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Uncertainties and coping strategies in the regulatory review of orphan medicinal products

Zafiropoulos N.[1], Koenig F.[1], Pignatti F.[2], Kouroumalis A.[2], Guizzaro L.[2], Roes K.[3], Torres F.[4], Posch M.[1]

[1]Medical University of Vienna, [2]European Medicines Agency, [3]University Medical Center Utrecht, [4]Autonomous University of Barcelona

Background - Objective

In 2011 the European Medicines Agency (EMA) introduced a new structure for documenting the benefit-risk assessment of new drug applications, distinguishing between key benefits and risks, and their associated uncertainties, which are systematically published as part of the European Public Assessment Reports (EPARs).[1] Up to date, there has not been any systematic review on how drug regulators cope with uncertainty in evaluating the benefit-risk balance of medicines. The purpose of this work was to develop a framework for classifying uncertainties and coping strategies, and apply it on a set of approved products.
We aimed at characterising the profile of pending uncertainties at time of approval and explore systematic differences based on orphan status or other variables.

Methods

We performed literature review to identify frameworks for classification of uncertainties that could be applied to regulatory evaluation of pharmaceuticals. After developing a fit-for-purpose framework, we applied it retrospectively on all oncology products approved by EMA since 2011. Uncertainties and coping strategies were identified in the benefit-risk section of the EPARs and classified using the framework. For identifying coping strategies, we relied also on the Risk Management Plan and the Annex II.
Each uncertainty was classified according to

- **ISSUE** (*what is the EMA uncertain about*) and
- **SOURCE** (*what causes this uncertainty*).

For every uncertainty we identified a

- **COPING STRATEGY** (*how the EMA deals with the uncertainty*) distinguishing cases where EMA
  - requires additional data for **reducing** an uncertainty, or
  - is satisfied at the level of **acknowledging** the uncertainty.

The categories were defined such as to avoid overlap in meanings and the framework was tested by independent reviewers to check for reproducibility.

Results

In total n=64 products were included, 26 had orphan designation. In figure 1 we give the absolute numbers of issues identified separately for orphan and non-orphans. In Table 1 and Figure 1 the number of issues identified, underlying sources and coping strategies are reported. As far as the issues are concerned, no major discrepancies between orphan and non-orphans could be identified.

	Non-Orphan (38 EPARs)	Orphan (26 EPARs)	All MAA (64 EPARs)
Issues	152	111	263
Balance of BR	19 (13%)	10 (9%)	29 (11%)
Efficacy/Benefit	66 (43%)	51 (46%)	117 (44%)
Safety/Risk	67 (44%)	50 (45%)	117 (44%)
Source			
Conflicting data	4 (3%)	6 (5%)	10 (4%)
Lack understanding of relevance	2 (1%)	3 (3%)	5 (2%)
Not enough data	126 (83%)	71 (64%)	197 (75%)
Unreliable data	20 (13%)	31 (28%)	51 (19%)
Coping Strategy			
Acknowledge	51 (34%)	36 (32%)	87 (33%)
Reduce	101 (66%)	75 (68%)	176 (67%)
Issues per EPAR (mean number per EPAR±std)			
# all issuess	4.0±1.99	4.3±2.41	4.1±2.15
# efficacy issues	1.7±1.27	2.0±1.28	1.8±1.27
# safety issues	1.8±1.55	1.9±1.57	1.8±1.55
# B/R issues	0.5±0.51	0.4±0.75	0.5±0.62
Sources (mean number per EPARS±std)			
Not enough data	3.3±1.85	2.7±1.97	3.1±1.90
Unreliable data	0.5±0.80	1.2±1.50	0.8±1.17
Conflicting data	0.1±0.45	0.2±0.51	0.2±0.48
Lack of understanding	0.1±0.23	0.1±0.33	0.1±0.27
Coping Strategies (mean number per EPARS±std)			
Acknowledging	1.3±1.56	1.4±1.68	1.4±1.60
Reducing	2.7±1.66	2.9±2.25	2.8±1.91
Approval Type			
Conditional/Except.	6 (16%)	12 (46%)	18 (28%)
Regular	32 (84%)	14 (54%)	46 (72%)
Cancer Type			
Haematological	3 (8%)	16 (62%)	19 (30%)
Solid	35 (92%)	10 (38%)	45 (70%)
Unmet Medical Need			
High	19 (50%)	18 (69%)	37 (58%)
Medium	14 (37%)	8 (31%)	22 (34%)
Low	5 (13%)		5 (8%)
Design			
No RCT	8 (21%)	9 (35%)	17 (27%)
RCT	30 (79%)	17 (65%)	47 (73%)

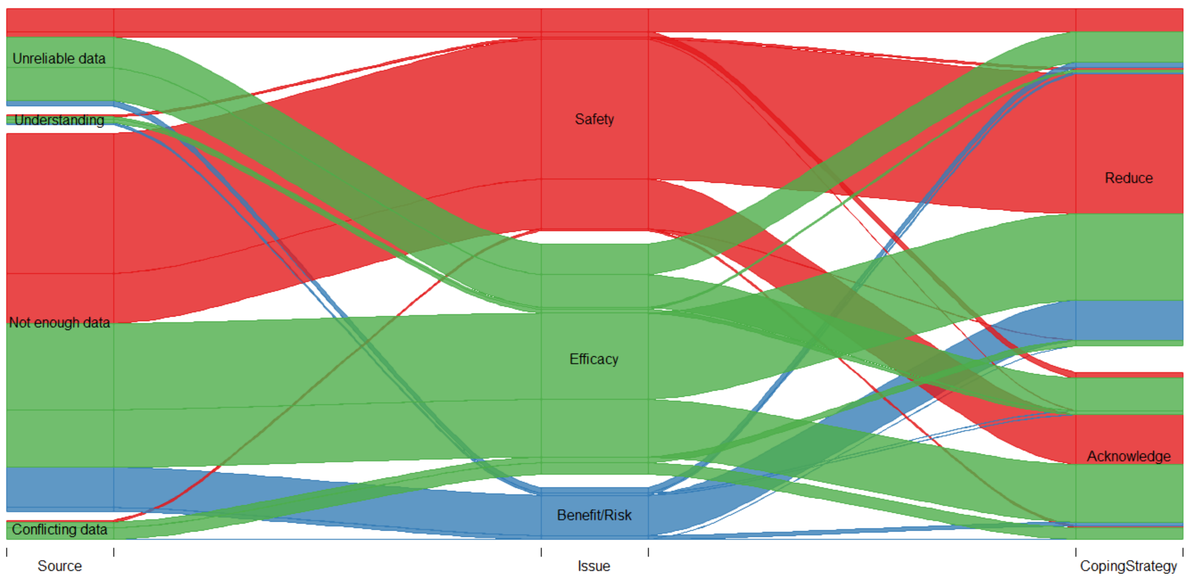

Figure 1: Alluvial diagram illustrating the distribution of the three main categories of issues in relation to their sources and the relevant coping strategies. The majority of issues were equally distributed between uncertainties specific to Efficacy and Safety, with only a small number relating to the more general category of Benefit-Risk. The leading source of uncertainties was Not enough data and the main coping strategy was Reduce (i.e. more data are expected/required)

In a GLM, the mean number of issues raised did not differ by orphan status (p=0.98) or cancer type (p=0.97), but there was a statistically significant difference (p=0.004) between EPARs with RCT (3.6±1.8) and those without RCTs (5.4±2.55). Further analysis revealed that this difference was mainly driven by safety issues. However, for orphans the proportion of EPARs with RCT was smaller than for non-orphans (see Table 1), but this difference was not statistically significant (Fisher´s Exact Test p=0.26).
To analyze what impacts the coping strategy (reduce vs acknowledge), a logistic regression model using EPAR as random factor revealed that the factor Orphan (Yes/No), Source and Cancer Type had no statistically significant impact, but Design (RCT Yes/No, p=0.0045) and Issue (p=0.0044). If the issue is related to BR, then the coping strategy was mainly Reduce (93%), where as for safety and efficacy the proportions of the strategy Reduce were smaller (74% and 54%, respectively). Similarly, for No RCT the proportion of strategy “Reduce” was higher (83%) compared to 58% for EPARs with RCTs.

Conclusions - Discussion

We noted that several uncertainties, crucial to the assessment of new pharmaceutical products, remained at the time of market authorisasion. The majority of issues was due to insufficient data that led to the requirement for submission of post-approval data. This highlights an adaptive approach to the authorisation of new products, where the resolution of uncertainty is a continuous process that extends beyond approval. Safety issues showed a higher rate for requirement of post-approval data, which could be explained by a hypothesized risk-aversion by regulators and a focus on safety or a “first, do no harm” approach[4,5].
Orphan status had no major impact. The only main difference was a higher number of uncertainties driven by unreliable data, which can be expected, since rare indications are common to have inadequate trial designs.
EPARs with lack of RCT were correlated with higher number of uncertainties, driven by safety issues. This could be explained by the fact that lack of RCTs is usually connected to inability to recruit sufficient number of patients, leading to important deficiencies in the characterisation of the efficacy and safety profile, which require more follow-up data. Nevertheless, these approvals should be based on exceptional efficacy results in a small population, leaving the safety profile poorly defined.

Observations - Limitations

Since we based the identification of uncertainties on the benefit-risk section of EPARs, one limitation of our work is that uncertainties presented in other parts of the report where not included. At present, we did not account for the difference in importance/impact of each uncertainty and coping strategy. E.g., the impact of lack of RCT design versus lack of data on 85+ year old patients. This work was focused only on oncology products. Other therapeutic areas could present different findings. We recognise the progress that has been done so far by EMA in improving the presentation of the key uncertainties. Our work aims at providing a framework to systematically describe uncertainties at the time of approval of a pharmaceutical product. This can be further developed to support EMA in describing uncertainties during the whole assessment procedure. In future, this might facilitate a more standardised approach to present uncertainties related to benefit-risk throughout the lifecycle of a product.

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Contact: nikolaos.zafiropoulos@meduniwien.ac.at