Draft
COMMISSION REGULATION (EC) No …/..
of […]
on the conditional marketing authorisation for medicinal products falling within the scope of Regulation (EC) No 726/2004 of the European Parliament and the Council of 31 March 2004

Whereas:

(3): The Marketing Authorisation Applicant and the Committee for Human Medicinal Products share a common responsibility to make products fulfilling the criteria defined in Article 2 available to patients in a reasonable time frame.

Justification

The conditions to obtain a conditional marketing authorisation are the outcome of a dialogue between the CHMP and the MAA. Agreement on the conditions requested and commitment to provide the responses respect the interest of the targeted patient population in a timely manner.

Article	Modification
Article 2 The following categories of medicinal products may benefit from a conditional marketing authorisation: 1. Medicinal products for human use as defined in Articles 3(1) and 3(2) of Regulation (EC) No 726/2004 which aim at the treatment, prevention or medical diagnosis of chronically or seriously debilitating diseases or life-threatening diseases. 2. Medicinal products for human use designated as orphan medicinal products in accordance with Article 3 of Regulation (EC) of the European Parliament and the Council No 141/2000 of 16 December 1999[2]. 3. Medicinal products for human use to be used in emergency situations, in response to public health threats duly recognised either by the World Health Organisation or by the Community in the framework of Decision No 2119/98/EC of the European Parliament and of the Council of 24 September 1998	No changes
Article 3 3. The Committee for Medicinal Products for Human Use may, during the assessment procedure of Article 7 of Regulation (EC) No 726/2004, propose a conditional marketing authorisation, after having consulted the applicant. This proposal has to be accompanied by detailed explanatory reasons and has to be communicated to the applicant.	No changes

5. Any request to, or proposal by, the Committee for Medicinal Products for Human Use for a conditional marketing authorisation shall be made publicly available.	5. Any request to, or proposal by, the Committee for Medicinal Products for Human Use for a conditional marketing authorisation shall be made publicly available <u>at the time when the request is made by the applicant or when the proposal is made by the Committee.</u>

Justification

If not explicit, timing of the public announcement could be significantly heterogeneous: at the time when the request is made by applicant? Or weeks later when request accepted by CHMP? Or at the time when the CHMP proposal is agreed by applicant? Or even later when marketing authorisation is granted?

	5bis. Any rejection by the applicant of a proposal for a conditional marketing authorisation by the Committee for Medicinal Products for Human Use or any refusal by the Committee of an application for a conditional marketing authorisation shall be made publicly available.

Justification

The applicant may refuse the CHMP proposal for a conditional approval. Only if the applicant agrees, then the proposal becomes public. If the applicant refuses, then the CHMP can not announce the proposal was made and the reasons why it was rejected by the applicant are not disclosed. As this applies to severe diseases, orphan drugs, or health threats, it does not seem to be a transparent enough process.

Article	Modifications
Article 4 Criteria for the granting of a conditional marketing authorisation	
1. A conditional marketing authorisation may be granted subject to the following conditions: (a) The medicinal product falls within the scope of this Regulation. (b) The applicant is able to demonstrate the public health interest of the medicinal product. (c) The applicant is able to demonstrate the presumed positive benefit-risk balance of the medicinal product, based on scientific evidence and pending completion of further studies. (d) The quality and, unless duly justified, the non-clinical safety data of the product complies with the requirements laid down in Annex I of Directive 2001/83/EC of the European Parliament and the Council of 6 November 2001. (e) The applicant is required to finalise the on-going studies or to conduct new studies necessary to verify that the benefit-risk balance is positive and to resolve remaining uncertainty in this	1. A conditional marketing authorisation may be granted subject to the following conditions (<u>all conditions to be fulfilled</u>): (b): the notion of public health interest is vague, and even though Article 11 refers to guidelines for the application of Article 4 points b, c, and d, this concept needs to be clearly defined in the regulation to avoid confusion and misinterpretation.

regard. Any specific obligation and the timeframe for their completion are to be clearly specified in the conditional marketing authorisation. The obligations and the timeframe shall be made publicly available. (f) The specific obligations and time frame for their completion will be reviewed annually by the Committee for Medicinal Products for Human Use. The conclusions of the Committee shall be made publicly available.	**New paragraph (g)** The indication of the conditional marketing authorisation should strictly respect the patient population for which data are available. In early phases of clinical development, the whole scope of the patient population is not represented in clinical trials, e.g. participants to phase II trials are not representative of the targeted population that is usually more heterogeneous than phase II participants. The indication should reflect the inclusion criteria of the studies that were analysed at the time of the positive opinion for granting conditional marketing authorisation. Additional studies are needed to represent a larger part of the patient population.

Article	Modifications
Article 6 Procedure for the renewal of the conditional marketing authorisation 4. At any time, when the obligations referred to in Article 4, point e, are satisfied, the Committee for Medicinal Products for Human Use may adopt an opinion in the meaning of Article 9 of Regulation (EC) No 726/2004 and the procedure foreseen in Articles 10 and 11 of said Regulation will be applied. Article 14(1) and (2) will apply thereafter. 6. If the marketing authorisation holder does not apply in due time for the renewal of the marketing authorisation, the marketing authorisation ceases to be valid at the expiry date.	Procedure for the renewal of the conditional marketing authorisation Maybe a **step by step approach** would be possible: 1. Letter to NCA / MS to inform them that the MAH did not fulfil the conditions. This may help to renegotiate the price, to re-evaluate the therapeutic added value at the MS level. Pricing and reimbursement are the responsibility of Member States; the opinion of European experts as expressed by EMEA is an important information for these negotiations at the national level. This could be appropriate as the benefit-risk ratio is used to evaluate the therapeutic added value, among other information. If the MAH fails to provide the information, then the added value should be reconsidered. This financial consequence could help forcing the MAH to fulfil the conditions in due time. 2. If not enough, then a second step could consist in deciding Restrictions for the use of the product (Restriction for hospital use only, or prescription restricted to specialist doctors, or a provision to continue providing treatment to patients who were already using the product but not accepting new prescriptions…). There could be a safety issue that would justify the restriction for the use of the product: hospital use only, only to be prescribed by a specialist, or a risk management programme to be implemented at the expense of the MAH etc. 3. Else, a provision of funds (obtained from MAH) should be allocated to an independent institution to conduct appropriate research, in the case where the MAH is unable to conduct the research by itself. 4. Finally, if previous steps fail to convince the MAH to fulfil the condition, then marketing authorisation could be withdrawn.

Justification

I**t does not seem to be very flexible:** the only measure that can be taken when timelines are not respected by the applicant or if the demonstration of the positive benefit/risk ratio is not achieved within the time limits is the expiration of the marketing authorisation. When patients are already using a product, it is not realistic to consider the authorisation can simply be withdrawn.
Else, the conditional approval can be renewed, or transformed into full approval, or not renewed.
Not renewed: means that the product is withdrawn from the market; when the product is in fact useful, but only the incompetence or negligence by the applicant are in question, and then maybe the price to pay for the applicant to be incompetent is too high for the patients. When the applicant does not respect the condition because for example lack of financial resources to conduct appropriate studies, it is a problem

to withdraw from the market a potentially useful product that maybe has a positive benefit-risk ratio.

Article 7 Information and package leaflets Without prejudice to Title V, Labelling and Package leaflets, of Directive 2001/83/CE, the information included in the summary of product characteristics and package leaflet of the medicinal product authorised in accordance with this Regulation shall contain a clear mention of the fact that a conditional marketing authorisation has been granted and of the annual renewal of this authorisation.	**Comment** Not only the mention should appear on the package leaflet, but products with conditional approval should, by priority, come with a patient self-report form for adverse events as recommended by the EMEA/CHMP/WGPO working group. Patients as a source of information on the safety of a product are particularly relevant when a product is just released on the market, and even more when not all the information is known. Products authorised under conditional approval are probably those with less safety information available when they are placed on the market, and this is one more reason to develop special efforts to collect all sources of information on safety, including the patient.

Article 9	
Periodic safety update reports	
1. By derogation to Article 24(3) of Regulation (EC) No 726/2004, the periodic safety update reports shall be submitted to the Agency and Member States immediately upon request or at least every six months after authorisation until the placing on the market and immediately upon request or at least every six months after the placing on the market.	1. By derogation to Article 24(3) of Regulation (EC) No 726/2004, the periodic safety update reports shall be submitted to the Agency and Member States immediately upon request or at least every six months <u>after conditional authorisation until the full marketing authorisation</u>.

Comment

Is there a repeat at the end of this sentence "and immediately upon request or at least every six months after the placing on the market"? I have difficulties to understand it.

If the sentence is to be read:

"Upon request or at least every six months after authorisation until the placing on the market ", then one question: how to define the "placing on the market"? How is this date determined? It is different from authorisation, but varies so largely by country and by product that no clear cut definition can be proposed.