25 April 2019

**EFPIA Comments on** **Targeted consultation on the guideline on the format and content of applications for designation as orphan medicinal products and on the transfer of designations from one sponsor to another**

Comments from:

| Name of organisation or individual |
| --- |
| EFPIA – European Federation of Pharmaceutical Industries |

1. General comments

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| EFPIA welcome the opportunity to comment on the ‘*Guideline on the format and content of applications for designation as orphan medicinal products and on the transfer of designations from one sponsor to another*’ and are pleased to share with the EU Commission our considerations for modification, driven by our EFPIA member practical experience and requests for clarification.  We have the following main issues for consideration:   * **Submission of orphan designation application based on a product mechanism of action:** additional guidance would be appreciated to support such application since there is a huge gap on this field and there already OD accepted by FDA. * **Prevalence calculation:** studies may not always be the only source of information to estimate prevalence, this is why other data sources, such as epidemiological literature, databases, case reports or registries will need to be considered. * **Magistral or officinal formulations as satisfactory treatment if they are well known and safe and if this is a general practice in the EU**: the draft guideline includes reference and paragraphs from the Notice released by the EC in Nov. 2016. Since the release of the EC Notice the use of magistral / officinal formulations to demonstrate the significant benefit has been challenged. Such formulations may have different pharmaceutical presentations, and may vary from one member state to the other, and even from one hospital to the other, and are used without a proper safety surveillance. Unlike authorised medicines, magistral / officinal formulations are not subject to appropriate clinical trials / dossier requirements and regulatory oversight, and hence are believed to be inappropriate comparators. Any other interpretation would affect the foundations of the pharmaceutical legal system, which rely on medicines approval by regulatory authority on the basis of a full dossier demonstrating the appropriate safety and efficacy profile of the product and its positive risk-benefit balance. * **Acceptability of (*in-vitro*) models to support OD plausibility:** more detailed guidance including validation and robustness of the models, would be useful. * **MedDRA as a disease classification system:** appropriateness and usefulness of MedDRA is questioned as known to have been designed as a ‘medical terminology to facilitate sharing of regulatory information internationally for medical products’ and not as a disease classification system. EFPIA recommends the use of other dictionaries. We would recommend using other dictionary that could be also used in an international context for health information exchange purpose, such as the orphaned database: [www.orphadata.org](https://clicktime.symantec.com/3WniQrJJ2jhKPewbRvzeLwv6H2?u=http%3A%2F%2Fwww.orphadata.org) (Aymé S. et al. Orphanet Journal of Rare Diseases 2015; 10:35 DOI 10.1186/s13023-015-0251-8)     In addition, we have the following comments:   * For consistency with the EMA User Guide, we recommend using the same terminology, i.e. ‘**Regulatory & Scientific Information Management Platform’** instead of ‘industry portal’ and also to mention that the portal is called IRIS. * As EFPIA member companies are struggling with the processes, further improvement of the IRIS User Guide would be welcome, with inclusion of more streamlined guidance on setting up companies, compounds and admin/managers and contributors, the link with SPOR, and day-to-day practicalities when using IRIS. * Consider establishing a dedicated help desk to notify bugs/errors and rapidly correct the errors. We would be happy to share our practical experiences. * Since EMA encourages parallel applications for orphan designation with regulatory authorities outside the EU, some additional guidance would be useful knowing that such parallel submissions are/will be challenging since not supported by IRIS. * Lastly, we propose to include a reference to Regulation (EC) No 141/2000 (the Orphan Regulation), Art 5(12) for further information on ODD withdrawal.     EFPIA would welcome the opportunity to discuss and clarify further these issues at the occasion of a specific workshop, which could be the opportunity to share experience since the implementation of the EC Notice in November 2016.    Finally, we have some comments on the text and proposed rewording as detailed below. |

**Specific comments on text**

| Line number(s) of the relevant text | Comment and rationale; proposed changes |
| --- | --- |
| **History Table** | |
| 1) Line 13 | **Comment:**  The revised guideline also introduces important revisions from EC notice 2016/C 424/03. It is proposed to complete the revision history for version 5.  **Proposed change (if any):**  Revision 5: addressed the **EMA's** ~~Agency's~~ new online platform to submit applications for designations as orphan medicinal products **and the clarifications introduced by the EC notice 2016/C 424/03.** |
| **Introduction** | |
| **Definitions** | |
| 2) Line 50-124 | **Comment**:  The amendment of the definition of “orphan condition”, the removal of the definition of “orphan indication” and the replacement of “orphan indication” by “orphan condition” throughout the guideline appear to be without a due consideration for the meaning of these terms under Regulation 141/2000 and 847/2000.   * There should be a bridge between “orphan indication” and “orphan condition” or a clarification, for example in a footnote, on how “orphan indication” and “orphan condition” under Regulation 141/2000 and 847/2000 are to be interpreted. Otherwise these terms and underpinning concepts, including the “prevalence” criterion (Art. 3 of Reg 141/2000), are left for interpretation. For example, at least two interpretations of the prevalence criterion appear now possible: the prevalence of “condition” in less than five in 10 000 persons (Regulations) or prevalence of those “treated for condition”, or “diagnosed for condition” that must remain below five in 10 000 persons (this Guideline). * The replacements of “orphan indication” by “orphan condition” do not appear to work in some places in the guideline. See for example **line 442-443**, which now states: “In addition, for applications where the proposed orphan ~~indication~~ **condition** refers to a subset of a particular condition…” * The EC Register of designated Orphan Medicinal Products lists “Designated Orphan Indication” * The current EMA template for designation application (sections A-E) requests to fulfil the “A2. Proposed orphan indication” after the subsection “A1. Details of the conditions”. |
| 3) Line 129-132(c) | Comment:  We would suggest rephrasing the following sentence, in order to avoid any confusion with line extensions.  Proposed change (if any):  The granted therapeutic indication at the time of marketing authorisation or extension**of indication** will be the result of the assessment of the quality, safety and efficacy data submitted with the marketing authorisation application and may be different to the one proposed at the time of orphan designation application. |
| 4) Line 127-128 | **Comment**:  We suggest defining more clearly what “completely covered” means; due to the broadness of currently accepted orphan conditions it is possible that the initial proposed therapeutic indication is smaller than the granted orphan condition.  **Proposed change (if any):**  Any future therapeutic indication ~~must be completely covered~~should fall within the scope of the designated ‘Orphan Condition’. |
| **Timing of submissions** | |
| 5) Line 141-142 Para 2, | **Comment:**  We propose to rephrase to clarify that this pre-submission meeting is before the submission of the orphan designation, not of the MAA. It should also be clarified whether such pre-submission meetings remain free of charge as this sentence has been deleted.  **Proposed change (if any):**  Sponsors are strongly encouraged to request a pre-submission meeting with the EMA, **free of charge**, prior **to submitting the orphan designation application**, in particular if it is the first submission for an orphan designation. |
| 6) 148-150 | **Comment:**  The second part of the following paragraph is unclearas different situations may exist “A sponsor may apply for designation of a medicinal product as an orphan medicinal product for an already approved medicinal product provided the designation applied for concerns a different orphan condition as compared to the approved therapeutic indication. In this case, at the time of application for a marketing authorisation, the marketing authorisation holder shall apply for a separate marketing authorisation (with a different (invented) name) which will cover only the orphan condition(s).” This last sentence only applies if the product in cause is a non-orphan product. In the case of two subsequent orphan conditions / indications for the same product, the tradename is maintained for the whole product (i.e. a product benefits from multiple orphan designations for different orphan conditions).  **Proposed change (if any):**  ~~In this case, at the time of application for a marketing authorisation,~~ If the medicinal product has already a non-orphan marketing authorisation, the marketing authorisation holder shall apply for a separate marketing authorisation (with a different invented name) which will cover only the orphan condition(s). In the case of two or more subsequent orphan indications for the same orphan medicinal product, the new indication(s) can be added to the existing orphan MAH. In this case the invented name remains the same. |
| **Information to be supplied** | |
| 7) Line 195 Para 1 | **Comment:**  The application should be signed electronically by the sponsor indicating that the documentation provided is complete and accurate – propose to clarify  **Proposed change (if any):**  We propose to clarify that the application can be signed electronically by another person than the sponsor provided that a delegation letter is available. |
| 8) Line 198-199 | **Comment:**  Propose to delete this statement since it is repeated below (**Line 231-232**)  **Proposed change (if any):**  ~~If designation is sought in more than one orphan condition for the same product, separate applications should be submitted for each orphan condition.~~  **Retain the following statement here (Line 231-232):**  If more than one orphan condition is applied for the same product, separate applications should be submitted for each orphan condition. |
| **Information to be included in the application** | |
| 9) Line 209  Section 1:  Name of the Active Substance | **Comment:**  Companies are instructed to provide the substance for registration using the exact scientific designation when no other name can be used (common name or INN). Typically, the exact scientific designation is used when a compound is submitted for designation as an early stage of development.  Substances name(s) are recorded and published in the Substances list of the EMA ([https://www.ema.europa.eu/en/documents/other/eudravigilance-extended-medicinal-product-dictionary-xevmpd-substances\_en.xlsx)](https://www.ema.europa.eu/en/documents/other/eudravigilance-extended-medicinal-product-dictionary-xevmpd-substances_en.xlsx).%20The%20fact%20that%20a%20substance%20has%20been%20recorded%20by%20EMA%20in%20the%20context%20of%20an%20orphan%20drug%20application%20must%20remain%20confidential%20until%20this%20procedure%20is%20completed%20and%20the%20designation%20has%20been%20either%20granted%20or%20refused.%20It) The fact that a substance has been recorded by EMA in the context of an orphan drug application must remain confidential until this procedure is completed and the designation has been either granted or refused. It is therefore important that information regarding the substance is not being disclosed by EMA until the procedure is completed and the designation has been granted (with no disclosure if the application is withdrawn) as is done for the COMP agenda, where products are not disclosed until an opinion is reached. |
| 10) Section 2 Line 228-229:  Proposed orphan condition | **Comment**:  Disease classification:  We note that throughout the document, references to classification schemes such as ATC codes and ICD (International Classification of Diseases) have been deleted, and thatMedDRA is recommended as a disease classification. We note that MedDRA has been designed as a ‘medical terminology to facilitate sharing of regulatory information internationally for medical products’ and not as a disease classification and we do not recommend that it is used for rare diseases.  In addition:   * Recommending the use of MedDRA in this guideline is not in line with other EC initiatives, such as those that stem from the EUCERD activities (<http://www.eucerd.eu/?page_id=282>) which recommended the use of ICD-11 * We noted that EC launched on 28 February 2019 the **European Platform on Rare Disease Registration** ([https://eu-rd-platform.jrc.ec.europa.eu/](https://urldefense.proofpoint.com/v2/url?u=https-3A__eu-2Drd-2Dplatform.jrc.ec.europa.eu_&d=DwMFAw&c=ZbgFmJjg4pdtrnL2HUJUDw&r=S50DDZqv3R_9dSu-77XGwlWz26fEniuQTxdCGYryA6c&m=lbfskwFlMNDSopq9P1ZPT9xCv8kbDafT5cn1hpOzsJY&s=fB-zAdj8bI_PcWnqwOYphxlKtTQCi_j1SImPDG3pbAA&e=)) and a set of common data elements on rare diseases is available under the following Link:[https://eu-rd-platform.jrc.ec.europa.eu/sites/default/files/EU%20RD%20Platform\_CDS%20\_final.pdf](https://urldefense.proofpoint.com/v2/url?u=https-3A__eu-2Drd-2Dplatform.jrc.ec.europa.eu_sites_default_files_EU-2520RD-2520Platform-5FCDS-2520-5Ffinal.pdf&d=DwMFAw&c=ZbgFmJjg4pdtrnL2HUJUDw&r=S50DDZqv3R_9dSu-77XGwlWz26fEniuQTxdCGYryA6c&m=lbfskwFlMNDSopq9P1ZPT9xCv8kbDafT5cn1hpOzsJY&s=vg-pbz2MnCAo7pqBI1yAkGXgL7khklsbQQaMDBSDxHE&e=). This acknowledges the value of ICD. Additionally, Orphanet maintains the Orphanet nomenclature of rare diseases under the following Link: [http://www.orphadata.org/cgi-bin/rare\_free.html](https://urldefense.proofpoint.com/v2/url?u=http-3A__www.orphadata.org_cgi-2Dbin_rare-5Ffree.html&d=DwMFAw&c=ZbgFmJjg4pdtrnL2HUJUDw&r=S50DDZqv3R_9dSu-77XGwlWz26fEniuQTxdCGYryA6c&m=lbfskwFlMNDSopq9P1ZPT9xCv8kbDafT5cn1hpOzsJY&s=cHcAOM-NZPOQ2mOH3yXA0BAf0-hB5r8h0Pqy-PhIxy8&e=)   We recommend that EC considers global consistency of coding of rare disease in health systems throughout the EU (in an international context for health information exchange), which is very unlikely to be achieved through MedDRA. In addition, experience of using MedDRA in other areas such as for Paediatric Investigation plans has shown that the dictionary may not sufficient for areas such as cancers. |
| 11) 319-320 Section 4 Sponsor/contact Person | **Comment:**  The sentence “Different applicants belonging to the same mother company have to be taken as one sponsor” is confusing. At the time of an application for an orphan designation applicant can define different legal/entity/addresses as sponsor of the ODD, hence within the same mother company we have orphan drug designations with different sponsors.  **Proposed change (if any):**  ~~Different applicants belonging to the same mother company have to be taken as one sponsor.~~ **Applicants belonging to the same group of companies can only submit one application per orphan condition for a given active substance. The same group of companies or another company can submit another application for the same active substance provided it is for a distinct orphan condition.** |
| 12) Section 4 Sponsor/contact person Line 323-324 | **Comment:**  The sentence “For sponsors whose main business is operated from outside of the Union, the address of those premises and a contact name should be provided” is confusing. When applying to an orphan designation, only the address and the contact person in the Union need to be provided.  **Proposed change (if any):**  For sponsors whose ~~main~~ business is operated from outside of the Union, the address of those premises **in the Union** and a contact name should be provided. |
| 13) Line 330  Section 4 Sponsor/contact person Para 4 | **Comment:**  In this sentence we would like to introduce additionally sponsor’s contact point since many times the sponsor’s contact point may be different from the person authorised to communicate with the EMA on behalf of the sponsor.  It is understood that any authorized person registered within IRIS submit (i.e. submission of the OMR) can manage applications and submission.  **Proposed change (if any):**  “ **additionally** ~~T~~**t**he sponsor’s contact point” |
| **Information to be included in the scientific part of the application**  **A. Description of the condition** | |
| 14) Line 450-454 Section A.2 para 3 | **Comment:**  It is noted that reference to the "elements to support medical plausibility and justification of significant benefit" , EMA/COMP /15893/2009, has been removed. However, it is understood that this guidance is still valid and so it would be preferable to see this reference reinstated. If there are plans to update the guidance then notification of this (as early as possible) and providing the opportunity to comment on it through a public consultation, would be much appreciated.  **Proposed change (if any):**  Reintroduce the statement deleted: **“Sponsors are advised to consult the recommendation on elements required to support the medical plausibility and the assumption of significant benefit for an orphan designation 2 March 2010 EMA/COMP/15893/2009 Final prior to completing the application.”** |
| 15) Line 450-458 | **Comment**:  We would like to add “genomic” to the definition of specific characteristics with respect to the WHO definitions of genetics and genomics (references: Genomics and World Health: Report of the Advisory Committee on Health research, Geneva, WHO (2002) and WHA 57.13: Genomics and World Health, Fifty Seventh World Health Assembly Resolution; 22 May 2004):  Genetics is the study of heredity. Genomics is defined as the study of genes and their functions, and related techniques.  The main difference between genomics and genetics is that genetics scrutinizes the functioning and composition of the single gene whereas genomics addresses all genes and their inter relationships in order to identify their combined influence on the growth and development of the organism.   “The fact that a subset of patients exists in whom the medicinal product is expected to show a favourable benefit/risk (as defined in the proposed therapeutic indication) would generally not be sufficient to define a distinct condition.”: this does not apply to the recognised distinct medical entities defined in the general requirements, part (a) (see below).  **Proposed change (if any):** General requirements:  ***(a)***Recognised distinct medical entities would generally be considered as valid conditions. Such entities would generally be defined in terms of their specific characteristics, e.g. pathophysiological, histopathological, genetic **subtype */genomic*** or clinical characteristics. *~~The fact that a subset of patients exists in whom the medicinal product is expected to show a favourable benefit/risk (as defined in the proposed therapeutic indication) would generally not be sufficient to define a distinct condition.~~*  ***(b)*** The characteristics defining a distinct condition should determine a group of patients in whom development of a medicinal product is plausible, based on the pathogenesis of the condition and pharmacodynamic evidence and assumptions.  ***(c)*** Different degrees of severity or stages of a disease would generally not be considered as distinct conditions. […] **Comment:**  It is unclear why the reference to the "elements to support medical plausibility and justification of significant benefit" , EMA/COMP /15893/2009, was removed, clarification is needed to understand if the EMA guideline is the correct reference to use. |
| 16) Section A.2. para 5 Line 458 | **Comment:**  “Broader entity” does not appear to be the right word. It could be replaced by for example “broader medical condition”.  **Proposed change:**  It is the broader ~~entity~~ **medical condition** that should be considered for the purpose of justifying the criteria of designation. |
| 17) Section A.2. para 5 (point a) Line 452 | **Comment:**  We propose to complete the sentence, as per EC Notice 2016 wording.  **Proposed change (if any):**  In particular, the genetic **subtype/profile** and/or pathophysiological characteristics associated with this subset should be closely linked to the ~~pharmacological action~~ **diagnostic and/or preventive and/or treatment action** of the medicinal product in such …….. |
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| **Information to be included in the scientific part of the application**  **B. Prevalence of the condition** | |
| 18) Line 514-516 Intro: | **Comment:**  **Text in the document:**  Sponsors are advised to consult the COMP Points to Consider document on ‘Calculation and Reporting of the Prevalence of a Condition for Orphan Designation’ prior to completing this section of the application.  There used to be another document about sources of data per condition <https://www.ema.europa.eu/documents/other/relevant-sources-orphan-disease-prevalence-data_en.pdf> it is unclear why this document has been made obsolete and additional guidance is requested. |
| 19) Line 519-521 Section B.1.1 Reference Information para 1 | **Comment:**  For clarity, we suggest replacing “databases of registry data” with “information from registries” and keep databases as a stand-alone source of information. “Databases of registry data” is a narrow term as it implies that only the databases for registry data (typically disease type registries) can be used, whereas there exist other sorts of databases. In addition, a suggestion to state “including sources such as” as the list of permitted sources might not be exhaustive here.  **Proposed change (if any):**  “The information should include a comprehensive review of authoritative reference (**including sources such as** published epidemiological literature, ~~and~~ databases ~~of registry data~~ **and information from registries**) which demonstrate that the disease or condition for which the medicinal product would be administered…” |
| 20) 532-536  Section B.1.1 Reference Information para 3 Line 332-334 | **Comment**   * Additional wording is suggested to indicate that assumptions must be justified for all calculations, not only for indirect calculations. In addition, “Generic level only” might not be the most appropriate word and “higher, disease level” is proposed instead. * There is also a need to clarify the meaning of “indirect calculations”. * The terms “Full or partial prevalence” are unclear and should be explained. * An additional statement is proposed to allow for an adjusted prevalence when this would be more appropriate and justified. Using crude data might not always be appropriate. For example, applying or comparing incidence rates from a non-Union country (e.g. Japan) to a Union country that has much younger (or older) age structure, may lead to under- (or over-) estimation, which could be minimized through age-standardization to the EU population.   The crude prevalence may result in an overestimation for disease including new products that would allow curability (cured patient included in the calculation.  **Proposed change (if any):**  “For **all calculations, including** indirect calculations (e.g. calculating prevalence of a specific disease which is described on a ~~generic level only~~ **higher, disease level**), all assumptions need to be justified by referring to appropriate scientific literature **and calculations must be transparent**. Since age-standardisation may result in underestimation of the disease frequency at the time of designation, only crude data should be presented. **In a situation in which an adjusted prevalence, such as age-standardization, is more appropriate than a crude estimate, then a justification for this should be provided.”** |
| 21) Section B.1.1 Reference Information para 4 Line 537-538 | **Comment**:  As studies will not always be the source of information for estimating prevalence, data sources, as listed in revised lines 519-521 of the guideline, have been included for more clarity.  **Proposed change (if any):**  ~~“Studies~~ **References for epidemiological literature, databases, registries and other sources of information used to estimate prevalence** should be summarised in tabular format**, cited and includi~~ng~~** all relevant information such as ~~definition~~ **characteristics** and size of the study population**,** ~~and~~ case definition, etc.” |
| 22) Section B.1.1 Reference Information para 5 Line 539-540 | **Comment**  Proposed wording with the same justification as for lines: 519-521  **Proposed change (if any):**  “If up-to-date references (**including sources such as** published epidemiological literature, ~~and~~ databases ~~of registry data~~ **and information from registries**) are not available **or not of sufficient quality,** the sponsor should provide a clear basis for the assumption that the disease or condition will…” |
| 23) Section B.1.2 Databases para 1 545-557 | **Comment**:  Prevalence data are pulled not only from databases on rare diseases like Orphanet, but also from other national and international registries and other databases collecting administrative claims data, general practice data, electronic health records data, etc. Hence, would help to add clarification if other databases would be acceptable apart from Orphanet, especially for conditions when Orphanet does not supply a prevalence estimate. An extra statement is proposed for situations where there is absolutely no epidemiological or databases available and the only source of data for estimating prevalence can be found for example in case reports.  Furthermore, we propose a change in order not to limit the source of information to databases and registries. Same justification as for Section B.1.1 para 1.  **Proposed change (if any):**  Information from relevant **sources of data, including** databases and registries in the Union (e.g. Orphanet, **European Rare Disease Registry Infrastructure (ERDRI) or relevant national and international databases and registries, electronic health records, health insurance claims databases**) should be provided, if available. **In the absence of epidemiological or databases in any region, then case reports or other sources of data may be used as evidence of disease rarity to support orphan drug designation.** |
| 24) Section B.1.2 Databases para 2 Line 560 | **Comment**  For consistency throughout the guideline text, the Community should be replaced here by “Union” rather than by “EU”.  **Proposed change:**  In the absence of epidemiological or databases and when only case reports of the disease are available in the Union, reference may be made to epidemiological data and databases available in third countries, provided an explanation of the extrapolation to the ~~EU~~ **Union** population is made. |
| **Information to be included in the scientific part of the application**  **D. Other methods for diagnosis, prevention or treatment of the condition** | |
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| 25) Section D.1. Details of any existing diagnosis, prevention or treatment methods para 3  Line 633-638 | **Comment**:  ‘Magistral or officinal formulations’ does not fit here and should be deleted. At the very minimum, we propose that the guideline should state that this would apply only in very exceptional cases. The addition of “magistral or officinal formulations” goes beyond the legal provision under Article 3. 1b of Reg 141/2000. This Article requires that significant benefit to those affected by the condition in question is demonstrated in cases where there exists methods of diagnosis, prevention or treatment of this condition that are authorised in the EU. Magistral or officinal formulations are not subject to authorisation and they should not be compared against in the context of significant benefit as this would place medicinal products subject to marketing authorisation at a disadvantage. There is also not a comparative provision in the centralised procedure. Data required to do a meaningful analysis is likely not to be present, neither is there likely to be the commercially scalable, GMP tested manufacturing capability to ensure a consistent formulation with which to compare an originating orphan product with. Furthermore, such a comparison (which does not maintain a robust PV and quality system) would not be an equal nor fair comparison with an orphan product and may undermine future research and development of orphan products if the economic incentive is removed.  We should also clearly distinguish (i) **regulated products (ie. medicines and medical devices)** – for which only the approved products (with marketing authorisation or CE-marked) and on-label indications / uses should be taken into consideration; and (ii) **and other methods that are not subject to regulatory approval** (eg. surgical procedure, diet and other medical approaches), which could be considered satisfactory based on relevant scientific / medical literature.  It is important to emphasise that the magistral / officinal formulations constitute a derogation to the requirement for a marketing authorisation for medicinal product as per **Article 3 Directive 2001/83**. Such exemption should only apply in exceptional circumstances (thus no general / industrial use) on the basis of individual patient needs. These methods cannot be considered ‘satisfactory methods’, with well-known / general practice in the EU and established safety profile and should not become an alternative to approved medicines, the same way off-label uses / hospital exemptions can also not be considered a satisfactory method. Unlike authorised medicines, such magistral / officinal formulations are not subject to appropriate clinical trials / dossier requirements and regulatory oversight, and hence are inappropriate comparators. This also conflicts with the paragraphs below and former wording that refer consistently to authorised (medicinal) products.  Any other interpretation would affect the foundations of the pharmaceutical legal system, which rely on medicines approval by regulatory authority on the basis of a full dossier demonstrating the appropriate safety and efficacy profile of the product and the positive risk-benefit balance for the product.  It is difficult to take into consideration these types of magistral or officinal formulations. It is difficult to have an overview of the safety profile since there is no data on safety and efficacy. Therefore, it would be difficult to demonstrate clinical benefit. The strengths of evidence are limited.  In addition, there are also assumptions made about and uncertainties on the qualifiers for magistral and officinal formulations: *“if they are well known and safe and this is a general practice in the EU”*. Who would decide if this is indeed the case and they are known and safe and based on what criteria?  **Proposed change (if any):**  Ideally, we would request amended wording as follows:” The sponsor should include in his review, as far as possible, other approaches to diagnosing, preventing or treating the disease or condition in question, such as surgical interventions, radiological techniques, ~~magistral or officinal formulations,~~ diet, physical means, etc. “  As a minimum we would propose amending the wording as follows: “The sponsor should include in his review, as far as possible, other **(non-medicinal/ non-pharmaceutical)** approaches to diagnosing, preventing or treating the disease or condition in question, such as surgical interventions, radiological techniques, **medical devices** ~~magistral or officinal formulations,~~ diet, physical means, etc. and in very exceptional cases, magistral or officinal formulations, when trustworthy data is available.” |
| 26) D.1. Details of any existing diagnosis, prevention or treatment methods Line 639 | **Comment:**  See also comment above. Regulated products (devices / medicines) should be treated differently to other medical method not subject to regulatory approval. For devices, only CE-marked devices and on-label use should be considered as part of the analysis for satisfactory methods.  The text is not clear how a medical device would be considered. Please clarify.  **Proposed change, if any:**  Clarify the wording as follows: “Commonly used methods of diagnosis, prevention or treatment that are not subject to marketing authorisation (e.g. surgery, **radiotherapy, CE marked** medical devices **used on-label**) may be considered satisfactory…” |
| 27) Section D.1 Details of any existing diagnosis, prevention or treatment methods para 4 Line 645-650 | **Comment:**  See comment above (Line 639).  **Proposed change, if any:**  “In the case of medical devices, this should include medical devices (including active implantable medical devices) placed on the EU market in accordance with the relevant legal framework **and in accordance with the approved label**.” |
| 28)  Line:655-658  Section D.1. Details of any existing diagnosis, prevention or treatment methods | **Comment:** To prevent that significant benefit is being assessed against medicines in off-label settings, a small revision is proposed.  **Proposed changed:**  “Details provided should include: (invented) name(s), Member State(s) where authorised, holder of the authorisation, and the authorised indication (medicinal products taken into consideration should be authorised for the treatment of the disease as such or, ~~at the very least,~~ **authorised to** address exactly the same set of symptoms).” |
| 29) Section D.2. Justification as to why methods are not satisfactory  Line 667 | **Text in the document:**  When there is evidence that magistral or hospital formulations are well known and safe and this is a general practice in the EU, the sponsor is expected to address those methods in this section and to discuss why they are not considered as 'satisfactory methods'  **Comment:**  Hospital formulations are excluded per commission notice (2016/C 424/03)  See also our comment on Section D.1 para 3 (**Line 633).**  **Proposed change (if any):**  **It should not be used even,** **w**~~W~~hen there is evidence that magistral or ~~hospital~~ **officinal** formulations. |
| 30) Section D.2. Justification as to why methods are not satisfactory 662-670 | **Comment:**  Replace “**satisfactory**” by “**currently authorized** or recommended by relevant medical/science community therapy guideline”.  Rationale: The terminology “satisfactory” is very problematic in this context as not truly referenceable and open to very divergent interpretation. |
| 31) Section D.3. Justification of significant benefit para 2 Line 678-679 | **Comment:**  Sponsor may not have “generated” (much) data at this stage so would be better to delete this wording. We would also like to improve clarity in the sentence by introducing the word “clinical.”  **Proposed change, if any:**  “At the time of designation, significant benefit should be based on assumptions, which are well justified by non-clinical or preliminary **clinical** data ~~generated~~ in the specific context of the sought condition.” |
| 32) D.3. Justification of significant benefit para 2 Lines 681-682 | **Comment:**  The verb “may” should not be replaced by “should” as the revised statement would require that an orphan designation application must also include preliminary clinical information in addition to non-clinical data. This would be highly restrictive and in contrast to lines 242-243 and 479-481 that state that for an orphan designation application “non-clinical or preliminary clinical data are generally required”. *(emphasis added)*  **Proposed changes:**  Non-clinical data and preliminary clinical information should **may** be added as supportive evidence. |
| 33) Section D.3. Justification of significant benefit para 2 Line 682 | **Text in the document:**  In general, a demonstration of potentially greater efficacy and/or an improved safety profile may be considered to support the notion of significant benefit. When significant benefit is argued on major contribution to patient care due to significantly improved adherence in treatment, due to a change in pharmaceutical form, this should be accompanied by a discussion on the serious and documented difficulties with the existing formulation and data to demonstrate that the proposed product can overcome such difficulties.  **Comment:**  If methods without marketing authorization are accepted as satisfactory treatment options as per the suggested language, how can a structured evaluation of these products be carried out to demonstrate significant benefit of the proposed orphan medicine? Very often, methods without MA are not consistently documented. |
| 34) Section D.3. Justification of significant benefit para 2 Line 684-688 | **Comment:**  We propose to complete the sentence, as per EC Notice 2016 wording  **Proposed change (if any):**  …..due to significantly improved adherence in treatment due to a change in pharmaceutical form, **new strength or a new route of administration,** this should be accompanied by a discussion on the serious and documented difficulties with the existing formulation**, strength or route of administration** |
| 35) Section D.3. Justification of significant benefit para 4 and 5 Lines 671-677 | Satisfactory is not defined in EC/EMA guidance  Replace “satisfactory” by “currently authorized or recommended by relevant medical/science community therapy guideline”.  Rationale: The terminology “satisfactory” is very problematic in this context as not truly referenceable and open to very divergent interpretation. |
| **G. Transfer of the Orphan designation to another sponsor and change in the name of the Sponsor and/or the address of the sponsor.** | |
| 36) Section G.1 Transfer to another sponsor para 3 Line 841-843 | Comment: It is not stated that the sponsor needs to be registered in SPOR  Proposed change (if any): The sponsor should submit an application according to procedural guidance available on the EMA website, **following the insertion of the sponsor data in the Agency’s controlled term list in case the sponsor is not yet registered in EMA’s Organisation Management Service (OMS)**. The EMA will not be in a position to provide an opinion on the transfer should the application be incomplete or unsatisfactory. |
| **H. Amendment of an existing designation** | |
| 37) Section H para 2 Line 869-871 | **Comment:**  Depriving the possibility for Sponsors to make some updates to the orphan designation through the annual report and requiring submitting a new orphan designation application is not proportional. There should be a possibility for Sponsors to update or amend aspects of the orphan designation (e.g.; new salt or INN) that do not pertain to the key orphan designation criteria, that is orphan condition and prevalence.  .  Proposed change (if any): Any other changes (e.g. new salt or INN) not affecting the condition as reflected above are not concerned by this procedure and ~~should be addressed by submitting a new application for an orphan designation~~ **do not fall into the scope of submitting a new application for an orphan designation**. **These other changes mentioned above should fall into the scope of the annual report on development.** |
| **Footnotes** | |
| 38) Notes 4 (page 3) and 7 (page 7) | **Comment:**  In reference to the Regulation EC 141/2000, the Commission Regulation EC 847/2000 and the Lisbon treaty, and specifically article 3; Community and Union refers to the European Union not to the EEA. The guideline would need to be harmonised to ref to the Community, i.e. the 27 Member states. [comments: harmonisation of position need to be throughout the guideline] |