REVIEW PAPER

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Impact of ORBIS on public policies – open consultations of draft regulatory documents and the Pharmaceutical Strategy for Europe

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ABSTRACT

Public policies and regulations strongly influence research and manufacturing in pharmaceutical sector. Therefore, it is of critical importance that these policies and regulations are of high quality as well as appropriately balanced between general rules and detailed solutions. The process of public consultations prolongs adoption of novel documents. On the other hand, comments from different stakeholders like academia, industry, public administration and patients allow 360-degree critical evaluation of the document and a better understanding of the topic.

This mini-review summarizes the contributions of numerous members of ORBIS project team in open consultations of draft regulatory documents published by European Medicines Agency (EMA) and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). ORBIS project feedback on the Pharmaceutical Strategy for Europe is also presented.

ORBIS project members contributed to open consultations of two ICH draft guidelines, and three EMA draft documents. ORBIS project was also active during the European Commission's efforts to develop Pharmaceutical Strategy for Europe.

The interaction between representatives of academic and industrial sectors allowed to form balanced comments. We hope that this paper will inspire more researchers to participate in future open consultations on public policies.

Introduction

Public policies and regulations strongly influence our lives, including research and manufacturing in pharmaceutical sector. Therefore, it is of critical importance that these policies and regulations are of high quality as well as appropriately balanced between general rules and

detailed solutions. The well-established democratic approach in Europe promotes discussion over enforcing rules by the empowered person or institution like it is practiced in authoritarian countries. The democratic approach is at its full display during the open consultations when different stakeholders – like academia, industry, public administration and citizens – may express their opinion. The 360-degree critical evaluation leads to a substantially better understanding of the topic. The public consultation process is definitely more time-consuming than the authoritarian approach, but allows to form wise and practical documents which stay up-to-date for a long period of time. And not only in the case of pharmacy, these documents form a stable base for the development of the research areas and industrial sectors.

This mini-review summarizes the contributions of numerous members of the ORBIS project team – listed in **Table 1** – in the open consultations of the European and international draft regulatory documents. Most of them are associated with biopharmacy (ORBIS Work Package 3): bioanalysis, pharmacokinetics and bioequivalence [1-5]. The list also includes the Pharmaceutical Strategy for Europe [6] developed by the European Commission. More information about ORBIS may be found at project website at https://orbis-project.eu.

Members of the ORBIS project team contributed to open consultations by the European Medicines Agency (EMA), the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and the European Commission (EC) as specified in **Table 1**.

Table 1. Listing of documents under public consultations and authors contributing to ORBIS comments.

Ref.	Topic	ORBIS members involved*	Year
[1]	EMA Pharmacokinetics and pharmacodynamics in the obese population	G. Garbacz (PHY) F.K. Główka (PUMS) E. Gniazdowska (PRI) M. Karaźniewicz-Łada (PUMS) P.J. Rudzki (PRI) E. Szałek (PUMS)	2018
[2]	EMA Quality and equivalence of topical products	M. Kaza (PRI) B. Michniak-Kohn (RUTG) B. Milanowski (PUMS) T. Osmałek (PUMS) E. Pesta (PRI) P.J. Rudzki (PRI)	2019
[3]	EMA Lapatinib product-specific bioequivalence guidance	E. Gniazdowska (PRI) P.J. Rudzki (PRI)	2018
[4]	ICH guideline M10 on bioanalytical method validation	K. Buś-Kwaśnik (PRI) E. Gniazdowska (PRI) M. Karaźniewicz-Łada (PUMS) M. Kaza (PRI) P.J. Rudzki (PRI)	2019
[5]	ICH guideline M13A on bioequivalence for immediate-release solid oral dosage forms	O. Czerepow-Bielik (CLN) D. Danielak (PUMS) A. Gierczak-Pachulska (CLN) I. Grabnar (UL) M. Romański (PUMS) P.J. Rudzki (CLN)	2023
[6]	Pharmaceutical Strategy for Europe	A. Dumicic (ZNT) J. Lulek (PUMS) P.J. Rudzki (PRI) L. Tajber (TCD) A. Voelkel (PUT)	2020

* listed alphabetically
CLN – Celon Pharma SA (Poland), PHY – Physiolution GmbH (Germany), PRI – Pharmaceutical Research Institute (Poland), PUMS – Poznan University of Medical Sciences (Poland), PUT – Poznań University of Technology (PUT), RUTG – Rutgers, the State University of New Jersey (US), UL – University of Ljubljana (Slovenia), TCD – Trinity Collage Dublin (Ireland), ZNT – Zentiva a.s. (Czechia)

Pharmacokinetics and pharmacodynamics in the obese population [1]

As most pharmacokinetic studies are conducted in healthy subjects of normal weight, we agreed that more pharmacokinetic data is needed for rational decision-making and optimized therapy in the obese population. We have drawn attention to:

- inclusion of obese subjects in a bioequivalence study, especially for drugs intended for the obese population;
- studying pharmacokinetics and pharmacodynamics only in the obesity class III subjects and extension of the study to classes I and II in the case of significant differences in relation to normal weight;
- addition of a decision scheme to determine the need to study pharmacokinetics and pharmacodynamics in obese patients;
- providing well-defined criteria for the degree of obesity in pediatric populations.

We proposed expanding information on oral drug interactions and gastrointestinal transit conditions with emphasis on gastric emptying, concomitant pharmacotherapy, and neuropathies affecting pharmacokinetics in the obese population.

Quality and equivalence of topical products [2]

We welcomed the idea of guideline on equivalence of topical products as specific regulatory procedures for these products are lacking or are dispersed in other documents. We have commented on:

- dermal microdialysis as a possible replacement of clinical equivalence studies for topical products due to its similarity to bioequivalence with pharmacokinetic endpoints;
- lack of recommendations regarding homogeneity testing, nanoparticles-loaded products, virtual bioequivalence approach and reporting;
- need for specific recommendations and methodology of the rheological properties comparison between comparator and test products as well as the equipment/instrumentation used for dissolution testing and *in vitro* drug release testing.

Product-specific bioequivalence guidance for lapatinib [3]

This was limited to only one ORBIS beneficiary. The comments were related to evaluating bioequivalence in both fasting and fed conditions [7].

ICH guideline M10 on bioanalytical method validation [4]

This guideline was a long-awaited step towards the global unification of bioanalytical regulatory recommendations. Numerous recommendations were appreciated [8]:

- extrapolating stability at -20°C to lower temperatures for small molecules;
- detailed description for endogenous compounds;
- table specifying reporting.

We proposed specific comments regarding the matrix effect and incurred sample reanalysis in line with ORBIS publications [9, 10].

ICH guideline M13A on bioequivalence for immediate-release solid oral dosage forms [5]

Harmonization of bioequivalence recommendations by the ICH is an important step to increase the supply of high-quality medicines for the global community of patients. Our comments underscored the significance of:

- minimizing the number of bioequivalence studies to avoid the unnecessary exposure of healthy subjects to clinical trials;
- implementing decision schemes to establish a standardized interpretation;
- providing clarifications, well-defined criteria and resolving terminology discrepancies to achieve clarity and accuracy;
- adding recommendations on sampling points, data exclusion criteria, and statistical analysis methods.

Our collective comments and recommendations will be presented in a future paper.

Pharmaceutical Strategy for Europe [6]

We agreed that the provision of safe and affordable medicines to European patients is of critical importance and highlighted the following topics [11]:

- better cooperation between the industrial and academic sectors;
- manufacturing of active pharmaceutical ingredients (APIs) for essential generic medicines in Europe;
- antimicrobials need public intervention;
- environmental risks, including many current technologies used in the production of APIs and drug products rely on toxic intermediates and inefficient processes that result in unnecessary pollution of the environment.

We were pleased for the opportunity to provide ORBIS feedback on important documents for the pharmaceutical sector. The interaction between representatives of academic and industrial sectors allowed to form balanced comments. We hope that this mini-review will inspire more researchers to participate in future open consultations on public policies.

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The views expressed in this paper are those of the authors and do not necessarily reflect the European Union's, the Polish Ministry of Science and Higher Education or the affiliated institutions position on the subject.

Conflict of interest statement
P.J. Rudzki and O. Czerepow-Bielik are full-time employees of Celon Pharma S.A. The authors declare no conflict of interest.

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Conceptualization: P.J. Rudzki, O. Czerepow-Bielik and M. Karaźniewicz-Łada; methodology: P.J. Rudzki, O. Czerepow-Bielik and M. Karaźniewicz-Łada; writing original draft preparation: P.J. Rudzki, O. Czerepow-Bielik and M. Karaźniewicz-Łada.

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