ORPHAN DRUGS: WHAT FACTORS IMPACT THE PRICE IN FRANCE?

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BACKGROUND

In 2000, Europe introduced incentives for orphan drugs. With the introduction of these new drugs and their increasing share in health expenditures, attention to the price of these products has increased over time. in France, **the price is not based on production costs**, or return on capital, but rather on an estimate of the benefit provided by the product: its value. While **value cannot be quantified**, in France it can be approached by indicators

This study aims to determine the criteria that seem to correlate with a high price of orphan drugs on the French market.

METHODS

A **focused literature review** identified the determinants of a drug's value. All orphan drugs with a price available in France were included. For each orphan drug that had a published opinion of the French Health Technology Assessment Agency, the orphan drug designation reports and the European Public Assessment Report from European Medicine Agency were analyzed.

The calculation of the annual price per patient was based on the dosage specified by the label and the duration of treatment. For the qualitative variables, a **univariate analysis** was performed using the Wilcoxon and Kruskal-Wallis tests based on the number of possible modalities that the variable could take. Kendall correlation was used for quantitative variables. The **multivariate analysis** was performed using a generalized linear model with a Log Normal distribution on the variables from the univariate analysis that had a p-value of less than 0.05. Analysis were done using the R software.

RESULTS

1 DATABASE

A total of 177 drugs (209 orphan indications) were extracted from lists of the EMA website. Of these, 134 drugs (166 indications) had a TC opinion, 129 (147 indications) of which were for the first reimbursed indication. 96 drugs (113 indications) had a price published in the French Official Journal. Finally, after the last exclusions (generic drug, insufficient AB, loss of orphan drug designation before price), **82 drugs (98 indications) were included in the analysis.**

During the **Focused Literature Review**, 268 citations were obtained in Embase and 22 in the Cochrane database. After screening on title and abstract, 14 studies were included for quantitative analysis of orphan drug values' criteria. From the **14 studies included for analysis** (2,4,7–18), nearly 60 parameters were identified and classified according to four main dimensions: disease characteristics, treatment elements, economic and societal elements, HTA and market access elements. Of these 60 parameters, 30 were retained for econometric analysis. The choice was based on the feasibility of collecting data and the relevance of the determinant.

Table 1: Characteristics of orphan drugs included in the study

PARAMETERS	VARIABLES
Treatment' annual cost	mean (sd) 78,863€ (124,972.1€), median 34,044€ [Q25: 17,231€-Q75: 67,219€]
Severity	invalidating 12 (12%), life-threatening 47 (48%), both 39 (39%)
Unmet need	none 36 (37%), one 26 (27%), ≥2 37 (37%)
Treatment type	curative 60 (60%), symptomatic 31 (32%), other 8 (8%)
Safety	Major Adverse Effect (MAE) 65 (65%), no MAE 34 (35%)
Repurposed	no 84 (85%), yes 15 (15%)
Improvement Quality of L.	no 80 (81%), yes 18 (19%)
Improvement morbidity / mortality	no 60 (61%), yes 38 (39%)
Chronic (≥ 6 months)	no 20 (20%), yes 79 (80%)
Posology based on weight	no 59 (59%), yes 40 (41%)
ATC	A 20 (20%), B 6 (6%), C 5 (5%), G/R/V 5 (5%), H 5 (5%), J 7 (7%), L 45 (45%), N 6 (6%)
Treatment line	first 56 (57%), other 43 (43%)
Administration	inhalated 4 (4%), injectable 38 (39%), oral liquid 7 (7%), oral solid 50 (50%)
Class of molecule	biological 23 (23%), chemical 76 (77%)
Population age	adult 66 (66%), both 22 (22%), pediatric 11 (11%)
Target population size	mean (sd) 918.5 (1,252), median: 300 [Q25 : 100 - Q75 : 1,237.5]
Company size	small 20 (21%), medium 18 (19%), big 60 (61%)
MA approval year	median: 2008 [Q25 : 2006 - Q75 : 2013]
US availability	no 39 (40%), yes 60 (60%)
RCT	no 38 (39%), yes 60 (61%)
other HTA	no 56 (57%), yes 43 (43%)
Pivotal study	phase II 33 (36%), phase III 60 (64%)
Patient inclusion studies size	mean (sd) 210 (211.1), median 143 [Q25 : 74 - Q75 : 304.5]
Comparator	active substance 25 (24%), none 37 (38%), placebo 37 (38%)
Endpoints	hard 40 (42%), surrogate 54 (58%)
Incremental AB	I 7 (7%), II 25 (26%), III 23 (23%), IV 26 (27%), V 18 (17%)
Added Benefit	important 93 (94%), moderate 5 (5%), weak 1 (1%)
Commercialization year	median 2010 [Q25 : 2007 - Q75 : 2015]
delay HTA - commercialization (days)	mean (sd) 350.8 (283.56), median 252 [Q25 : 174 - Q75 : 457]
delay Marketing Approval - commercialization (days)	mean (sd) 582.5 (365.7), median 468.5 [Q25 : 312.8 - Q75 : 806.8]
French Compassionate program (ATU)	group 17 (16%), individual 11 (11%), both 17 (17%), none 54 (55%)
MA type	conditionnal 11 (10%), exceptional circumstances 25 (26%), standard 63 (64%)
Public Health interest	none 66 (71%), weak 20 (22%), moderate 7 (8%)
Clinical trials follow up (wk)	mean (sd) 44.7 (41,7), median 31.0 [Q25 : 17.5 - Q75 : 52.0]

FDS: full dataset | **SDS:** screened dataset | **ATC:** Anatomical Therapeutic Chemical classification system

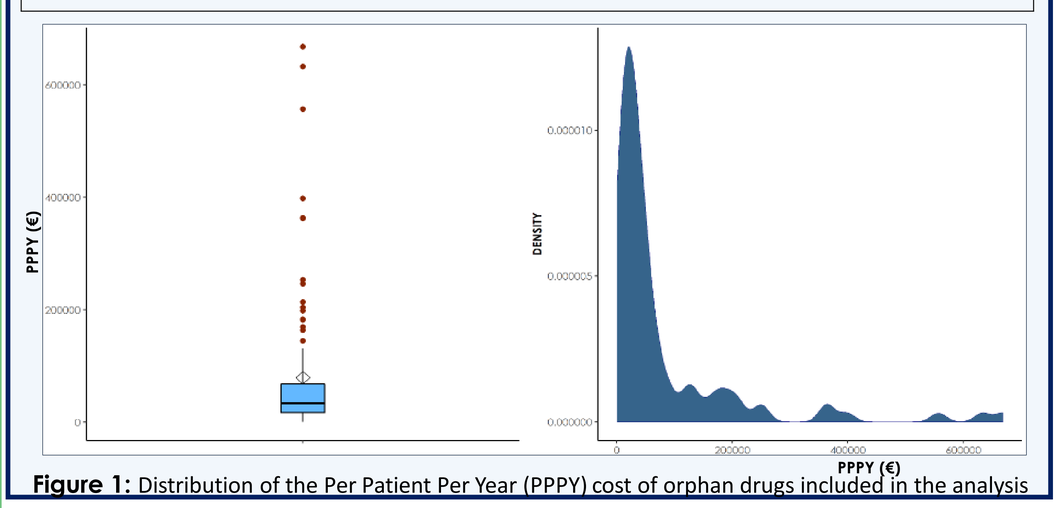

Figure 1: Distribution of the Per Patient Per Year (PPPY) cost of orphan drugs included in the analysis

Table 2: Univariate analysis results

PARAMETER	P-value
treatment line	0.83
repurposed	**< 0.0001**
posology based on weight	0.076
chronic (> 6 months)	**0.020**
improvement in survival or morbidity	0.46
improvement in quality of life	0.35
safety profile	0.64
class of molecule	**< 0.0001**
US availability	**0.020**
other HTA	0.62
AB	0.89
AIB	0.16
company size	0.31
administration	**0.015**
MA type	0.051
Compassionate use (ATU)	0.12
unmet need	0.077
pivotal study	0.78
randomized clinical trial	0.77
type of comparator	0.64
type of endpoint	0.077
target population's age	0.25
type of treatment	**0.027**
Public health interest	0.47
severity	0.073
ATC class	**< 0.0001**
Commercialization year	**0.039**
MA year	**0.024**
delay MA - commercialization	0.58
delay HTA - commercialization	0.16
clinical trials follow up	0.068
patient inclusion studies size	**< 0.0001**
target population	**< 0.0001**

2 ANALYSIS

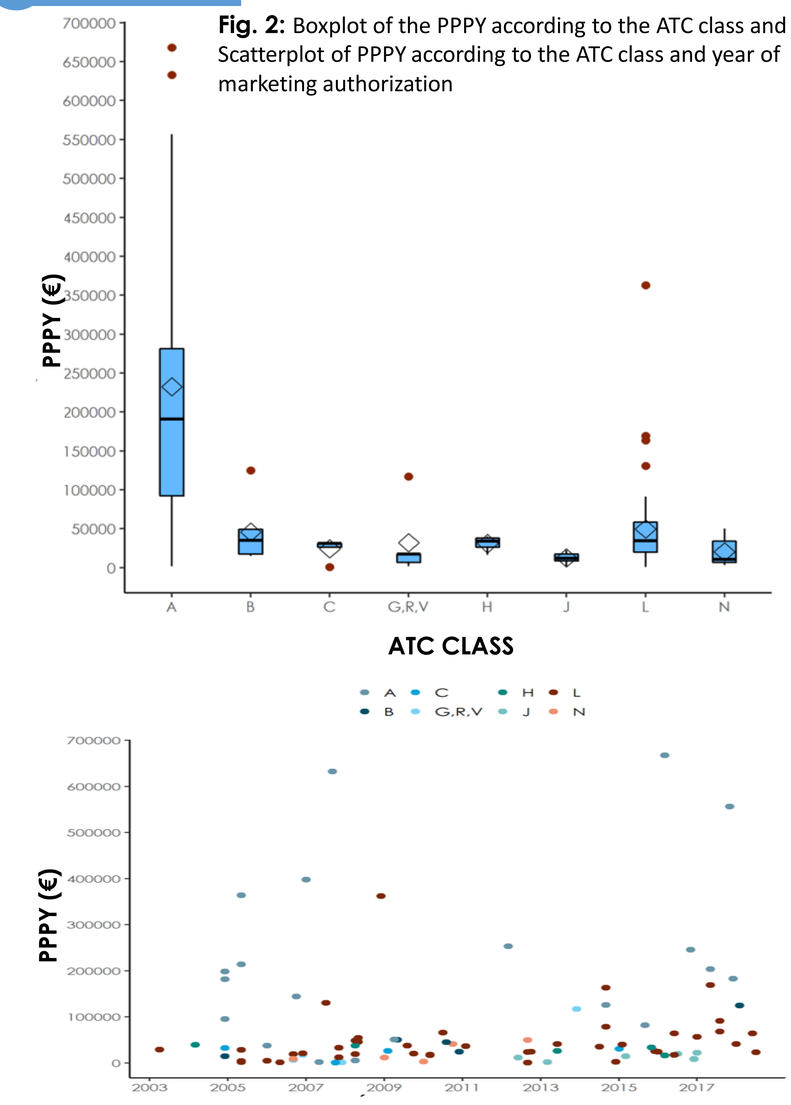

Fig. 2: Boxplot of the PPPY according to the ATC class and Scatterplot of PPPY according to the ATC class and year of marketing authorization

Due to a residue distribution that did not follow a Normal distribution and due to the heteroscedasticity of the residue variance, the multivariate analysis was performed using a GLM, which was more conservative than the general linear model.

The GLM model had a R^2 of 0.66 and a good significance (p-value=0.96).
The significant variables were **repositioning** (p=0.0015), **class of molecule** (p=0.0003), **ATC class** (p<0.0001), **commercialization year** (p=0.005) and the **number of patients included in clinical studies** (p=0.025).

Table 3: Multivariate analysis results

PARAMETER	ESTIMATE	SE	OR	2.5%	97.5%	WALD TEST
(Intercept)	-106.43	42.74	-	-	-	
Repurposed						**0.0015**
no	0.00	0.00	-	-	-	-
yes	-0.83	0.26	0.44	0.26	0.75	0.0021
Chronic use						0.49
no	0.00	0.00	-	-	-	-
yes	0.16	0.23	1.17	0.73	1.83	0.5
Class of molecule						**< 0.001**
biological	0.00	0.00	-	-	-	-
chemical	-0.92	0.26	0.40	0.23	0.68	0.0006
US availability						0.89
no	0.00	0.00	-	-	-	-
yes	-0.03	0.20	0.97	0.64	1.47	0.89
Administration						0.93
inhalated	0.00	0.00	-	-	-	-
injectable	0.17	0.59	1.18	0.32	3.93	0.78
oral liquid	-0.05	0.65	0.95	0.25	3.38	0.94
oral solid	0.19	0.56	1.21	0.35	3.68	0.74
type of treatment						0.5
other	0.00	0.00	-	-	-	-
curative	-0.36	0.33	0.70	0.35	1.30	0.28
symptomatic	-0.19	0.36	0.83	0.40	1.67	0.61
ATC class						**< 0.0001**
ATC A	0.00	0.00	-	-	-	-
ATC B	-1.41	0.41	0.24	0.11	0.58	< 0.001
ATC C	-1.45	0.46	0.23	0.09	0.62	0.002
ATC G,R,V	-1.12	0.43	0.33	0.15	0.78	0.1
ATC H	-1.54	0.40	0.21	0.10	0.51	< 0.001
ATC J	-1.98	0.44	0.14	0.06	0.34	< 0.001
ATC L	-0.97	0.24	0.38	0.23	0.61	< 0.001
ATC N	-1.91	0.41	0.15	0.07	0.35	< 0.001
Commercialization year	0.06	0.02	1.06	1.02	1.11	**0.005**
Patients in studies	< 0.001	< 0.001	0.99900	0.99815	0.99996	**0.025**
Target population	< 0.001	< 0.001	0.9999	0.99973	1.00002	0.062

CONCLUSION

Scientific literature counts **numerous publications that highlight the sky-high prices of orphan drugs**, often raising the question of the sustainability of national health systems. Among these studies, some identified the parameters that could explain more or less significant prices among these drugs.

This **study confirms that the ATC class is frequently associated with a higher cost** per patient per year. This is mainly true for the ATC class A (fig. 2). Drugs in the ATC A class target metabolic and enzymatic diseases and often have same characteristics such as very small target population, they are biological drugs and are targeting severe diseases. By removing them from the analysis, the ATC class lost significance in the univariate analysis (p=0.055).

GLM showed a negative correlation between a **repurposed drug** and its cost, as well as **chemical** (versus biological) drugs. These two elements seem to be in line with the principle of a willingness to pay for innovation.

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