer unique opportunities for exploring how rare diseases are made to count for the market and for society at large.

This paper examines the evidentiary practices related to the testing and the pricing of orphan drugs. It has a twofold objective. The first objective is to show that the evaluation of the clinical efficacy of a drug and the evaluation of its efficiency are two processes whose articulation is questioned by orphan molecules. Established practices of drug testing and pricing embed a sequential model: in a first step, clinical trials are supposed to generate knowledge about the efficacy of a drug; in a second step, medico-economic assessments consider its efficiency by weighing its benefits against its costs. The latter are central to the negotiations between public authorities and pharmaceutical companies, which determine the price that is ought to be paid to treat one given disease at the national and European level. Studying the pricing of drugs thus entails studying the mechanisms through which medico-economic assessments are performed.

In our approach we examine both the clinical and economic valuation of drugs, to which we refer as testing and pricing. In so doing, we draw inspiration from the emerging literature that calls for empirical studies of valuation processes (Helgesson & Muniesa 2013; Berthoin Antal, Hutter & Stark 2015; Dussauge, Helgesson & Lee 2015; Kornberger et al. 2015). From this perspective, Doganova (2015) has shown the entanglements between valuation and ontological processes, demonstrating how economic calculations intervene in the shaping of the characteristics of future goods. As we will see, orphan drugs are an excellent standpoint for pursuing Doganova’s analysis, for they not only question the underlying hypotheses and evidentiary practices that support the testing and pricing of drugs, but also the very articulation between clinical and economic evaluation.

The second objective of this paper is to describe alternatives to established practices of drug testing and pricing which are put forward by different actors in the field of rare diseases, in particular patient organizations and policy makers at the national and European level. Randomized Control Trials (RCT) and Health Technology Assessments (HTA) are two key devices that intervene in the clinical and economic valuation of new drugs. Both rely heavily on the production of quantitative evidence. In the case of rare diseases, the production of quantitative evidence is problematic due to the low number of patients and the key metrics according to which drugs are valued. This raises the question of whether these evidentiary practices should be rejected, adapted, or composed with.

This is a key issue for the actors in the field of rare diseases, and one that has been recurrently observed in research on the sociology of quantification (Desrosières 2008; Diaz-Bone & Didier 2016). As the quantified measurement of performance reaches more and more domains of professional and personal life, resistance initiatives emerge and take different forms: some oppose any use of quantification, seeing it as an instrument of government and domination; others, in contrast, propose that quantification can also be an instrument of emancipation. The notion of “statactivism” developed

by Bruno et al. (2014) illustrates this latter approach, pointing to situations where actors play with the numbers that they are expected to produce and divert them from their intended purpose, use statistics to build new collective identities, or construct alternative metrics. In a similar vein, Rabeharisoa, Moreira & Akrich (2014) contrast health movements that deploy a form of critique “from the outside”, to patient organizations that embrace what the authors call “evidence-based activism”, granting a central place to the production and mobilization of a variety of bodies of knowledge in their attempts at circulating new quantitative and qualitative evidence which disrupt established ones. In line with these authors’ thinking, we look at how actors in the field of rare diseases address the failing fit between established practices of drug testing and pricing, and the particularities of rare conditions. We observe three types of solutions that are put forward: adapting established practices, creating exceptions within them, and composing with them.

To address these points, we draw on interviews, observation and document analysis. We reviewed the legislation on orphan drugs in Europe, France and UK, and recent grey publications on this issue. We participated to RARE 2015, a conference organized once every two years by the professional consortium EuroMedicine, which gathers stakeholders in the domain of rare diseases in France (medical research and health institutions, data providers, pharmaceutical and biotech firms, patient organizations, national authorities). RARE 2015 held several round-tables on the business models for orphan drugs, where issues of testing and pricing were discussed. We collected and studied the reports issued by EURORDIS Round Table of Companies (ERTC), created in 2005 by EURORDIS (European Organization on Rare Diseases), the umbrella organization of national groups of patients and families concerned with rare diseases in Europe. Twice a year, ERTC puts together meetings where European and national stakeholders in the area of rare diseases reflect on the dynamics of R&D in the field of orphan drugs. We conducted fieldwork in a charity called AKU Society UK, which is involved in a multi-sited clinical trial of a molecule called nitisinone against a rare disease called alkaptonuria. AKU Society UK is also involved in a referral center of the National Health Services that provides nitisinone “off-label” to patients. Finally, we interviewed a few people in leading patient organizations, including the CEO and staff of EURORDIS and people at AFM-Téléthon (the French Association against Myopathies), which is a major player in the area of rare diseases in Europe and in France, and which is currently involved in negotiations with the French national authorities on issues of accessibility of orphan drugs.

This paper has four sections. The first section briefly reverts to the gold standard clinical trial (RCT), which constitutes the main testing device of molecules prior to their marketing. We show that the “modernist” project underlying RCT challenges, and is challenged by orphan molecules which fail to comply with the statistical reason of cohort medicine. This prompted American and European legislators to promulgate specific regulations for orphan drugs, which portrayed rare disease patients as valuable targets for the market. As a result, a growing number of orphan drugs have been put on the market; the high prices of these drugs, supposed to compensate for the low number of patients served, in turn raised the issue of their costs and benefits and challenged their evaluation through HTA procedures.

The small size of rare disease populations not only challenges RCT and HTA; it also comes with knowledge gaps on these diseases due to the low number of patients and their dispersion. So much so that these molecules question the relevance of testing efficacy against “hard” clinical endpoints, which are mired into multiple uncertainties in the case of rare conditions. Similarly, orphan drugs question the relevance of testing efficiency against indicators derived from cost/benefit analysis. The second section examines these issues and shows how attempts to address evidence hostile to rare diseases have resulted in adapting the criteria onto which the efficacy and efficiency of orphan drugs are evaluated.

However, some argue that accommodating orphan drugs on the fringe of established evidentiary practices is not entirely satisfactory for it overlooks the “reality” of rare diseases and their burdens. They rather favor the mobilization of exceptional modalities within existing procedures for evaluating orphan drugs. The third section looks at calls to move beyond economic calculations, on the one hand, and “off-label” use of drugs and compassionate programs, on the other hand, as examples of this “exceptionalism” approach.

The fourth and final section looks at a different type of initiatives that attempt to compose with established evidentiary practices while at the same time revisiting the very foundations these practices are built on, and challenging the distribution of competences they rely on. We first focus on “drug repurposing” and “adaptive pathways”: two initiatives that intertwine the delivery and the testing of drugs, thereby merging pre- and post-marketing activities and recomposing clinical trials for them to be able to absorb “real life”<sup>1</sup> data. We then discuss patient organizations’ attempts to open discussions on the fairness and accuracy of prices. We thus witness several testing and pricing rationales and devices in the field of orphan drugs, each articulating “evidence-based medicine” to the market and to issues of social justice.

# 1. Orphan drugs and the problem of numbers

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Drugs are peculiar goods. With the exception of “over-the-counter” medications, drugs cannot be bought without medical prescriptions. Prior to their marketing, drugs must undergo a series of toxicity and efficacy trials under the jurisdiction of the EMA (European Medicines Agency)<sup>2</sup>. The main testing device upon which the EMA relies is the clinical trial, and the gold standard clinical trial is RCT. Once the EMA gives marketing approval for a drug, national Health Technology Assessment (HTA) agencies calculate its efficiency and advice public authorities either to buy (or to reimburse) the drug or not. RCT and HTA rely on processes of quantification and statistical analysis; when involved in these procedures, orphan molecules are faced with the problem of numbers.

## 1.1. RCT and the limits of statistical reasoning

Let us first focus on the “pre-marketing” of drugs, e.g. the mechanisms through which the toxicity and the efficacy of drugs are processed. A firm willing to launch a drug on the market must submit an application to the EMA, which details, amongst other information, the inclusion criteria for the trial, the clinical endpoints against which the molecule is tested, the hospital departments that conduct the trial, and the protocol for monitoring included subjects. RCT consists of a double blind randomized and controlled mechanism, where neither the clinician nor the “subject” knows whether the latter receives the drug under test or a placebo (and/or an existing medication, if any).

RCT transforms the would-be medication into an experimental molecule by abstracting it from its “real life” utilization. In addition, it strictly delineates the “pre-marketing” and the “post-marketing” life of a drug. Prior to marketing, the efficacy of the molecule is under test. Once the EMA gives

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<sup>1</sup> “Real life” is the actors’ term.

<sup>2</sup> The EMA is the European regulatory body for the marketing of drugs. The EMA is the equivalent of the US Food and Drug Administration.

marketing approval, the efficiency of the drug is evaluated. RCT thus not only separates the clinical evaluation of the experimental molecule and the medico-economic assessment of the drug; it also prioritizes the former over the latter.

Moreover, RCT clearly relies on numbers. Once a molecule has successfully undergone pre-clinical studies, whose aim is to test the functioning of the molecule on cell models and animal models, it enters clinical trials, e.g. trials on humans. Clinical trials are usually composed of three phases, starting with the testing of the toxicity of the molecule on a few healthy volunteers, and terminating with the testing of its efficacy on a few hundreds of patients. The extension of the tested populations is consistent with a conception of drugs as pharmaceuticals for the general population, whose clinical and economic value is grounded in statistical reasoning. Besides, clinical trials must comply with ethical rulings that require the informed consent of included subjects. As a consequence, RCT can be conducted only on large samples of informed and consenting subjects, and de facto excludes the testing of certain drugs which either target vulnerable populations (notably children, pregnant women, people with dementia), or populations too limited in size (like rare disease populations). These de facto exclusions brought in the issue of orphan drugs and led to specific regulations.

## 1.2. Orphan drugs regulations: “politics of numbers” and niches markets

Of notice, the term “orphan drugs” was first coined by the industry as early as the 1960s-1970s to capture the negative market externalities induced by RCT (Lyle 1975; No authors listed 1968). The industry claimed for specific regulations for orphan drugs, and was soon joined by groups of rare disease patients and families in the 1980s in the US, and in the late 1990s in Europe, in the name of social justice. The 1983 American Orphan Drugs Act, and the 1999 European Directive on Orphan Medicinal Products both offered two sets of solutions: (i) economic incentives to firms which are willing to develop orphan drugs, namely public subsidies and/or tax credits for clinical research and trials, fee waivers for registration at the EMA or the FDA, and market exclusivity for the disease targeted by the molecule in addition to the patent protection the molecule benefits from; and (ii) protocol assistance by a statutory body of experts at the FDA or the EMA in order to accelerate the evaluation of the molecule. The legislator thus aims to supporting the development of orphan drugs, yet adamant that clinical trial must remain the testing device of these molecules, and that the market must remain the main route through which patients access these drugs.

The active involvement of rare disease patient and family organizations into the drafting of orphan drugs regulations brought in a crucial element in the emergence of an orphan drugs market. Indeed, these groups of patients and families handed in figures on the number of patients who actually suffer from rare diseases. Thanks to their close contacts with concerned populations and with the few specialists interested in rare diseases, they were able to identify and to count patients, if tentatively, and to propose a threshold for defining what a rare disease is. NORD, the National Organization on Rare Disorders, which gathers American groups of patients and families, came to convene with the legislator that a rare disease is a disease affecting less than 200,000 individuals in America. EURORDIS, the European Organization on Rare Diseases, pushed the epidemiological thinking a step further, so much so that the European Directive on Orphan Medicinal Products defines a rare disease as a disease affecting less than 1 person within 2,000 or 5 persons within 10,000 in one given area. This “politics of numbers” as we term it (Rabeharisoa et al. 2014) constitutes a watershed in the history of rare diseases and orphan drugs. Indeed, as EURORDIS argues, if taken altogether, rare diseases potentially concern 30 million European citizens. From then on, making rare diseases count for society has been tantamount to making orphan drugs count for the market.



To recap, the modernist project of RCT has been arranged through an alignment of the epidemiology of rare diseases, economic incentives for orphan drugs development, the opening of niche markets aided by public subsidies, and social justice concerns.

### 1.3. HTA and the quantity/price equation

Economic incentives for the development of orphan drugs were meant to alleviate the unattractiveness of rare diseases for pharmaceutical companies, which reason in terms of metrics such as market size. Their effects manifest in the number of drugs for rare diseases, which has steadily grown over the last decades. In 2015, the FDA approved 21 new orphan drugs, that is, nearly half of all new drugs approved for the year, and more than half of all the orphan drugs approved before the Orphan Drugs Act was passed.

Ironically, some observers (Dolgin 2010) today think of orphan drugs as “blockbusters of a new type”, which occupy very profitable niche markets due to their high prices. For instance, Cerezyme®, a drug developed by the biotech firm Genzyme for Gaucher’s Disease, is often cited as one of the most expensive molecules ever developed: indeed, its provision skyrockets up to US\$400,000 per patient per year, depending on the age of the patient (Côté & Keating 2012). Whether justified or not, such price levels have alarming consequences and trigger doubts about the sustainability of the rare diseases business model and their compatibility with standard HTA procedures.

Indeed, HTA involves cost/benefit analysis in which the costs incurred by a new drug are compared to the benefits it brings to patients. Take for instance the cost per QALY (Quality Adjusted Year Life) in the UK. QALY is evaluated on the basis of the clinical efficacy of the drug, and of the provision that NICE<sup>3</sup> considers legitimate for patients with the targeted disease. Then NICE goes on calculating the cost per QALY, e.g. the price that the Department of Health will be paying for getting the QALY. Of notice, the UK health system is based on an agreement between the Department of Health and the industry: the industry is free to determine the price it proposes for a drug, on the condition that its return on investment is below a certain threshold<sup>4</sup>. This macro-economic rationale<sup>5</sup> results in a cost per QALY of £20,000 to £30,000 as a reasonable ratio for the Department of Health. Assessed against such metrics, the performance of orphan drugs is poor. Due to the low number of rare disease patients and the difficulty to generate clinical evidence, the cost per QALY of orphan drugs ranges between £300,000 and £400,000, and should lead policy makers to restrict access through the NHS (Tordrup, Tzouma & Kanavos 2014).

We will revert to these discussions below; for the moment, let us just emphasize that rare diseases disrupt not only the production of clinical evidence through RCT, but also that of economic evidence through HTA. Ongoing discussions question the role that cost-efficiency calculations should play in the evaluation of drugs for rare diseases (Hyry et al. 2014), the need to establish a “special status” for their funding (McCabe et al. 2006), or to include other criteria such as their “societal value” (Drummond et al. 2007).

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<sup>3</sup> National Health and Care Excellence. NICE is the UK Health Technology Assessment agency.

<sup>4</sup> Houses of Parliament, Parliamentary Office of Science & Technology, *Drug Pricing*, PostNote Number 364, October 2010.

<sup>5</sup> On QALY and health economics in the UK, see (Moreira 2012).

## 2. Adapting and adopting established practices on the fringe

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Orphan drugs regulations certainly pave the way to the marketing of medications for rare diseases, though the rareness of these diseases continue to threaten clinical trials. Politics of numbers does a good job for mainstreaming rare diseases, but it is of little help when it comes to testing one given molecule for one singular condition. Rareness also comes with additional problems. In a 14-page position paper it published in 2005<sup>6</sup>, EURORDIS mentioned that rareness is the cause of sparse knowledge on these diseases due to the dispersion of patients. As a consequence, the definition of clinical endpoints is not an easy task; neither is the assessment of the clinical benefits and economic costs of an orphan drug. In the following sections, we use the case of AKU Society UK and our observations at the RARE 2015 conference to describe different solutions put forward to deal with the problem of uncertainty: adapting established evidentiary practices, creating exceptions within them, or inventing new models that compose with them. The definition of surrogate endpoints in clinical trials and the inclusion of indirect costs in economic evaluations pertain to the first type of solution.

### 2.1. Addressing clinical uncertainties: the mobilization of surrogate endpoints

AKU Society UK was created in 2002 with an aim to supporting patients and families concerned with a rare disease called alkaptonuria, to producing knowledge on its causes and manifestations, and to finding a cure. Alkaptonuria is a rare genetic disease<sup>7</sup> resulting in the accumulation of homogentisic acid in the body due to the lack of an enzyme that is supposed to break down this acid. This metabolic dysfunction causes ochronosis, e.g. the degradation of cartilages that damages joints. In the mid-2000, AKU Society UK identified a drug called nitisinone licensed for another rare metabolic disease, tyrosinemia type 1, which has features similar to alkaptonuria. Previous clinical research conducted in the US suggested that nitisinone could reduce the levels of homogentisic acid. However, clinical trials were inconclusive, though patients who were put on nitisinone reported that they “felt better”.

According to the CEO of AKU Society UK we interviewed, the American trial failed against the endpoint then chosen: an improvement in the functioning of the hip joint. He hypothesizes that this clinical endpoint does not capture the whole story. Indeed, the clinical picture of alkaptonuria is heterogeneous. In addition, alkaptonuria remains silent until adulthood when joints start to deteriorate. The only symptom that alerts parents is black urines in babies affected with the disease<sup>8</sup>, a symptom that medical doctors have dismissed for years because it does not accompany other visible problems.

This prompted AKU Society UK to launch a consortium called DevelopAKUre which designed a totally different trial: (i) instead of the “hard” clinical endpoint tested in the American trial, they put to the fore a “surrogate endpoint”, e.g. the reduction of levels of homogentisic acid; (ii) they enlarged the sample of subjects included in the trial to patients whose clinical manifestations of the disease vary in

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<sup>6</sup> EURORDIS (2005) *Rare Diseases: Understanding this Public Health Priority*.

<sup>7</sup> AKU Society UK has estimated the prevalence of alkaptonuria at one out of every 250,000-500,000 people (see <http://www.akusociety.org/what-is-alkaptonuria>). To date, AKU Society UK has identified 62 patients in the UK and 3 in Scotland.

<sup>8</sup> Hence the popular name of alkaptonuria: “black urines” or “black nappies” disease.

nature and in severity; and (iii) they put together a protocol for testing the correlation between the dosage of nitisinone, the development stage of the disease, and the time period during which the subject is put on the drug. The trial is underway. If successful, DevelopAKUre will go on licensing nitisinone for alkaptonuria.

The difficulty to define clinical endpoints is not specific to AKU; this issue was discussed during RARE 2015 conference, at a round-table titled *"Is orphan drug at risk while developed according to the state of the art?"* The facilitator, a representative from the industry, warned the audience that exchanges might be *"agitated"* (sic). He started by formulating the following problem:

"It is difficult to recruit patients for clinical trials. There is great heterogeneity in the clinical manifestation of these diseases. Moreover, data on their natural history is generally lacking. As a result, the definition of judgment criteria (endpoints) for clinical trials is complex; resorting to indirect proofs of efficacy (surrogate endpoints) allows quantifying the efficacy of a treatment, but these proofs are rarely accepted by authorities, namely the EMA."

A representative of AFM-Téléthon gave the example of a molecule tested for Duchenne de Boulogne dystrophy: the FDA first rejected the level of dystrophine (the protein missing in muscles of patients suffering from the disease) as a surrogate endpoint; then, once the clinical trial had already been designed, it changed its mind and asked for the surrogate endpoint being tested. *"Rare diseases are put under much more stringent constraints"* than other diseases such as cancers, he complained.

*"Orphan drugs should not be subject to a 'second class' evaluation"*, replied a representative from the French National High Authority for Health, recalling one of the recitals of the European orphan drugs regulation:

"It is important that patients suffering from rare diseases have the right to drugs whose quality, safety and efficacy are equivalent to that of the drugs from which benefit other patients; it is therefore necessary to submit orphan drugs to the standard evaluation procedure."

This discussion echoes a central concern for many actors in the field of rare diseases: how to adjust clinical trials so that they can produce evidence that does not discriminate against rare diseases, and is as robust as evidence for other diseases? This concern is also present when it comes to the economic evaluation of orphan drugs.

## 2.2. Addressing economic uncertainties: the inclusion of indirect costs

At another round-table, titled *"Reality and sustainability of the business model of rare diseases"*, participants in the RARE 2015 conference engaged with the intricacies of the economic evaluation of orphan drugs. A representative from a French consultancy firm specializing in health economics pointed to the lack of robust evidence on the efficacy of orphan drugs that hinders their pricing. He explained that studies on *"the cost of a disease"* are based on *"surveys of the population identified as presenting the disease, with a prospective or retrospective collection of data on health care consumption, indirect consequences, and secondary valuations"*, or on the exploitation of medico-administrative databases (e.g., national health insurance databases). He mentioned a series of obstacles that such evaluations face in the case of rare diseases, among which the importance of indirect costs and the difficulty to evaluate them.

It is precisely this issue that AKU Society UK attempted to tackle by commissioning a consultant to conduct a study on the indirect costs of alkaptonuria. The consultant conducted a survey on a small sample of *"real patients"* to collect *"real life"* data on the costs of the disease, notably the costs of multiple surgeries that patients have undergone, mentioned *"intangible"* costs due to inaccurate diagnosis and inappropriate care, and indirect costs (lost wage and production). The study concluded

that a “conservative approximation” of the total costs of alkaptonuria in the UK, including indirect costs, ranges from £1.4 million to 2.0 million per year<sup>9</sup>.

Defining surrogate endpoints and including indirect costs are two ways of adapting established evidentiary practices – respectively, RCT and HTA – to the specificities of rare diseases. Both are criticized for weakening the quality of evidence on the clinical and economic value of new drugs. They also trigger a different form of critique, which points to the fact that adapting established evidentiary practices also means adopting them. We now turn to alternative solutions that take this critique on board and propose to create exceptions within established evidentiary practices to deal with the specificities of rare diseases.

### 3. Exceptionalism as a mode of regulation

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Adapting clinical and economic criteria to the peculiarities of orphan drugs helps to fit to RCT and HTA on the fringe. However, patient organizations consider that these fixes do not adequately account for “social outcast” that rare disease patients have long suffered from. Regulatory bodies too have come to introduce exceptional modalities into the legislation for it to be able to address the moral sentiments towards underserved categories of patients. This in turn reshuffles debates on the economic and clinical evaluation of orphan drugs.

#### 3.1. Beyond economic calculation

While attempting to calculate indirect costs, AKU Society UK also argued that cost per QALY which NICE measures for evaluating the efficiency of drugs is not relevant for orphan drugs because of the incommensurable burdens of rare diseases though they affect limited proportions of the population<sup>10</sup>. NICE itself seems to acknowledge this problem: in a report<sup>11</sup> on “social value judgments”, which describes the principles to be followed when deciding about the efficiency (namely, cost-effectiveness) of drugs, NICE restated cost-utility analysis as a key tool for decision-making, but added that:

“Decisions about whether to recommend interventions should not be based on evidence of their relative costs and benefits alone. NICE must consider other factors when developing its guidance, including the need to distribute health resources in the fairest way within society as a whole.”

Questions about whether orphan drugs are amenable to economic calculations were raised at the RARE 2015 conference. In response to the presentation by a representative from a French consultancy firm on the difficulty to assess the costs of rare diseases (mentioned in the previous section), a representative of AFM-Téléthon responded:

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<sup>9</sup> Source: AKU Society UK application to the Advisory Group for National Specialised Services, June 2011: 18. On courtesy of AKU Society UK.

<sup>10</sup> Many rare disease patient organizations put this argument to the fore. In its application, AKU Society UK notably refers to the following study: Rare Disease UK (2011) Improving Lives, Optimising Resources. A Vision for the UK Rare Disease Strategy.

<sup>11</sup> NICE (2008a). Social value judgements: principles for the development of NICE guidance (second edition)

"In the area of rare diseases, the benefits of orphan drugs for patients and for society at large cannot be reduced to economic calculations. Think a moment: decorating a roundabout with flowers does not stem from economic calculations, but from a political decision. This should also hold true for orphan drugs: we should together convene that rare disease patients are worth paying the price! This however should not permit the industry to benefit from unduly high prices."

These discussions point to a different solution to the problem of uncertainty: while including indirect costs means adapting, and hence adopting, established evidentiary practices, claiming that the evaluation of orphan drugs "cannot be reduced to economic calculations" and that other criteria should be put in play implies creating a separate evaluation space for rare diseases and treating them as an exception. Legal provisions on off-label use of drugs offers an illustration of this form of regulation "by exception".

### 3.2 Accounting for moral sentiments: off-label use of drugs and compassionate programs

In parallel to the clinical trials conducted by DevelopAKUre, AKU Society UK took the initiative to set up the Robert Gregory National Alkaptonuria Center, named after the patient who co-founded the charity and located in Liverpool Hospital under the medical supervision of Pr. Ranganath. In the UK "off-label law", a referral center for an unmet medical need, can be created as a national health special service. AKU Society UK applied to the NHS in 2011. Core to AKU Society UK application is a demand for implementing clinical guidelines that include the provision of nitisinone off-label, monitoring patients, and collecting "real life" data on the history of the disease under treatment (nitisinone along with pain killers, surgeries, social and psychological support, etc.), including patients' reported outcomes. As the CEO of AKU Society UK told us:

"The Robert Gregory National Alkaptonuria Center is the first specialized referral center for our condition, and also the first longitudinal observation study of our patients."

When asked about how this longitudinal observation study is articulated to the clinical trials of nitisinone, he answered that "real life" data will count in some way. Indeed, Pr. Ranganath is the principal investigator of the trials underway, and the issue of dosage of nitisinone is core to the trials and to the longitudinal observation study. The articulation between exceptional provision of orphan drugs and established evidentiary practices is indeed core to discussions on the European Directive on Compassionate Programs that regulates off-label use of drugs.

The Directive permits a Member State to ask for a promising molecule under test being provided for free to patients who either undergo the terminal phase of their disease (notably cancers), or suffer from a debilitating condition for which the prognosis is bad and there is no other cure available (for instance rare diseases). As its name denotes, this Directive has compassion as its main motive: more precisely, it balances urgent, underserved and desperate situations against the complex and long process through which patients eventually access the drug on the national market<sup>12</sup>.

Like the EU Directive on Orphan Medicinal Products, the EU Directive on Compassionate Programs does not aim to taking the molecule away from clinical trials, and the drug away from the market: clinical trials must go to their end; if they succeed, then the molecule enters the "post-marketing"

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<sup>12</sup> Compassionate programs date back to the early days of HIV/Aids epidemics, when activists fought for getting access to molecules under trial for the sake of patients who were prepared to take the risk since they were dying anyway (Epstein 1996).

stage; if not, then it cannot access the market; in any case, the compassionate program stops at the end of clinical trials. Accordingly, the Directive clearly states that should the molecule “work” during the compassionate program, this should in no way be considered as an evidence of its clinical efficacy.

In contrast, patient organizations argue that compassionate programs should be thought of, and eventually redesigned as appropriate testing devices for orphan molecules, insofar as they bring in “real-life”-based evidence on the clinical efficacy of molecules and on their medical and social values thereof. Indeed, compassionate programs and “off-label law” generally speaking, take debates out of the strict realm of economic evaluation and pricing to issues of unmet medical needs, accessibility and social justice. In the last section of our paper, we examine configurations within which stakeholders in the field of rare diseases contemplate these issues.

## 4. Composing with established evidentiary practices

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Compassionate programs raise the issue of the articulation between the exceptional spaces that rare diseases come to occupy within established evidentiary practices. How can the knowledge produced in these exceptional spaces feed in the production of evidence on the clinical and economic value of new drugs? The initiatives that we discuss in this section address this issue and sketch a third type of solution that consists in composing with evidentiary practices, rather than adapting them or creating exceptions. In so doing, they question the key hypotheses underlying established evidentiary practices – namely, the separation between the testing site and the “real world”, and between clinical and economic value – and the distribution of competences among the actors involved.

### 4.1 Recommendation for Temporary Use and “adaptive pathways”: blurring the boundaries between pre- and post-marketing

A first initiative that we discuss here is a new legal provision of the French “off-label law” arsenal, known as the RTU (Recommandation Temporaire d’Utilisation – Recommendation for Temporary Use). RTU permits French pharmacy hospitals to prepare and deliver a drug that has a marketing approval for one given indication, but for another condition than the one that had been tested during clinical trials. RTU is put under the control of the ANSM (Agence Nationale de Sécurité des Médicaments – French National Agency for Drug Safety), which recommends the molecule being tested in “real life” for this additional indication by the company which developed it in the first place (the company is reimbursed for this), and eventually being put on the market should it “work”.

RTU presents similarities with the off-label provision of nitisinone discussed above: both suggest repurposing a drug that is licensed for one given indication for a different condition, on the basis of promising evidence drawn on the “real life” utilization of the drug. However, RTU goes further than compassionate programs: it transforms the off-label use of the drug as a brand-new testing site, and it bypasses the pre-marketing process. French rare disease patient organizations push RTU as an appropriate option for orphan drugs: after all, they argue, there are numerous molecules that had already passed a series of tests, notably toxicity tests, and that can be re-worked for rare diseases should they have shown some “real life” bio-clinical impact on certain aspects of these diseases. Some companies however consider RTU as an unbearable attack against the rationale of therapeutic R&D and the functioning of the market, arguing that: (i) public authorities should not patronize corporate R&D; (ii) providing a drug for another condition than the one tested in the first place may

bring risks to patients; and (iii) national authorities should not supersede the European regulatory bodies in the legislation on drugs<sup>13</sup>.

In contrast to compassionate programs, RTU conjoins the delivery and the testing of drugs and bring in pharmacy hospitals as privileged loci for these “drug repurposing markets”, a situation which companies are definitely not ready to accept. During RARE 2015 conference, an argument took place on RTU and the pricing of drugs it pertains:

“Companies must comply to a series of legal requirements concerning the manufacturing of drugs. The financial impact of these requirements is huge, and in the case of orphan drugs, it certainly raises the prices. Pharmacy hospitals do not face the same requirements, nor are they obliged to follow the same quality procedures and to conduct pharmacovigilance.” (A representative from the industry)

“So then, from a financial point of view, shouldn’t we improve the quality of pharmacy hospitals production of orphan drugs instead of delegating manufacturing to the industry?” (A rare diseases expert)

Needless to say that this exchange induced commotion amongst the audience, for it opened up the question of who is responsible and accountable for the testing, the manufacturing and the pricing of orphan drugs.

On these issues, patient organizations and regulatory bodies bring in one additional initiative called “adaptive pathways”, which blurs even further the boundaries between pre- and post-marketing. The idea behind adaptive pathways is the following. The molecule is tested against hard and/or surrogate endpoints, and as soon as promising evidence are produced, it is delivered to a selected number of patients and licensed at a fairly high price. During this first post-marketing stage, the company, in collaboration with hospitals, infrastructures in charge of the management and monitoring of rare disease cohorts, and patient organizations, collects “real life” data to be re-injected in the testing of the molecule. The molecule then is put to test against these additional data and re-designed if necessary. Should this second testing stage be successful, the molecule is delivered to a larger proportion of the targeted population and licensed at a lower price<sup>14</sup>. And so on. For the company being kept on track, it is given a marketing exclusivity for the entire targeted population.

In 2014, the EMA launched a pilot project on adaptive pathways: ten products were selected, half of which were orphans. In its report on the initial phases of the pilot project, the EMA identified three criteria that define adaptive pathways: (i) an iterative development plan (gradually expand the tested population, or reduce uncertainty moving from surrogate to harder endpoints); (ii) the use of real life data as a complement to RCT data; and (iii) the ability to engage HTAs and other downstream stakeholders. While the pilot is still ongoing and it is yet unclear whether adaptive pathways will be adopted and what forms they will take, the criteria retained indicate a profound evolution in the ways clinical and economic evaluation are conceived and organized, with “downstream stakeholders” such as HTAs being granted a role to play upstream the drug development process.

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<sup>13</sup> See for instance the position of The European Federation of Pharmaceutical Industry Associations (EFPIA) (Taylor P. (2015) Industry files complaint against France’s off-label law. Protests against promotion of Roche’s Avastin as cheap eye medication. *PMLiVE*). Critics however point to the fact that the real motive for companies to reject “off-label” use of drugs is because they fear that an existing and less expensive drug will be privileged over a brand-new and potentially more profitable molecule.

<sup>14</sup> This is consistent with the volume-price equation pertaining the “blockbuster model” of pharmaceuticals, and of consumer goods largely speaking: the larger the targeted population, the lower the price.



## 4.2 What is “fair” and “accurate”? Opening discussions on pricing

A similar trend can be observed “upstream”, with patient organizations engaging with the issue of orphan drugs prices. At the RARE 2015 conference, a representative of AFM-Téléthon called for a collective discussion on pricing:

“The classic business model is not compatible with extremely rare diseases. We need to be collectively creative. We have thus put forward the concept of a “fair and controlled price””.

During an interview we had with this representative of AFM-Téléthon, he repeated his argument. The prices of orphan drugs, he said, should be “fair”. There is no point in capping<sup>15</sup> the budgetary impact of orphan drugs, if only because rare disease patients have long been forgotten and deserve collective investment. He however warned the industry that prices should also be accurate. He particularly criticized the opportunistic behaviors of certain companies which game the orphan drug regulation with what he called “salami slicing”, e.g. the splitting of one disease into multiple rare conditions for ripping the benefits of orphan designations offered by regulatory bodies. But how fair and accurate are the prices of orphan drugs, one may ask?

EURORDIS, the European Organization on Rare Diseases, also tackles this issue. In 2010, EURORDIS commissioned a consultancy firm to study the correlation between the prices of orphan drugs and a series of variables such as the prevalence and the severity of diseases, the innovative dimension of molecules, and improvement in morbidity and mortality<sup>16</sup>. As a matter of fact, correlations turn out to be inconclusive. Besides, the study reported on enormous discrepancies of prices across Member States due to national specificities of health technology assessment procedures. These findings were presented to the EURORDIS Round Table of Companies meeting on December 12, 2010. Several solutions were put to discussion. EURORDIS suggested that data from different sources, including “real life” data, be collected, re-injected into the testing of drugs, and circulated amongst Member States, with an ultimate goal to sharing facts and figures on the value for money of orphan drugs.

Discussions on the fairness and accuracy of prices for orphan drugs reveal the capacity of prices to serve as a problematizing device of how and to what extent we collectively prize things. Conceived as such, prices become a matter of public discussion in which patient organizations increasingly claim a role to play.

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<sup>15</sup> Capping is a mechanism through which certain Member States contain the budget allocated to orphan drugs. The French government for instance is ready to reimburse an orphan drug on the condition that its costs for the French Public Health Insurance Fund do not exceed 30 million euros per year (Tordrup, Tzouma & Kanavos 2014). Patient organizations oppose this mechanism, which they consider unfair and ineffective: molecules, they say, will eventually be sorted out according to obscure negotiations between the industry and national authorities as regards their capping threshold, with limited, if no consideration for their benefits for patients.

<sup>16</sup> The results of the study are presented in the report of the ERTC 13th Workshop, entitled “Patients' access to Orphan Medical Products, Innovative Pricing Schemes, and National Measures in Global Financial & Economic Crisis Environment” (December 13, 2010). On courtesy of EURORDIS.



# Conclusion

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In this paper, we examined the testing and the pricing of orphan drugs. Our fieldwork and analysis enable us to come up with two main findings.

Firstly, we observed that the evaluation of the clinical efficacy and the evaluation of the efficiency of orphan drugs are amenable to several orderings. Politics of numbers, adaptation to RCT and HTA, “exceptionalism”, and composition with RCT and HTA today coexist in the field of orphan drugs. This coexistence opens up the question of who is accountable for the evaluation of orphan molecules, as much as it puts to the trial their modes of existence. Should orphan drugs be given a chance in real life on the sake of moral sentiments? Should orphan drugs be entitled exceptional provision in the name of social justice? Should orphan drugs be evaluated according to standard procedures in order to secure the same quality as for non-orphan products? These questions, and the answers which stakeholders in the field of rare diseases contemplate, show that the testing and the pricing of orphan drugs not only are interlinked, but are also core to the emergence of rare diseases as a collective concern.

Our second finding is about the prominent role which rare disease patient organizations endorse in the pricing of orphan drugs. Strikingly, groups of rare disease patients and families plea for the market being a do-able route for accessing orphan drugs. This is consistent with the early history of rare disease activism, and is lastingly marking the war on rare diseases. Groups of rare disease patients and families are working towards the mainstreaming of their conditions, if only because they regularly confront social criticism against “exceptionalism” they have managed to get. As one of our interlocutors at AFM-Téléthon explained to us: “*Rare diseases cannot stand out of the common law.*” And common law, in his argument, includes the market as the main path for accessing orphan drugs, provided that the market is re-composed to be able to absorb these drugs. For this reason, the role of rare disease patient groups in the fabrics of markets is worth to be further studied.

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