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. This response will have the following structure:

1. Introductory Comments
2. Response to Consultation Topics Outlined by the European Commission
3. Final Remarks

1. Introductory Comments

EURORDIS (www.eurordis.org), the European Organisation for Rare Diseases, is a non-governmental patient-driven alliance of patient organisations representing 705 rare disease patient organisations in 63 countries to date. EURORDIS represents the voice of an estimated 30 million people living with a rare disease in Europe.

In response to the Consultation on the Notice from the Commission on aspects of the application of Article 3, 5 and 7 of Regulation (EC) N° 141/2000 on orphan medicinal products, EURORDIS is pleased to send its comments from the rare disease patients’ perspective. The responses provided in this document are based on the consultation with its members, the work performed and the experience

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1 As requested in the consultation, we hereby opt for option “A” and confirm that the present response can be directly published in whole or in part, including the name of EURORDIS, and that nothing within it is unlawful or would infringe the rights of any third party in a manner that would prevent publication.
gained by EURORDIS since its creation in 1997 in the area of orphan medicinal products, from the
contribution to the adoption of the Regulation to the active participation of its members in relevant
committees at the EMA.

Before moving on to the detailed replies on the various consultation topics, EURORDIS believes that
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 120\(^2\) (from a mere 8 prior to the Regulation). This has all been to the direct
benefit of patients across Europe who can potentially benefit from them when they have access.

The Regulation on Orphan Medicinal Products 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 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 many as 8 to 14 years of research and
studies – 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.

\(^2\) Of which 85 have maintained their orphan status to date. Beyond this, Regulation (EC) No 141/2000 has also stimulated
the development of an average of 100 new therapies approved without orphan status (Source: « Lists of medicinal products
for rare diseases in Europe », Orphanet Report Series, Orphan Drugs collection, January 2016,
• 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, 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, 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.

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, and across which access is still not structured to date with a common approach.

Finally, the high levels of uncertainty in terms of data associated with orphan medicinal products even at the time of authorisation lead to the burning need for continuous generation of real-world evidence post-authorisation; this is increasingly disconnected from the still very fragmented landscape of requirements set by EU Member States when it comes to such evidence generation (registries, comparators, etc).

Overcoming this market fragmentation is especially urgent because of the widely recognised specific characteristics of rare diseases: scarcity of patients, scattered expertise, limited data available, to name but a few. In order to do so, 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.

We are calling for action by the European Commission in support of –within the framework of respective competences- these European-level cooperation initiatives, undertaken by a number of Member States, that address the issues faced by patient access. We also call on the Commission to consider taking actions to improve access to orphan medicinal products based on the spirit and text of the Regulation (EC) No 141/2000, including re-examining the interpretation of its Article 8.2 for potential review of criteria at five years and ultimately providing a more responsible and structured approach to patient/market access in a unified EU market, enhancing the real value of EU market exclusivity.

We suggest that these additional issues are addressed in a second Notice or, even better, a Commission Communication with a broader scope to embrace both these issues and those considered in the draft Notice currently under consultation. Please see our “Final Remarks” (section
3 of this document) on the scope of the consultation and the use of a “Commission Communication” as an alternative to the “Notice”.

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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 welcome this intention, provided that the proposed Notice does not alter the spirit and the performance of Regulation (EC) No 141/2000, – particularly the provisions 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 remains of as much importance today as it was 15 years ago to ensure that the field of rare diseases remains attractive for the investments of the pharmaceutical research community, as many people living with rare diseases are still waiting for effective therapeutic solutions. An essential need in this regard will be the level of predictability offered by any new or modified legislation for companies throughout the orphan medicinal product 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. EURORDIS and other European patient organisations have been strongly supporting this notion as early as 1994-1999, at the time when they were advocating in favour of what was to become Regulation (EC) No 141/2000. “Significant benefit” 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. This is 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. Significant benefit 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 recently 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. If Regulation (EC) No 141/2000 were to be written anew today, it would be fair to wonder whether it should still be considered so 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. We are experiencing, on the one hand, the growing amount of evidence required and/or expected at the time of assessment of the significant benefit of a candidate orphan medicinal product, and on the other, the need for ever increasing flexibility and time for post-authorisation evidence to be generated in real-world use. We need to find the most appropriate trade-off between two potentially conflicting realities.
In our view, keeping the current system “as it 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. This is in contradiction with different policies promoted by the European Commission, and particularly the encouragement of companies to come to market early and to look at the orphan medicine life cycle in a more flexible way, supporting it with continuous 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:

- To either “push the envelope” of Regulation (EC) No 141/2000 and “upgrad” 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;

- Or to decide 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 into the system a more seamless interface between the EMA and HTA agencies. This is especially considering that, from 2016 onwards, EUnetHTA shall increase the intensity of early dialogues through the SEED platform towards the production of common assessment reports.

In our opinion, an important choice needs to be made. It is either one or the other. Only pushing the envelope without providing the opportunity to re-assess significant benefit at a time point when more data would be generated would be very detrimental to the orphan medicinal products policy.

From our internal reflections and consultations with members, a clear majority emerges to support and prefer the first option as the one most likely to preserve the spirit of the system built to date, particularly with regard to thresholds for data requirements. This, of course, accompanied by an increased link between the work of the EMA and HTA bodies in Europe.

If the desired flexibility cannot be achieved in the first option (i.e. in terms of opening up a broader possibility for re-assessment of significant benefit), then there will be no other choice than to explore and implement the second option – i.e. decrease the level of required evidence, considering that today, the very resembling assessment of relative effectiveness is being performed by HTA bodies, and increasingly so at EU level through the new EUnetHTA Joint Action. This second option is widely seen as being far from ideal, but there is consensus to acknowledge that the system currently in place cannot go ‘as it is’ for much longer.

2. Response to Consultation Items 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, shall be read and understood in the context of the broader considerations listed in the preceding section.

3 And last accessed here:
As extensively laid out in section 1 of the present document (“Introductory 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, 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.

With this in mind, it appears fair to us to openly ask whether this notion still has today the same relevance and appropriateness it once had with regard to fulfilling 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 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 objectives of Regulation (EC) No 141/2000. We have observed sponsor uncertainty delaying applications for orphan designation and/or MA solely out of insecurity as to whether or not they will need to first collect more data to provide a significant benefit. Ultimately this comes at the price of (timely) patient access to those therapies.

EURORDIS therefore while supporting the concept of significant benefit, calls upon the European Commission to seek an approach that fulfills the need to provide sufficient information to demonstrate a significant benefit, while not imposing too high requirements contrary to the interest of patient access. EURORDIS advocates for an early-onset approach associated to the provision of available evidence on a continuous basis.

It is essential that the Notice brings unequivocal clarity on what constitutes significant benefit or the assumption of benefit, and the level of evidence required, especially considering that, in the field of orphan drugs, relevant evidence is typically scarcely available. Such a clarification could guide a pharmaceutical company, which may otherwise be hesitant, to put a drug forward sooner, thus gathering more and more reliable data more quickly. A difference in the time of market access of even only one or two years, and sometimes fewer, can mean a lot to the people that are supposed to be protected by the Regulation on the Orphan Medicinal Products. For example, if a company decides to prolong a designation or MA application to ensure the available data sufficiently supports an assumption of benefit; many rare disease patients do not have that much time.

EURORDIS is of the opinion that significant benefit should be assumed more easily, and re-assessed after the product is placed on the market. This is instead of companies applying without sufficient clarity on what constitutes a significant benefit or the assumption of benefit respectively. This would not lead to less evidence, but rather the same or a larger amount of evidence, with higher chances to obtain the level of requirement expected, albeit spread over time; time, in which patients would have access to orphan drugs and pharmaceutical companies could gather real-life and clinical experience. EURORDIS therefore is not asking for a lower threshold to the detriment of the quality of orphan therapies, but rather a realistic approach to a field with inherent difficulties, and a patient-oriented risk assessment.
Finally, this approach would smoothly align with 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, such as via new medicine adaptive pathways to patients.

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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 to apply it taking into due account the specific circumstances. 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.

On the issue of satisfactory methods against which the possibility to grant orphan status shall be considered, and against which the significant benefit of a given orphan medicinal product shall be measured, EURORDIS believes from our exchanges with our member organisations that generics and hospital preparations should be considered in the scope, as long as their safety is demonstrated, well documented and therefore cannot be questioned. The possibility to also include medicinal products used off-label is much more disputed, particularly as they cannot be considered as “authorised medicinal products” per se, but they sometimes contribute to ensure an accurate representation of current medical practices and the reality of patients’ experiences in Europe; we are not yet in a position to be conclusive on this point.

Other individual comments:

- Line 143 to line 148: We believe that the concept of a “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 putting stronger emphasis on the use of protocol assistance. Protocol assistance is the ideal regulatory tool for applicants to obtain guidance on which specific data are required to demonstrate significant benefit over existing authorised products and satisfactory methods at very early stages of drug development. Particularly important is the advice on how to incorporate patient-relevant outcome measures into clinical development, hence aligning these data requirements with those that will be evaluated later on during HTA appraisal and price and reimbursement negotiations.
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 outset, and EURORDIS advocated for 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, 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 that the average frequency of CHMP meetings in a given year, being around once a month, 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 would 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 in comparison with the first one approved. We draw the attention of the European Commission to the fact that, should such a requirement materialise so late in the process, the second company might find itself unable, with such short notice, to provide all necessary data, thus leaving as the only option and outcome to request the postponement of the CHMP decision.

It is very concerning that such a scenario might occur even at a very late stage in the process, 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 from the outset of the process for both the second and the first company, means that we would not recommend introducing such a provision in the Notice.

**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 (i.e. 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 first glance. However, we believe this proposal contains a high risk of desincentivisation. What is at stake here for a company, in the event it should fail to demonstrate the significant benefit of its product on the subset for which the extension of indication is asked, is the need to then split the market authorisation between two different products, one being orphan and the other non-orphan. We understand that the advantage of not having to undergo a reassessment of the orphan criteria in this particular case is intended as an additional reward for the sponsor, fully in line with the spirit of the Regulation (EC) No 141/2000. For the above reasons, **we do not recommend introducing this provision in the notice**.

The same rationale should apply in the event when the terms of the extension are not focused 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 (e.g. in the field of oncology, when a product firstly developed for third line is submitted for an extension of authorisation to first line).

This being said, we do acknowledge the fact that this non-reassessment of the orphan criteria when a sponsor extends the use of its product after marketing authorisation may seem to be a competitive advantage compared to a company that would have to demonstrate a significant benefit in the same subset or in the same line of treatment at the time of marketing authorisation application. We are of the opinion that such drawbacks may be overcome elsewhere by a system of rewards. Additional incentives might be put in place in order to reward and support even more the development of products for unmet medical needs (regardless of whether or not there are already other products or methods on the market for the same condition or subset).

**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.

### 3. Final remarks

#### 3.1. Communication vs Notice
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. 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. The nature of such revisions would logically require the involvement of the legislator that adopted in the first place the provisions whose application is now being revised. EURORDIS therefore wonders how far the other European Institutions have a say in the legal interpretation conducted in the Draft Notice, what weight the Commission attaches to possible consultations with the European Parliament or the Council and ultimately whether a Commission Notice is the right instrument for all the important subjects addressed in it. In an area as sensitive as medicinal products and rare diseases, the use of "soft law" needs to be carefully explained, possibly more than in other areas, or else it may constitute a democratic deficit. While we do not seek in a way a revision of the actual Regulation, we would however invite the Commission to consider whether for its interpretation a Communication to the European Parliament and the Council would not be a more suited act to seek proper ways to involve the legislator in such a reflection, and in particular the European Parliament, an Institution which has historically played a crucial role in securing greater recognition for rare diseases. As explained below, ideally such a Communication would cover a broader scope than the Notice currently under consultation, so to address what is currently not included in the scope of the consultation.

3.2. Scope of this consultation

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 regrets that the European Commission did not also open the consultation on Article 8, especially paragraph 2, where provisions on the reassessment 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.

3.3. Interaction between the Notice and the Communication

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. If the purpose of the Notice is to replace the Communication, loopholes would result from this replacement, as the proposed Notice does not cover or address the provisions and measures contained in the Communication in its entirety. In turn, if the purpose of the Notice is to complement the Communication, the new framework might prove even more cumbersome, complex to handle and difficult to implement, as no less than three legislative texts altogether would need to be analysed (the original Regulation, the Communication and now the Notice) to form a full picture of the obligations in place. EURORDIS therefore recommends that the interactions between the Notice and the Communication be clarified, for the sake of transparency, legal certainty and predictability.