EURORDIS Response to the European Commission’s Public Consultation on a Commission Notice on the Application of Articles 3, 5 and 7 of Regulation (EC) No 141/2000 on Orphan Medicinal Products

Dear Sir, Madam,

EURORDIS welcomes the initiative of the European Commission to propose orientations for a potential review of its Communication 2003/C 178/02 on Regulation (EC) No 141/2000 on Orphan Medicinal Products, and hereby takes the opportunity to submit our comments in response.

1. Overall Comments

In the present consultation, the European Commission indicates its intention to review Communication 2003/C 178/02 and streamline available guidance in the form of a Commission Notice, as per “the new working arrangements of the Commission”. EURORDIS expresses its concerns as to such a decision. Considering that at the very least a number of revisions to the guidance contained in Communication 2003/C 178/02 may be of a substantial and significant nature, and may bear important consequences for the future, we are of the resolute opinion that it would be much preferable and much more respectful of the democratic process and of the spirit of the legislation to seek proper ways to involve in such a reflection the European Parliament, an institution of the European Union which has historically played a crucial role in securing greater recognition for rare diseases.

The present consultation also leaves substantial uncertainty as to whether the future Commission Notice shall complement Communication 2003/C 178/02 or rather replace it.

As per its title, the present consultation is defining its own scope as restricted to articles 3 (criteria for designation), 5 (designation and removal from register) and 7 (marketing authorisation) of Regulation (EC) No 141/2000. While we do welcome the opportunity to comment on and hopefully
help improve these very important provisions, EURORDIS strongly regrets that the European Commission did not deem necessary to open the possibility for the stakeholder community to comment on article 8 as well – especially its paragraph 2, where provisions on the re-assessment of criteria granting orphan designation are currently located. We believe, as per the points farther below on the notion of significant benefit, that some important modifications may also need to be considered in relation to that specific article.

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Before moving on to our detailed replies on the various consultation topics, we trust it is important to take a step back and look at the broader landscape for orphan medicinal products in the European Union today.

EURORDIS believes that Regulation (EC) No 141/2000, adopted by the Council of the European Union and the European Parliament in 1999, needs to be viewed not only as a historic breakthrough at the time of its adoption but also, more than 15 years later, as a remarkable success of EU policy, in many respects.

First and foremost, Regulation (EC) No 141/2000 is a health policy success, inasmuch as it has significantly helped to accelerate the translation of science into therapies for patients with rare diseases: today, the number of orphan designations has risen to over 1,500 and that of approved medicines to almost 1201 (from a mere 8 prior to the Regulation!) – all of this to the direct benefit of approximately 3 million patients across Europe who can potentially benefit from them when they have access.

It is also a success of the European Union’s action in support of entrepreneurship and industry. Regulation (EC) No 141/2000 has encouraged the unprecedented development of innovative pharmaceutical and biotechnology undertakings, as well as the creation of countless start-ups and jobs. It continues to represent today a strong and distinct competitive advantage of the European Union on the global marketplace, and fully underpins the EU’s current strategic focus on growth, innovation and jobs.

The current outlook is that this very positive trend is set to continue in the near future, with between 30 to 50 new orphan medicinal products coming to market per year by the year 2020. At such an unprecedented pace, one of the major goals assigned to the International Rare Diseases Research Consortium (IRDiRC) – i.e. the delivery of 200 new therapies for rare diseases by 2020 – shall be reached ahead of schedule, provided of course that the right policy environment and incentives are in place. This is the fundamental backdrop against which the merits of any potential review of the legislation currently in place should be carefully considered.

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Another important element of context is that, despite so much progress in so few years, advances in medical research still fail to be translated with sufficient speed into approved therapies effectively reaching, at the end of the line, the patients who need them most urgently. Today, a positive or negative decision regarding authorisation and/or reimbursement of an orphan medicinal product occurs generally after as much as 8 to 14 years of research and studies – which, in turn, raises the

1 Of which 90 have maintained their orphan status to date. Beyond this, Regulation (EC) No 141/2000 has also stimulated the development of XXX (Check whether OrphaNet has that figure at hand.) new therapies approved without orphan status.
issue of the need for new, more adaptive pathways for the development and approval of innovative medicines, a concept currently explored by the European Medicines Agency with initiatives like MAPPs (Medicine Adaptive Pathways to Patients).

Even after authorisation and reimbursement may be granted, about one third of European patients living with a rare disease still have no access whatsoever to the orphan medicinal products they require for their condition. And yet another third may obtain access but only after further substantial delays of several more years (far later than foreseen by the EU Transparency Directive!) as a given product may end up being introduced first in major EU Member States and only later, years after authorisation, in other, smaller EU Member States. Most recently still, it is problematic that the availability of orphan medicinal products of major importance may have been restricted by EU Member States solely due to cost and budget considerations. This persisting reality is living proof that the original ambitions laid out in Regulation (EC) No 141/2000 remain far from being fully achieved, especially when it comes to patient access to approved orphan medicinal products – an issue which, we believe, should be subject to greater attention and more resolute action on the part of the European Union.

EURORDIS views this situation as a missed opportunity of dramatic proportions, and a burning issue to which Communication 2003/C 178/02 brought no answers, and to which the proposed 2016 Commission Notice shall apparently bring none either. We are calling for renewed action by the European Commission. Poor access to orphan medicinal products is, above all, detrimental to patients and a very disappointing outcome from a societal standpoint. But it is also profoundly undermining the value of the market exclusivity granted by Regulation (EC) No 141/2000, hence the overall attractiveness of the European orphan status, and ultimately the performance and legacy of Regulation (EC) No 141/2000 as a whole. The principle of EU market exclusivity applies today to a European market for orphan medicinal products which is far from being unified or complete, to say the least, and across which access is still not structured to date in a common way.

Finally, we see an increasing disconnection between, on the first hand, the high levels of uncertainty in terms of data associated with orphan medicinal products even at the time of authorisation and, therefore, the burning need for continuous generation of real-world evidence post-authorisation; and, on the other hand, the still very fragmented landscape of requirements set by EU Member States when it comes to such evidence generation (registries, comparators, etc).

In light of the widely recognised specific characteristics of rare diseases, we strongly believe that greater cooperation is urgently needed at the European level between competent national authorities for pricing and reimbursement, particularly with regard to a common assessment of the value of OMPs, to a joint table for price negotiation and, indeed, to the implementation of continuous evidence generation through the establishment of a structured dialogue.

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Through the present consultation, the European Commission manifests its openness to reviewing Communication 2003/C 178/02 “to streamline the available guidance and to adapt this Communication to the technical progress”. We consider this intention as welcome and worthy of interest, as long as the proposed Notice does not result in damaging or profoundly altering the spirit and the performance of Regulation (EC) No 141/2000 – particularly the provisions of which seek to create an attractive ecosystem for the development of orphan medicinal products and to foster investment in areas of high unmet medical need.
As per the projections indicated farther above, it is no less vital today than 15 years ago to ensure that the field of rare diseases, many of which are still waiting for effective therapeutical solutions, remains attractive for the investments of the pharmaceutical research community. An essential need in this regard will be the level of predictability offered by any new or modified legislation for companies throughout the pathway – from designation to authorisation and to reimbursement.

In that context, it comes as little surprise that the notion of significant benefit receives particular attention in the present consultation. That notion, in favour of which EURORDIS and other European patient organisations have been advocating as early as 1994-1999, at the time when they were advocating in favour of what was to become Regulation (EC) No 141/2000, was originally intended as a means to incentivise new products targeting unmet medical needs or offering a marked advantage over previously existing treatments, and therefore to encourage greater investment into research for innovative orphan medicinal products. In 1999, this concept was new. It still does not exist in U.S. legislation, nor in other regions of the world.

Over time, EURORDIS has observed that the notion of significant benefit has had a major and positive impact on the market environment – not only from the point of view of investors, companies and of their clinical development strategies, but also in terms of perceptions by payers of the value of new orphan medicinal products coming to market – and has contributed in no small measure to building a “virtuous circle” in support of the advent of many new orphan medicinal products.

This being posited, the notion of significant benefit as introduced in Regulation (EC) No 141/2000 and enacted since then does not reflect nor take into account the vast amount of crucial developments that have taken place over the last 15 years, notably in the field of health technology assessment (HTA) and most lately with new emerging concepts such as adaptive pathways, continuous evidence generation pre- and post-authorisation, and the search for new modalities for increased flexibility in the regulatory field. Should Regulation (EC) No 141/2000 be written anew today, it is fair to wonder whether it should still be considered as necessary to include the provisions related to significant benefit. And if so, then, would such provisions be labelled as “significant benefit” or rather as “relative effectiveness”?

This leads us to believe that the time is ripe to reconsider what a rightful place should be for the notion of significant benefit, particularly with a view to find the most appropriate trade-off between two potentially conflicting realities: one being the growing amount of evidence required and/or expected at the time of assessment of the significant benefit of a candidate orphan medicinal product, the other being the need for ever increasing flexibility and time for post-authorisation evidence to be generated in real-world use.

In our view, keeping the current system “as is” and strengthening the notion of significant benefit by requiring ever greater amounts of evidence upfront is only bound to increase the unpredictability for a company’s product to retain its orphan status. It is a strong contradiction between different policies promoted by the European Commission, and particularly the encouragement of companies to come early to market and to look at the orphan medicine life cycle in a more flexible way and as a continuum of evidence generation. Such uncertainty, in turn, can only result in de-incentivising long-term investment in the field of orphan medicinal products, which would go against the overall purpose of Regulation (EC) No 141/2000.
The solutions lying ahead are two-fold in our opinion:

- “pushing the envelope” of Regulation (EC) No 141/2000 and “upgrading” the notion of significant benefit, e.g. by opening either the possibility of granting “conditional” significant benefit in the context of a conditional approval, and/or that of a post-authorisation re-assessment of the significant benefit of a given product;

- deciding that the notion of significant benefit is no longer as relevant nor necessary as it may have been in the past, and seeking ways to build in the system a more seamless interface between the EMA and HTA agencies, even more so considering that, from 2016 onwards, EUnetHTA shall increase the intensity of early dialogues through the SEED platform towards the production of common assessment reports.

[Need to integrate content of responses to question 3 put out to our membership in the EURORDIS Member News of January 21, 2016.]

2. Response to Consultation Topics Outlined by the European Commission

The comments below, while written with a view to answering the specific questions and issues raised in the public consultation document released by the European Commission on 16 November 2015, must be always read and understood in the context of the broader considerations listed in the preceding section.

Consultation Item N° 1: Clarification of the definition of “significant benefit”

As extensively laid out in section 1 of the present document ("Overall Comments"), EURORDIS believes, and agrees with the European Commission, that the notion of significant benefit has proved, over the years, to be a central component of Regulation (EC) No 141/2000, and much for the better as it has had a positive, incentivising effect on the market for orphan medicinal products.

We do argue, however, that the notion of significant benefit remains firmly embedded in a certain historical context, and that it originated at a precise moment in time when the vast amount of crucial political and scientific developments in the field of health technology assessment (HTA) of medicines that we have observed over the last 15 years were yet to come still.

With this in mind, it appears fair to us to openly ask whether, despite being indeed in the original text of Regulation (EC) No 141/2000, this notion still has today the same relevance and appropriateness it once had with regard to attaining the purposes set out in the Regulation – one of which was to drive investment towards persisting unmet medical needs, i.e. for patients without any, or any satisfactory treatment available.

EURORDIS is concerned that moving towards a more restrictive definition of significant benefit or elevating the threshold for required evidence at the time of designation may eventually lead to a
conflict with the very purposes at the core of Regulation (EC) No 141/2000, and also defeat the purpose of other major initiatives and reflections currently under way, under the leadership of institutions of the European Union, with a view to increasing flexibility in regulatory procedures – e.g. via new medicine adaptive pathways to patients.

Another proposal formulated by the European Commission in the present consultation intends to suppress the possibility of claiming a significant benefit based on a potential increased supply. While EURORDIS does not oppose this suggestion as a matter of principle, we recommend not to apply it in an overly rigorous way. We have been made aware in the past of cases of serious, prolonged shortages due to exceptional circumstances (e.g. contamination of incubators used in the manufacturing of replacement enzymes), accompanied by substantial evidence that such situations were causing harm to patients in need of those therapies. In such well-documented instances, the possibility to recognise a significant benefit based on the capacity for a manufacturer to offer increased supply/availability in the very short term should still be considered explicitly.

[Add consideration on products prepared in a hospital pharmacy as per Question to Members #1 / Satisfactory methods to compare? Generics? Do the ERN have a role to play in the diffusion of useful hospital preparations or generics – need to approach generic manufacturers to ensure pan-European availability of those medicines?]

[Need to integrate content of responses to questions 1 and 2 put out to our membership in the EURORDIS Member News of January 21, 2016.]

Other individual comments:

- Line 143 to line 148: We believe that the concept of “satisfactory method authorised in the Union” could be better defined than currently as “a medicinal product authorised in one Member State of the EU [...] for the treatment of the disease as such or for its symptoms”. We advise to reformulate this to narrow down the scope to “products already authorised for the treatment of the exact same disease as a given product in the process of being developed, or at the very least products addressing the exact same set of symptoms”.
- Line 166: We recommend to replace “authorised methods” by “authorised products and satisfactory methods”, and to apply such wording consistently throughout the proposed notice (e.g. at line 227 and farther).
- Line 181: The concept of “major contribution to patient care” is obviously essential, but we recommend to also put the emphasis on patient reported outcomes and on the fact that additional real-life data shall be of primary value, especially at the moment in time when the orphan status of a given medicinal product may come into question for its maintenance (or not).
- Line 205 to line 207: We recommend to put stronger emphasis on the use of protocol assistance.

**Consultation Item N° 2: Encouraging the development of orphan medicinal products for communicable diseases (e.g. Ebola)**

EURORDIS supports the proposed actions. The possibility for Regulation (EC) No 141/2000 to be extended to cover neglected diseases existed from the early days on already, and EURORDIS advocated it throughout the 1990s, and later within COMP, in order to support treatment of neglected diseases.
We believe that the possibility to extend orphan status to therapies for communicable diseases that have not been reported to date in Europe but could break out in the future (e.g. Ebola) is relevant, considering the present need to develop effective therapies for those diseases, and the positive role that Regulation (EC) No 141/2000 could play to incentivise this from the outset.

**Consultation Item N° 3: Simplifying the procedure for the reassessment of orphan criteria when two authorisation application procedures are pending in parallel for two orphan medicinal products**

EURORDIS agrees with the general spirit of the proposal by the European Commission to increase the levels of simplification and flexibility in current procedures for the reassessment of orphan criteria.

However, we wish to raise a number of concerns as to the system proposed in the present consultation, particularly the considerations outlined from line 290 to line 307.

Based on the text of the present consultation, the European Commission is proposing that, when two marketing authorisation procedures for the same condition have been running in parallel at the EMA, but then stop doing so for any reason with the outcome that one product receives positive opinion from CHMP before the other, then the company sponsoring the second product (not yet approved) should have a maximum period of time equivalent to one (1) CHMP meeting to be exempted from having to fully demonstrate with established data significant benefit over the first product (approved earlier). If the CHMP opinion related to the second product is delivered as of the second CHMP meeting after the approval of the first product, or even later on, then no exemption is allowed indeed and demonstration of significant benefit is expected. Considering the average frequency of CHMP meetings in a given year, i.e. once a month or so, this amounts to a possible exemption time of no more than 1 month.

EURORDIS is concerned that such an exemption, if put in practice, would not lead to a real improvement over the current situation, and leave unchanged the undue burden placed on the second company. In effect, should the CHMP decision related to their product be scheduled for adoption even a mere 2 months after the approval of the first product for the same condition, this means that such approval shall be subject to the provision by the sponsoring company of a full package of data supporting the significant benefit of its product vs. the first one approved earlier on. We draw the attention of the European Commission to the fact that, should such a requirement materialise possibly so late in the process, the second company might find itself unable, with such short turnaround time, to provide all necessary data, thus leaving as the only option and outcome to request the postponement of the CHMP decision.

The fact that such a scenario might occur even at a very late stage in the process, and regardless of how long two procedures may have been running in parallel at the EMA, the massive impact it may bear on the second company, and the utter uncertainty and procedural unpredictability it may generate upstream at the very outset of the process not only for the second company but also for the first company, all add up to paint a very concerning picture.

**Consultation Item N° 4: Introducing the reassessment of the orphan criteria for a new subset of the condition when a sponsor extends the use of its product after marketing authorisation**
EURORDIS agrees with the European Commission that the issue of the extension of the use of approved orphan medicinal products onto other therapeutic indications is of great importance, and requires thorough review.

The proposal for reassessing the orphan criteria (ie significant benefit) for a new subset when a sponsor asks for an extension of indication within the same orphan condition seems like a rational approach at the first glance, however we see here a high risk of desincentivization. What is at stake here for a company is, in case it fails to demonstrate the significant benefit of a product on this subset for which the extension of indication is asked, is the need to split the market authorization in two different products, one being orphan and the other non-orphan. We understand the advantage of not having to undergo a reassessment of the orphan criteria in this particular case as a bonus of the Orphan Regulation.

The only situation, where we could see the proposal lying in item 4, to be applied would be in the case of the terms of the extension being not on another medical subset per se, but on a modification of the terms of the indication such as the line of treatment to which a product may be of use (eg in the field of oncology, when a product firstly developed for third line would like to see its authorization extended to first line).

**Consultation Item N° 5: Clarifications on processing the transfer of orphan designations between sponsors**

**EURORDIS is supportive of this proposal.** Although we acknowledge that the development of a new pharmaceutical form may bring significant benefit to patients, we understand the necessity of putting in place a system avoiding unfair transfer of orphan designation between sponsors. New pharmaceutical forms can be granted by varying the existing marketing authorisation.