EUROPEAN COMMISSION
HEALTH AND CONSUMERS DIRECTORATE-GENERAL

Health systems and products
Medicinal products – authorisations, European Medicines Agency

PHARM 629

PHARMACEUTICAL COMMITTEE
23 October 2013

Subject: **The Orphacol case**

Agenda item : 2(b)

I. Overview of the main legal questions.

1. Derogations under Article 5 of Directive 2001/83.

1.1 Conditions for the application of Article 5

COM position	General Court ruling
Strict interpretation of the derogation provided for under Article 5. Derogation under Article 5 is only possible after there has been specific assessment by the authorities on the merits of the use of a medicinal product for an individual patient	-Recalls *COM v. Poland* (*"provisions which are exceptions to a principle must, according to settled case-law, be interpreted strictly;" and "the concept of 'special needs', referred to in Article 5(1) of that directive, applies only to individual situations justified by medical considerations, and presupposes that the medicinal product is necessary to meet the needs of the patient.")* - Held that "hospital preparations" are in accordance with Article 5 because: *- "intended to fulfil 'special needs', in that they were supplied in response to individual situations which were justified by medical considerations and that they were necessary to meet patients' needs. It is common case that there is no medicinal product on the market capable of treating the liver disorders in question, which are likely to lead rapidly to the death of any person who is diagnosed with those disorders".* *- " they were prescribed by a doctor as a result of an actual examination of his patients and on the basis of solely therapeutic considerations*" *- "that provision [Article 5] does not state that a Member State may exclude medicinal products from the provisions of Directive 2001/83 only on a case-by-case basis, rather than on the basis of categories of medicinal products, such as hospital preparations."* *- "it is, in fact, the French Republic which has excluded hospital preparations from the provisions of that directive".*

1.2 Impact on pharmacovigilance obligations

COM position	General Court ruling
In its submission to the General Court, the Commission had referred to the existence of reporting obligations in connection with uses under Article 5, as provided for in the Pharmacovigilance guidance.	"*the Commissions arguments that there is an obligation to report and monitor medicinal products covered by Article 5(1) of Directive 2001/83 cannot be upheld, given that the wording of that provision does not state, or even imply, that any such obligation exists."*

2. Bibliographic applications (Article 10a of Directive 2001/83).

2.1. What uses can constitute "well-established medicinal use"?

COM position	General Court ruling
In general WEU requires use as an authorised medicine. However, orphan medicinal products benefit from specific derogation allowing WEU to be established by reference to uses in accordance with Article 5.	The Court did not explicitly address this point. However, the focus of the ruling on whether the hospital use was under Article 5 implicitly confirms that not all uses are capable of being WEU.

2.2. Which data is required?

COM position	General Court ruling
Bibliographic applications must contain comprehensive data on efficacy and safety. Reference to Scotia: *-"recourse to the abridged procedure is exceptional. The documents which have to be submitted in order to make use of that procedure are seldom likely to be found in scientific literature. None the less, that fact cannot justify the competent authorities having a discretion which makes it possible for them to relax the conditions for application of that procedure. Such an interpretation would run counter to the fundamental objective of Directive 65/65, which is to safeguard public health."* *-"the competent authority cannot be considered to have discretion to issue a marketing authorization under the abridged procedure where the scientific literature in the public domain concerning one of the tests required by the Annex to Directive 75/318 is incomplete. In such a case, the conditions laid down in point (8)(a)(ii) of the second paragraph of Article 4 of Directive 65/65, as amended, have not been satisfied and the application for authorization cannot be dealt with under the abridged procedure.."*	*-"Part II-1(c) of Annex I to Directive 2001/83 provides for the possibility of an MA being granted even where information is missing, as long as the demonstration of an acceptable level of safety and/or efficacy can be supported although some studies are lacking. Therefore, an MA may be granted without comprehensive documentation."* *-"the present case does not concern a relaxation of the requirements for proving well-established medicinal use, but the implementation of that use in exceptional circumstances, pursuant to Regulation No 726/2004 and Directive 2001/83."*

3. Marketing autorisation under exceptional circumstances (Article 14(8) of Regulation 726/2004).

COM position	General Court ruling

In the absence of an express provision in connection with the possibility to combine both derogations, it must be considered that derogations to general requirements are to be interpreted strictly. Derogations cannot be applied in contradiction: An applicant that submits a bibliographic application cannot request the derogation under Article 14(8) of the Regulation. A bibliographic application presupposes that there is comprehensive data in the literature, which is in contradiction with the claim that the applicant is unable to provide comprehensive data.	*"Nothing in Regulation No 726/2004 or Directive 2001/83 precludes the simultaneous application of the concepts of 'well-established medicinal use' and 'exceptional circumstances'. On the contrary, it should be noted that, in the specific context of orphan medicinal products such as Orphacol, Directive 2001/83 expressly refers to the possibility of applying both the provisions relating to exceptional circumstances and those provisions relating to a claim of well-established medicinal use. "*

II. Which consequences?

Orphacol was exceptional from a medical standpoint: it was intended to treat a very rare disease; the treatment of a few individuals representing a critical mass of the target population.

In the reasoning of this case, the General Court recalled general principles of interpretation (*e.g.* strict interpretation of derogations) but the application thereof to the specific facts of the case is not always obvious.

In the light of the above, it may be premature to extract general principles beyond the specific facts of this case. However, the following reflections can be made:

1) Article 5:

Beyond the specific facts of this case, the Court recalled the principle of strict interpretation of this provision. The principle remains valid for future cases, albeit the application thereof has become more difficult in practice.

Resort to Article 5 beyond the truly exceptional cases for which it was envisaged, would raise public health concerns as the level of information available for medicines used under Article 5 is much lower than in the case of medicinal products with a marketing authorisation. The consequences in term of pharmacovigilance should also be considered.

2) Bibliographic applications:

The case has not put in question the Commission's interpretation that not all uses can be relied upon for the purposes of demonstrating "well-established medicinal use". However, it is unclear whether *Scotia* has been reversed (or if it is no longer relevant) as the General Court avoided referring to that case.

A more flexible approach to bibliographic applications could incentive the submission of bibliographic applications as opposed to the realisation of clinical studies. Such a shift would be detrimental to public health, not only in terms of undermining the objectives of the paediatric regulation but more importantly because clinical trials remain the most reliable means to obtain efficacy and safety data.

3) Combination of derogations

The Court has ruled that the combination of bibliographic MAAs and exceptional circumstances are possible, at least for orphan medicinal products.

For future cases, it could be challenging to apply the principle of restrictive interpretation of derogations.