European Medicines Agency
Evaluation of Medicines for Human Use

London, 23 July 2007
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OVERVIEW OF COMMENTS RECEIVED ON DRAFT GUIDELINE

Table 1: Organisations that commented on the draft Guideline as released for consultation

	Name of Organisation or individual	Country
1	**European Cancer Patient Coalition's** (ECPC) – 03.07.06	EU
2	**European Federation of Pharmaceutical Industries and Associations** (EFPIA) – 30.06.06	EU
3	**EURORDIS** – 28/06/06	EU
4	**Raoul CM Hennekam MD PhD** Professor of Clinical Genetics and Dysmorphology, Institute of Child Health Great Ormond Street Hospital for Children, University College London Professor of Pediatrics and Clinical Genetics, Dept of Pediatrics Academic Medical Center, University of Amsterdam	UK
5	**BioIndustry Association** (BIA) – 03.07.06 Trade association for innovative enterprises in the UK bioscience sector. It represents over 300 members, the majority of which are involved in realising the human health benefits that bioscience promises.	UK
6	**Merck Sharp & Dohme** (MSD) – 23/06/06	EU
7	**IDIS pharma** – 30/06/06 Specialist in the provision of named patient and compassionate use services. IDIS on average make 1600 notifications to the MHRA a week with regard to named patient supply in the UK; IDIS supply to over 300 customers in Europe (3800 products).	UK
8	**EuropaBio** – 30/06/06 70 corporate members operating worldwide, 7 associate member organisations, 2 bioregions and 24 national biotechnology associations representing some 1500 SMEs involved in research and development, testing, manufacturing and distribution of biotechnology products.	World-wide

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Table 2:Discussion of comments

GENERAL COMMENTS ON THE GUIDELINE - OVERVIEW
European Cancer Patient Coalition's comments (ECPC): The ECPC fully endorses the comments from Eurordis. ECPC very much regrets that given the present legislation, there is little harmonisation on Compassionate Use across the European Union. While cancer medicinal products now benefit from an obligatory centralised procedure, Compassionate Use still depends very much on the measures taken by Member States. Many of our cancer patients lives will depend on whether they can enrol in a Clinical Trial or are eligible for a Compassionate Use Programme. All too often cancer is still a seriously debilitating disease, or a life threatening disease, which cannot be treated satisfactorily by an authorised medicinal product in Europe. Having access to Compassionate use programmes is often an unacceptable lottery and depends on the support and good will of a patient's medical doctor to fight through the paper maze. **E.F.P.I.A:** We want to commend the EMEA and the CHMP for their proactive approach to compassionate use programmes. In order for the new provisions to be most effective there is also a need in the longer term for greater harmonisation of compassionate use approach and process across Member States. The current initiative can hopefully be viewed as a first step towards that long-term objective. - Historically, compassionate use programs have been managed via a dialogue between the company/manufacturer (termed 'applicant' in the guideline and in this text hereafter) and the Member State(s) according to national legislation and at the instigation of the applicant. The guideline acknowledges that implementation of compassionate use remains a Member State competence. However, it does not explicitly recommend that a request by a Member State to the EMEA/CHMP should take place after consultations at the national level. The guideline should, to our mind, specify that a Member State should consult and reach an agreement with the applicant before submitting a request for a CHMP opinion. As a safeguard and for mutual planning purposes, the EMEA should also consult with the applicant before launching a CHMP procedure. This point may be implicit but would benefit from being made more explicit in the text. - It must be more clearly stated that there is no expectation that an applicant will have to prepare a distinct dossier when a CHMP opinion is requested, and that the use of available documents (e.g. as already prepared for Member States under existing compassionate use programmes) is supported by the Agency. To this end, it would be helpful to have more examples of the type of documentation that is commonly available at different steps in the development process and that might be required for a CHMP opinion. - Of concern is the possibility of a CHMP procedure if more than one Member State notifies the CHMP of a cohort compassionate access program for a medicinal product but without requesting a CHMP opinion. According to article 83(3), Member States must inform the EMEA of compassionate use programs, but are not obliged to seek a CHMP opinion on the matter (as reflected elsewhere in the guideline). Article 83 does not convey the power of automatic referral for opinion by the CHMP under any circumstance. - - Ultimately, as any opinion is not enforceable on the Member States, we believe that such a "forced referral" would not be constructive and might, in the worst case, prevent access to patients where Member States feel obliged to delay national decisions on compassionate use pending the CHMP opinion. - The guideline should include an indication of how long the CHMP opinion process will take. It is essential that all stakeholders understand and agree that the new CHMP procedure does not in any way hinder or delay established national processes. A transparent schedule is also essential to allow the applicant to manage the process on the company side (a process which in many cases is likely to coincide with marketing authorisation application preparation and/or assessment). - We find that the role of the applicant is unfairly minimised in the draft guideline. Organising and supplying product for a compassionate use program is a complex activity and it is the applicant who must ensure that it will not negatively impact the clinical development programme by either reducing the patient pool or causing drug supply shortages. Given the important role of the applicant in managing compassionate use and the need to ensure that the objectives of the guideline, as set out in "Section 2 Legal Basis and Purpose", are met, it appears important and reasonable that the guideline is modified to allow applicants the option (if justified) to directly contact the EMEA with a request for a CHMP opinion. In any case, the need for dialogue and involvement with a potential applicant at all stages of the procedure must be emphasised. - We find the use of the term "applicant" in the guideline misleading, although we have used it in these comments in the interest of clarity. The company/manufacturer is not submitting any request or application (unless this possibility is added as suggested above): as currently written, the request for a CHMP opinion originates from a Member State. The term 'applicant' should, to avoid confusion, be reserved for submissions of marketing authorisation applications, additional data and variations thereof.

- We fully agree that compassionate use programmes can never be a substitute for properly conducted and GCP-compliant clinical trials. Nevertheless, we would recommend that a sentence be added to remind that information captured from compassionate use programs (in full compliance with national laws and regulations) may be used as supportive information in marketing authorisation applications.
- We recommend that great care be taken in the wording of the CHMP/EMEA recommendations included in the planned EMEA compassionate use register, in order not to mislead the public by providing information that will by necessity not be applicable for all Member States.

BIA: The BIA supports the development of a procedural guideline in order to fully implement the new EU medicines legislation with regard to supply of medicines for compassionate use. We welcome the general principles as set out in this draft guideline, which acknowledge the need to adopt a EU-wide policy relating to supply and distribution of an unauthorised medicinal product for compassionate use. We believe that this policy is critical to patient access to innovative medicines under defined conditions, particularly where the disease is life-threatening and debilitating, and there is no satisfactory treatment available. That said, we believe that greater clarity is needed in this guideline about certain procedural issues as detailed below. Principally, these issues relate to: the definitions; the conditions of supply and distribution; the assessment of the request by the CHMP including informational requirements; the inter-relationship between supply of unlicensed medicines on a named patient basis and compassionate use.

MSD: MSD fully supports the intention of the legislation to make medicinal products available through compassionate use programs for patients with chronically or seriously debilitating or life-threatening disease which cannot be treated by an authorised medicinal product. However, we fear that the current draft guidance leaves too much room for interpretation from the Member States to be successful in its implementation. As this guideline operates in the boundaries between EU and national responsibilities it is essential that the scope of the guideline is clearly defined and clarified. In addition, MSD believes that more information related to the CHMP criteria applied for selection of the programs on which an opinion will be issued, the CHMP opinion adoption procedure and timelines as well as information and communication towards sponsors is needed to allow a transparent system with clear roles and responsibilities.

IDIS: - Article 83 of Regulation (EC) No 726/2004 seems to be a non value adding piece of legislation in as much as Article 5 of Directive 2001/83/EC allows for compassionate supply and the guidance relating to Article 83 of Reg No 726/2004 seems to give no beneficial alternative to this. It does not really allow the benefits of the stated aim in as much as it will not standardise legislation nor facilitate access.
- At present it is possible to supply a medicinal product on a named patient basis to member States with established methodologies and short time lines. It is difficult to see how going to the EMEA for an opinion will facilitate harmonisation when Member States will still have National legislation. It is equally difficult to see how patient groups will be able to get rapid access with this additional layer of bureaucracy. There seems no advantage for a manufacturer to pursue this compassionate use system when Named Patient supply serves them well.

EuropaBio: It is the view of industry that currently, national systems for supply of medicines under Compassionate Use programs exist and work reasonably well. This is particularly the case for Orphan drugs that are used to treat a patient suffering from a rare and life threatening disease. The role of companies is minimized in these guidelines. Offering them the possibilities to give their opinion is not sufficient. There is no opportunity for the
manufacturer or applicant to make a direct request to the CHMP for a CU program. The responsibilities to ask for CU should be clearly defined. The
initiative should also come from the sponsors and not necessarily from patient organization and Health Authorities. It is not clear if MSs are obliged to inform the CHMP when a request for CU is made to the MS. Any CU program needs to take into consideration supply of the product and compensation to the manufacturer. The guideline acknowledges that the implementation of CU remains as a MS competency, however it is not clear if a National CU program can run at the same time that a CHMP Opinion on CU is pending. The rationale for asking for CU is not clear in the document. Transparency, consistency and common approach should drive this process. The clarification that CU is not off label use and that it should not be used to allow off label use by the back door is welcomed.

SPECIFIC COMMENTS ON THE GUIDELINE TEXT

GUIDELINE SECTION TITLE

Line no.[1] + paragraph no.	Comment and Rationale	Outcome
	1. INTRODUCTION	
1- Compassionate use programmes facilitate the availability of promising medicinal products to patients at an early stage in the drug development process.	**EFPIA:** A pre-requisite for compassionate use is that the product must be undergoing clinical trials or the marketing authorisation application must already be under evaluation, which from a company's perspective by definition corresponds to a late stage of drug development. Secondly, the word "promising" should be replaced. Proposed wording: "*Compassionate use programs are intended to facilitate the availability of products under development to patients when the benefit/risk ratio of the medicinal product is presumed to be positive*."	The point is not endorsed, as the concept of "assessment of Benefit/Risk balance" is used for positive or negative CHMP opinion for MA applications (based on assessment of a positive or negative Benefit/Risk balance), whereas for compassionate use application the concept of positive or negative opinion is not used: The CHMP provides recommendations or not, based on the available data. This is however acknowledged that the term "promising" is vague. In line with the spirit of the legislation, the text has been amended: *"Compassionate use programmes are intended to facilitate the availability to patients of new treatment options ~~medicinal products at an early stage in the~~ under development".*
2	**BIA:** It would be helpful if the national programmes referred to in that paragraph were described in an appendix to the guideline. Alternatively, such information could be made available on the EMEA website.	The EMEA will ensure that links to the websites of the individual national competent authorities are included in the guideline and /or on the compassionate use section of the EMEA website.
	2. LEGAL BASIS AND PURPOSE	
3	**EFPIA / EuropaBio:** Change the 2nd indent under "The objectives of Article 83 (…):" to: *"*Favour *a common approach regarding the conditions of use (…)".* As Compassionate use as described in article 83 is not binding on EU Member States.	The text has been amended accordingly.
	3. SCOPE AND GENERAL PRINCIPLES	
4	**EFPIA:** It would be helpful if all examples of where the provision *does not* apply, e.g.: *"*Article 83, and therefore the present guideline, are not applicable to: 1/ Compassionate Use on a named patient basis (Article 5 of Directive 2001/83/EC). 2/ Medicinal products, already authorised via centralised procedure, even if the proposed conditions of use and target population are different from those of the marketing authorisation	The guideline has been amended accordingly.
5	**BIA:** In our view it is unethical to deny the supply on CU of a product, which is not the subject of a centralised MAA or undergoing testing in a	The EMEA will ensure that links to the websites of the individual national competent authorities are included in the guideline and /or on the compassionate use

[1] Where applicable

	clinical trial, to a patient that may benefit where there is no other treatment. As the guideline does not apply to the compassionate use of products on a named patient basis, it would be helpful to clarify what is the situation with regard to MS that only legislate for nominal supply of unauthorised products.	section of the EMEA website.
6	**EFPIA:** The CHMP compassionate use procedure is applicable to products eligible for authorisation via the centralised procedure: i.e., products within both the optional and the mandatory scope of the centralised procedure. It should be clarified that use of the compassionate use procedure introduces no obligation for products falling within the optional scope to subsequently being registered via the centralised procedure: the decentralised and mutual recognition procedures should remain an option. Reword 1st sentence to read: *"The use of Article 83 is applicable to unauthorised medicinal products for human use falling within the scope (…)* without prejudice to the subsequent marketing authorisation route as required or permitted by that Regulation.*"*	See clarification provided in the amended guideline.
7 - Art 83 is not application to a product, which has already been authorised *via* the centralised procedure, even if the proposed conditions of use and target population are different from those of the MA.	**BIA**: In our view it is not equitable that products that are approved for a therapeutic indication cannot be supplied on a compassionate use basis for another indication if there is no other satisfactory treatment.	This statement is the direct consequence of Art 83 (1) and (2): The use of Article 83 is applicable to unauthorised medicinal products for human use falling within the scope of articles 3(1) and 3(2) of Regulation (EC) No 726/2004.
8	**EFPIA:** A more precise definition of what is understood by unauthorised would be welcomed, e.g.: "Unauthorised means no existing marketing authorisation within the European Union.*"*	The definition of "authorised medicinal product" has been amended (see guideline).
9	**EFPIA:** The phrase "by an authorised medicinal product in Europe" should be changed to "by a medicinal product authorised in the Member State where compassionate use has been requested" for clarity. The phrase "in Europe" was not in the regulation. If an authorised treatment is available in one member state, it should still be possible for the unlicensed medicinal product to be made available under the	The definition of "authorised medicinal product" has been amended (see guideline).

	compassionate use programme in a second member state where an authorised treatment is not available. It is unrealistic to expect a Company to be aware of every comparable treatment marketed in every Member State by the national or MR procedures.	
10 - The medicinal product is either the subject of an application for a centralised MA (…) or is undergoing clinical trials in the EU and/or elsewhere.	**RCM Hennekam:** **1 -** If a medication is used for indication A in a clinical trial, is it then acceptable to ask for compassionate use for another indication B? 2 - If a disorder is an Orphan disorder with such a low incidence and prevalence that even within the whole of Europe not a sufficiently large number of patients can be gathered for a clinical trial, is performing of a clinical trial still a prerequisite for compassionate use?	As far as the product is not authorised and under investigation in clinical trials, there is no restriction about the specific indication and target population claimed in the application for compassionate use. The scientific data submitted should allow, on a case by case basis, the evaluation of the benefit and the risks of the product under specific conditions of use, for the intended target population, in the context of compassionate use. 2 - Art 83 can apply if the product is the subject of an application for a centralised MA or is undergoing clinical trials in the EU and/or elsewhere. For the situation described (i.e. absence of MAA and absence of any clinical trial), compassionate use on a named patients basis may apply at individual national levels.
	Definitions: Compassionate use versus clinical trials	
11	**ECPC:** We fully support that compassionate use should not slow down the implementation or continuation of clinical trials. However, for patients that cannot enrol in a clinical trial and lack an effective treatment option a compassionate use programme may offer a life-saving alternative.	This comment is endorsed. See Chapter 3 of the revised guideline: Scope and general principles.
12	**EFPIA:** We fully agree that compassionate use programmes can never be a substitute for properly conducted and GCP compliant clinical trials. Nevertheless, we would recommend that a sentence be added to remind that information (e.g. demographical, safety observations) captured from compassionate use programs may be used as supportive information in marketing authorisation applications. Add sentence: "*Any information collected from compassionate use programmes (in compliance with applicable national laws and regulations) may be added as supportive information in a subsequent marketing authorisation application*."	This comment is endorsed and will be considered in the paper on procedural aspects.
	Other principles and definitions: "Group of patients"	
13	**BIA:** It would be helpful to clarify what constitutes a "group of patients" - is there a minimum number of patients in order to fall within the scope of Article 83?	A "group of patients" can be a few (less than 10) patients (e.g. for rare diseases), or thousands of patients. See amended definition in the guideline.
14	**IDIS:** What would constitute a group of patients? Some medicines have very limited target groups. For rare conditions Member States may have very few patients affected but the European market may have a	See question 13

	significant number.	
	Other principles and definitions: "conditions for distribution"	
15	**ECPC:** We very much regret that conditions for distribution as far as compassionate use is concerned are not better defined in the pharmaceutical legislation and that therefore there is no common strategy for supplying the medicinal product in all the MSs. Despite the centralised approval process this creates inequities across Europe and leaves the lives of patients up to chance rather than a firm European approach.	See question 16
16	**EURORDIS:** To exclude the strategy for supplying the medicinal product in the MSs (e.g. quantity of product, choice of MSs) from the definition of "conditions for distribution" may be a missed opportunity to confer an even more useful role to the Agency in the implementation of *a common approach regarding the criteria and conditions for the compassionate use of new medicinal products under MS' legislation*, as stated in Recital 33 of Regulation (EC) No 726/2004. In discussing all aspects of the conditions for distribution with the applicant, the Committee, with all MSs represented, **would ensure higher equity in accessing a compassionate use programme**. 25 MSs together are in a better position **to negotiate the following key aspects of a compassionate use programme**, than each of them separately: 1. That the implementation of the programmes starts at the same time in all MSs. • actual recruitment may differ among MSs as different procedures exist, e.g. ethics committee opinion or not, but the discussions with national authorities should not be delayed from one MS to the other 2. That all MSs will be considered. • if the applicant does not intend to open a compassionate use programme in all MSs, then the reasons why should be evaluated at the time of opinion and made public. 3. That the procedures for drug distribution are similar in all MSs. • Access to a compassionate use programme should be fair and equitable. Recent examples of such programmes have shown great diversity:	The CHMP's remit concerns the assessment of scientific aspects and the legislation does not provide it with the power to regulate the market supply in Member States. Whilst the EMEA acknowledges the concerns expressed by patients organisations in respect of differential supply to Member States markets of compassionate use products, the legislation does not permit an interpretation of "conditions for distribution" whereby regulation of such matters is included within its scope, since there is no legislative provision to provide any basis for an extension of its remit into this field.

[2] Availability and Price survey Eurordis, based on data obtained from IMS-Health

	3.1. Centres opening the programme only if they could enrol patients in regulatory trials (as a gift to investigators), letting centres that decided not to participate to the product development out of the scope of the compassionate use, and thus discriminating patients. 3.2. Companies opening a programme only in MSs where they can charge for the product even for a compassionate use. 3.3. Programmes recruiting on a first come first served basis if the product supply is limited. This may not correspond to the objectives needs of those patients with the most severe medical condition and in the greatest need of a new product under a compassionate use, who can not rush to the hospital to become the first served. 3.4. Programmes recruiting at the sole discretion of the physicians, and selecting himself the patients to receive the product on a compassionate use, which is not satisfying when the product supply is limited. 3.5. Companies asking patient organisations to decide on the selection criteria if the demand exceeds the product availability. 3.6. Or Ethics committees advising to organise a lottery or a random process to select the eligible patients under such limited supply conditions. 3.7. Companies monitoring the shortage of product with a waiting list, transferring product from MSs where demand is lower to MSs where the demand is higher. 3.8. Programmes stopping enrolling new patients at the time of marketing authorisation but continuing providing the drug for free to those already in the programme, until pricing and reimbursement negotiations are completed. On the contrary, in other MSs, the same company continued enrolment, with no restrictions, or stopped delivering the product for free before the reimbursement decision was made, thus preventing the poorest patients to continue treatment. 4. That the procedures for the announcement of the programme should be similar in all MSs. • The details of this announcement is the responsibility of the MS. However some possible measures exist in all MSs: letter to doctors, public section on the web site on the NCA, information to patient organisations. There is a balance between promoting the product and neutrally informing on the compassionate use programme. As for the announcement that a new clinical trial is	

	enrolling, fairness in the announcement that a compassionate use programme is open is equally important. The current situation is that usually, the applicant and MSs negotiate all these points in a separate manner. This creates **inequality and discrimination among patients depending on where they live**. As drugs eligible for compassionate use are to treat life-threatening or severe diseases, such disparities are not acceptable. Inequity in accessing a compassionate use programme also exists when the disease is so rare that only a few member states develop the necessary efforts to open the programme. For example, a compassionate use programme for Carbaglu® started in France in August 2001. Marketing authorisation was granted on January 24th, 2003. During that period, half of the patients who benefited from the product as compassionate use were all living in France, reflecting the difficulties to open access in all MS. Other examples[2] with delayed access to orphan drugs due to absence of a compassionate use programme in some of the member states can be documented about Fabrazyme® (ATU started 80 days before EU marketing authorisation, whereas sales could be detected in Spain only 377 days after marketing authorisation), Glivec® (compassionate use started 90 days before EU marketing authorisation in France and Germany, whereas sales were detected 373 days after EU marketing authorisation in Belgium, 189 in Greece, 100 days in Ireland…), or Tracleer®. Another example is the compassionate use programme for HIV protease inhibitors started in April 1996 in France, and one to two years later in some other EU MSs: hospitalisation rates declined during the weeks that immediately followed the initiation of ritonavir and indinavir compassionate use programmes in France (ATU) in April 1996, that was six months prior to marketing authorisation. On the contrary, the Agency could certainly help developing the Regulation (EC) No 726/2004 common approach by incorporating all these aspects in the discussion with the applicant at the time of assessment of the compassionate use programme. Even if not all conditions are finally the same in all MSs, it is more transparent to announce these differences early and prior to the initiation of the programme. **The Agency should not renounce to this important role it can play in public health in Europe by over-restricting the definition of condition of distribution.**	

	Other principles and definitions: "chronically or seriously debilitating disease or whose disease is considered to be life threatening"	
17	**EFPIA:** The only given examples of chronically or seriously debilitating disease or life-threatening disease are HIV and AIDS. These are two obvious examples, but clearly the scope of the procedure should not be limited to these areas. Some more examples would be helpful to provide some insight as to where this procedure may be applicable. Please add more examples of chronically or seriously debilitating diseases falling within the scope.	The guideline has been amended accordingly. The assessment of the eligibility of will be done in accordance with art 83 (1).
	Other principles and definitions: "satisfactorily treated by an authorised medicinal product in Europe"	
18	**EFPIA / EuropaBio:** Suggest deleting the term "comparable or" which brings no added value and is ambiguous as little or no direct comparative data may be available for a medicinal product available for Compassionate Use. We further suggest replacing "as compared" with the authorised one (…)" on line 5, based on the same rationale as above. As a general rule, at the stage of a compassionate use programme, only (strong) presumption of a benefit can be brought for a new drug. The term "evidence" should be replaced by "presumption". The authorised products to be considered should be products registered in the EU. Proposed text: *(…) means patients for whom no ~~comparable or~~ satisfactory ~~alternative~~ medicinal product is available. In principle therefore, Article 83 is not applicable in situations where ~~an authorised medicinal product already exists~~* **another medicinal product is already authorised within the European Union** *for the same conditions of use. However, should compelling data ~~bring evidence~~* **lead to a presumption** *of benefit of a new medicinal product ~~compared with the~~* **with regard to an** *authorised one, the use of Article 83 may be considered ~~for this product~~."*	The definition of "satisfactory treatment" has been amended (see guideline).
	Other principles and definitions: "Applicant"	
19	**EFPIA:** The use of the term "applicant" to denote the company/manufacturer is inappropriate and inconsistent. As the guideline is currently written, the request for a CHMP compassionate use opinion is made by one or more Member States. We see two choices: Section 4 ("Initiation and Request for CHMP Opinion") may as we suggest below be revised to also allow the company/manufacturer to request for a CHMP opinion on compassionate use. In this case, the term "applicant"	The legislation clearly provides that it is for the MS to initiate the procedure for adoption of a CU opinion by "notifying" EMEA of intention for CU (albeit with subsequent company consultation). However, the MS are not "applicants" in the sense that they are merely providing notification of a decision taken, and in any event the legislation uses the term "applicant" in the sense that it is used elsewhere in the legislation i.e. company (Art 83(4)). The EMEA does not agree with EFPIA that this necessarily implies that the

	can be kept to denote “manufacturer or applicant”. If the suggestion is not acceptable to the EMEA, the term “applicant” is misleading and needs to be replaced throughout the text. What is to be presented as “applicant” merits to be carefully defined. Shall it be the company European headquarters or legal representative in the Community, the local representative(s) in the Member State(s) from which the request originated or all local representative in those Member States where compassionate use cohort programmes are permitted. **BIA:** It would helpful to clarify as to who the “Applicant” is. Is this a reference to the application process that exists in certain Member States (i.e. France and Italy) and therefore the applicant is the company that supplies the product? This paragraph also refers to “compassionate use **applications**”. Again, we would welcome clarification. Is this a reference to existing national compassionate use approval processes? We would suggest replacing “application” with “the request for an opinion on the conditions for the compassionate use of medicinal products”.	company should therefore have a right to initiate the CU opinion procedure - the use of the terminlogy and the scope of the "application" procedure for CU opinions are 2 separate issues - legislation provides ONLY for the MS (to "notify"). To avoid misunderstandings: - the term “companies” is now being used throughout the guideline for “manufacturer of applicant”, as meant in paragraph 4 of Article 83 of Regulation and denotes the person responsible for providing the scientific file to the CHMP, for the assessment of the compassionate use of a medicinal product under article 83 of the Regulation. This person is either “an applicant” if a centralized MA is being submitted, or “a manufacturer” if the medicinal product concerned is not subject of an application for centralized MA. - The term “application” is replaced by “scientific file”, and means the scientific dossier the company is being requested to submit to the CHMP for the assessment of the compassionate use of a medicinal product under article 83 of the Regulation. The term “application” is used to designate dossiers for MAA in this guideline.
20	**IDIS:** As a UK based Company would IDIS be able to act on behalf of an applicant company from outside the EU who wish to set a compassionate use programme within the EU?	See question 19.
	4. INITIATION AND REQUEST OF CHMP OPINION	
21	**EURORDIS**: The **EMEA could also refer the matter to itself and provide MS with an opinion**, <u>even if not asked</u> by any of the Competent Authorities that notified the EMEA. This would be particularly helpful in the case where different MS will define different patient groups eligible for compassionate use, or different conditions of use.	Without formal request, the CHMP may give an opinion based on two notifications from 2 different Member States, to favour a common approach in the recommendations, if it is considered of public interest.
22	**BIA:** It would be helpful to clarify the following statement “When a Member State envisages the need to make a medicinal product….available for compassionate use”. How is the Member State to “envisage” such a requirement unless it has in place a process by which companies must inform it of their intention to supply a product on compassionate use should the patient need arise? As drafted, this would allow Member States to require applicants to make medicinal products available for compassionate use, which may not be possible in certain situations for legitimate reasons, e.g. limited availability of the product. Moreover, there is no legal basis for such requirement.	The CHMP's remit concerns the assessment of scientific aspects and the legislation does not provide it with the power to regulate the market supply in Member States. The EMEA / CHMP will not require (at validation or later during the procedure) companies’ commitment to supply the EU market with a medicinal product, should a CHMP opinion is given for compassionate use. Decisions for initiating compassionate use programme within the member states are left to the companies and the MS.

23 - For medicinal products belonging to the categories referred to in Article 3(2) of Regulation (EC) No 726/2004 (the so-called "optional scope"), it is recommended to notify the EMEA.	**EFPIA, BIA, EuropaBio:** It is not understood why a Competent Authority must inform the EMEA when making a product available for compassionate use which falls under the mandatory scope of the centralised procedure, but can choose whether to do so for products falling within the optional scope. This does not appear to be in line with the text of the Regulation which sates Member States shall inform the agency if initiating compassionate use for a medicinal product falling under both the mandatory and optional scope of the Regulation. Propose to delete this sentence.	As a result of the comments received, this aspects of the procedure has been clarified as follows: When a MS envisages the need to make a medicinal product, as defined in paragraph (1) and (2) of Article 83, available for compassionate use, the Competent Authority of that MS must notify the EMEA. For medicinal products belonging to the categories referred to in Article 3(2) (the so-called "optional scope"), the EMEA (and the company) shall only be notified when the eligibility to the centralised procedure has been already confirmed by the CHMP. This is to be considered in conjunction with the following amendment proposed for paragraph 3 (scope): "The use of Article 83 is applicable to unauthorised medicinal products for human use falling within the scope (…) *without prejudice to the subsequent marketing authorisation route as required or permitted by that Regulation."*
24 - When a MS envisages the need to make a medicinal product, as defined in paragraph (1) and (2) of Article 83, available for compassionate use, the Competent Authority of that MS must notify the EMEA	**MSD**: Compassionate use programs are usually initiated for novel Oncology, HIV or Anti-infective treatments. It is not clear if Member States must notify the EMEA in case of compassionate use programs for all serious and life-threatening or chronically debilitating conditions or only for "mandatory" CP products (orphans, biotech, diabetes, cancer, HIV, neurodegenerative diseases). MSD believes that neither the "mandatory" nor "optional" scope of the Regulation should play a role for the application of this guidance and should be based only on the criteria as listed in Article 83. Hence, the first two paragraphs are confusing in this respect. In addition, MSD would like to request that a copy of the notification letter is sent to the sponsor to allow full transparency of the discussions and co-operation, if necessary. Please add: "...must notify the EMEA, and send a copy of the notification letter to the sponsor."	Art 83 applies to products which fulfil both the criteria mentioned in paragraph 1 and paragraph 2 of this article (see section 3 of the guideline: scope) See question 23. This comment is endorsed.
25 - Applicants should not directly contact the EMEA to request a CHMP opinion. However, companies may, of their own motion, inform the EMEA of CU applications in the MS, or of an ongoing procedure for CU at national	**ECPC**: Companies should be required to inform the EMEA of compassionate use applications in the Member States, or of an ongoing procedure for compassionate use at national level. In our view, this would lead to a more harmonised approach and exert pressure on the applicant not to pick and chose but have a consistent and common approach.	This provision is not part of the legislation.

level. The EMEA may then contact the relevant MS(s) for information only.		
26	**EFPIA:** The role, rights and responsibilities of a key partner, the company/manufacturer in the process, though critical, are largely ignored in the draft guideline. This needs to be addressed.	The recommendations of the guideline cannot go beyond the provisions of the legislation. A paper on procedural aspects will be developed at a later stage.
27	**EFPIA / EuropaBio:** Given that the applicant will potentially become involved in a CHMP process it needs to have an early warning and should therefore be informed that a Member State has notified the EMEA. The intricate logistics of a compassionate use program necessitates an adequate lead-time for the company. The proposed text: *"When a Member State envisages the need to make a medicinal product, as defined in paragraph (1) and (2) of Article 83, available for compassionate use, the Competent Authority of that Member State must notify the* **applicant (at an early stage) and** *the EMEA."*	This proposal is partially endorsed. There is no legal basis requiring a Member State to inform the company that it has informed the EMEA of compassionate use provision under Art 83 of Reg. 726/2004. However, whenever the CHMP considers that there is an need to give a CHMP opinion on compassionate use, the EMEA will inform the company (see amended guideline in section 5: "information to the company") The term "applicant" will be replaced by "company". The addition of "*at an early stage*" does not bring additional information.
28	**BIA:** The company supplying the product should be informed that the competent authority is notifying the EMEA. We suggest adding some wording in respect of the company.	The guideline has been amended accordingly.
29	**EFPIA/EuropaBio:** Given the critical role of the applicant in managing compassionate use and the need to ensure the objectives of the guideline, as set out in "Section 2 Legal Basis and Purpose", are met, it is important the guideline is modified to allow applicants the option (if justified) to directly contact the EMEA to request a CHMP Opinion. Propose deleting *"Applicants should not directly contact the EMEA to request a CHMP opinion. However, companies (…)"* and replace with: *"***If justified***, applicants* **may** *directly contact the EMEA to request a CHMP opinion. Companies (…)".* **BIA:** What should companies do with respect to informing the EMEA, if they wish to do so, where there is no national application process for compassionate use, as in the UK? We would recommend amending the guideline to allow companies to request a CHMP opinion where applicable.	These proposals cannot be endorsed as this is not provided in the legislation.
30	**EFPIA / EuropaBio:** To check the eligibility for a CHMP procedure with the applicant is not sufficient. The EMEA needs to consider situations where for legitimate reasons an applicant may choose not to make unlicensed product available for compassionate use. For example, **due to limited availability** of the product. Additionally, there is no legal	The criteria for eligibility are those mentioned in paragraph 1 and 2 of article 83. The EMEA / CHMP will not require (at validation or later during the procedure) companies' commitment to supply the EU market with a medicinal product, should a CHMP opinion is given for compassionate use. Decisions for initiating compassionate use programme within the member states are left to the companies

	basis for this requirement. To generate publicly available CHMP recommendations for compassionate use in a situation where the applicant is not in a position to satisfy requests for the drug would be unethical. Modify the sentence to read: *"Before assessing an application, the EMEA/CHMP will check, after consultation with the applicant, as necessary, the eligibility of the medicinal product to the centralised procedure* **and the supply situation for the medicinal product in question. Should the applicant consider compassionate supply to be untenable at this time, they will notify the EMEA in writing and the EMEA will inform the competent authority(s) involved. The applicant may also contact the competent authority(s) involved in case further discussion is required at a national level.** *"*	and the MS.
31	**EuropaBio:** Before assessing an application for compassionate use, the applicant should be consulted. A paragraph should be added "***The MS should systematically consult the applicant before an application is submitted for compassionate use and keep him informed of the notification to the EMEA".*** Before assessing an application, the EMEA/CHMP will check…centralized procedure. ***If a CHMP opinion is needed, the EMEA/CHMP should also*** *".*	See question 30.
32	**EURORDIS**: We propose the following wording: "Applicants should not directly contact the EMEA to request a CHMP opinion. However, companies **shall**, of their own motion, inform the EMEA of compassionate use applications in the Member States, or of an ongoing procedure for compassionate use at national level. The EMEA **shall** then contact the relevant MS(s) for information".	These proposals cannot be endorsed as this is not provided in the legislation. As for CHMP opinions for MAA, the CHMP may consult patients/consumers organisations and/or experts for the assessment of the compassionate use of medicinal products.
33	**EURORDIS**: The guidelines do not include the possibility for a patient organisation to request an opinion from CHMP on a compassionate use programme intended for a given indication. Only MS, when notifying the EMEA, may indicate whether they consider that a CHMP opinion on the conditions for compassionate use would be of interest. It may happen that a patient organisation and a national competent authority may diverge on the relevance of a compassionate use. In this case, it could be interested to ask the opinion of the EMEA/CHMP, as a referral procedure.	These proposals cannot be endorsed as this is not provided in the legislation. As for CHMP opinions for MAA, the CHMP may consult patients/consumers organisations and/or experts for the assessment of the compassionate use of medicinal products.
34 - Before assessing an application, the EMEA/CHMP will check, after	**BIA:** It would be helpful to clarify this statement, as there is no compassionate use process that involves the submission of an application centrally, or for national applications to be referred to the EMEA/CHMP.	The criteria are those mentioned in paragraph 1 of art 83, i.e. the criteria of eligibility of medicinal products to the centralised procedure checked for new MAA. Details on the procedure for validation will be included in a separate paper.

consultation with the applicant, as necessary, the eligibility of the medicinal product to the centralised procedure.		
	5. CHMP OPINION	
35	**BIA**: There are some issues as to how this procedure will work in practice. Clarity is required as to who will be responsible for assessing the data package. Will there be a rapporteur/co-rapporteur as for the centralised marketing authorisation procedure? If that is the case, will they be involved in the assessment of a future (or pending) marketing authorisation application for the product in question? The timeline for issuing the CHMP opinion should be stated in the guideline to ensure timely access of the medicinal product to patients. Moreover, the adoption of the opinion for compassionate use should not delay the assessment of the MAA, which may be carried out in parallel.	Procedural aspects will be developed in a separate paper. This guideline sets the general principles.
36	**MSD / EuropaBio:** The guideline is silent as to any timeframes under which a CHMP must review and issue its opinion.	Procedural aspects will be developed in a separate paper. This guideline sets the general principles.
37	**IDIS:** The Guidance could be enhanced via the inclusion of a clear process flow diagram including time frames.	Procedural aspects will be developed in a separate paper. This guideline sets the general principles.
38 - Detailed justification should be provided to support the claim that the product meets the criteria listed in Art 83(2), in accordance with the definitions provided in this guideline.	**MSD:** It is not clear if this justification has to be provided by the MS(s) requesting a CHMP opinion, or if this will be requested from the sponsor of the compassionate use program.	Justification will be provided by the applicant and validated by the EMEA/CHMP. Procedural aspects will be developed in a separate paper. This guideline sets the general principles.
39	**EFPIA / EuropaBio**: As currently written, the section does not give any indication on the delay for issuing a CHMP opinion. This is considered unsatisfactory for the reasons detailed below. Throughout this section there is a notable lack of timelines associated with the opinion process. This is not considered acceptable, as this would potentially delay compassionate access whilst Member States await the	Procedural aspects will be developed in a separate paper. This guideline sets the general principles.

	outcome of the opinion request. Details of timeline are of course essential so the applicant can plan the management of the process (which is likely to coincide with marketing authorisation application preparation and/or assessment). It is essential that there is no delay in providing urgent treatment to seriously ill patients. The delay to patients could in part be mitigated by the guidance stating that individual patients should not be delayed in seeking timely access and the use of nominative national systems must be used whilst awaiting an opinion. We believe it should be possible to adopt an opinion within 30 to 60 days, depending on the timing of the Member State notification to the EMEA relative to a CHMP meeting. In any event, a maximum delay has for transparency reasons to be defined. Add new section after the section entitled "Documentation to be supplied": *"**Timeframe for Submission of Data by Applicant and CHMP Assessment*** *Taking into account the interests of - and expectations from - the patients and health care providers concerned, the CHMP opinion shall not exceed 60 days further to the notification from the Member State or the Applicant to the EMEA and to a 5-day period of acknowledgment of receipt given to the EMEA. This timeline does not take into account any clock stop due to the need for any additional data requested by the CHMP.* *This timeframe is intended to be a maximum duration and may be shortened following consultation with the competent authorities involved and the applicant if this is considered warranted by the urgency of the request and the stage of assessment by the CHMP (if applicable).* *Member States are reminded they are able to use their national compassionate use systems to satisfy urgent requests whilst awaiting the outcome of the opinion.* *Guidance will be made available regarding timelines for when the EMEA will initiate the request to ensure Day 60 falls within CHMP week. To streamline the process there is no validation phase as the CHMP can ask for additional data during the review and there will be guidance on the basic documentation requirements."*	
40	**EFPIA / EuropaBio:** 1/ The EMEA may want to consider situations where a medicinal product is developed **in parallel for multiple indications**. Different Member States may well make requests for compassionate use opinions in different disease indications. The adopted CHMP opinion on conditions for use should be applicable to a given indication. We therefore propose a modification to clarify this point. 2/	1/ This proposal has been included in the revised guideline. 2/ **The CHMP opinion on compassionate use will not prevent from the assessment of safety and efficacy of any future marketing authorisation application**." This is redundant with the information provided in paragraph 3: "Compassionate use versus clinical trials".

	Further, it should be explicitly stated that the **CHMP opinion on the compassionate use programme is in no way a substitute for the assessment of safety and efficacy of any future marketing authorisation application**. 3/ Another consideration is whether the guideline should indicate the process, which can be undertaken **if the applicant company does not agree with the terms of the CHMP opinion**. Modify the first paragraph to read: *"Further to the notification of a Member State, the CHMP may adopt an opinion on the conditions for use, the conditions for distribution and the patients targeted for compassionate use* **in a given therapeutic indication**. *CHMP opinions are not binding on Member States; however, Member States shall take account of any available opinions.* *Adopted opinions are applicable to any subsequent notifications from another Member State concerning the same programme* **for the same therapeutic indication**. **The CHMP opinion on compassionate use will not prevent from the assessment of safety and efficacy of any future marketing authorisation application."**	3/ The opinion on compassionate use does not lead to the adoption of a Commission decision with binding legal effects. It is a scientific opinion, which MS must take into account. The assessment and content of the opinion is also very different from the assessment and content of an opinion concerning the granting or subsequent regulatory steps in a MA. Because of this fundamental difference between the opinions adopted in the framework of MA and in the framework of CU, the rules of Article 9 of the regulation do not apply in the framework of compassionate use. However, based on paragraph 4 of article 83: "*When compassionate use is envisaged, the CHMP, after consulting the manufacturer of the applicant, may adopt opinions* (…)", and for the sake of good administrative practices, hearings of companies, if requested, could be organized during the procedure (see last paragraph added at the end of section 5 of the guideline).
41	**EURORDIS**: Even though the legislation states that *Member States shall take account of any available opinions* (article 83 paragraph 5), it is our interpretation that the EMEA opinion should be accepted by MS (as MS are represented in the CHMP), to ensure consistancy of the centralised procedure in all its aspects. **In case a MS would not follow the EMEA opinion, it should explain and justify its divergent opinion**. This is to ensure equal access to compassionate use programmes for patients, whichever their state of residence.	The EMEA acknowledges the concerns expressed by patients organisations. However, there is no legal basis in this regulation to harmonise compassionate use via CHMP recommendations. Article 83 only aims to favour a common approach and facilitate access to patients.
	Grounds for assessing a request for compassionate use	
42	**EFPIA / EuropaBio:** We do not agree to the proposal that an automatic consideration to a **CHMP opinion may be required if more than one member state initiates a cohort compassionate** access program for a medicinal product. This is of concern as currently **there is no legal provision for this** and it would appear to be an unnecessary procedure. Member states must inform the EMEA of compassionate use programs according to article 83(3) but are not obliged to seek a CHMP opinion on the matter (as reflected in the text of the guideline). Nor does article 83 convey the power of automatic referral for opinion by the CHMP under any circumstance.	The regulation does not specify on which basis the CHMP could trigger an assessment and give an opinion compassionate use. The proposal is that notification from more that one member state on their use of Art 83 for the same compassionate use programme, or one notification sent with a request for opinion, would be considered for assessment and opinion by the CHMP. Notifications from more that one member state would be considered for assessment by the CHMP to facilitate a common approach (see recital 33 of Regulation 726/2004) to be followed as regards the conditions for compassionate use, conditions for distribution and target population.

	Although the **referral to the CHMP**, under the circumstance of two member states initiating cohort programs is not definite, it is unnecessary. If a member state were unsure or concerned about the compassionate use of a medicinal product (regulated under national member state law) they would seek CHMP opinion on the matter. Ultimately as any opinion is not enforceable on the member states it seems the outcome of such a "forced referral" would potentially not be used, as the member states did not feel it was required in the first place. However of more concern is that it may serve to prevent access to patients where member states feel obliged to **delay a national decision** on compassionate use pending a "forced referral" for an opinion. It is also an absolute requirement for the CHMP to assure themselves the applicant is confident with regards to supply. Replace the indent "If more than one Member State (…) by the following: ~~*If more than one Member State have notified the EMEA of their use of Article 83 for the same compassionate use program, without an explicit request for a CHMP opinion, the CHMP will consider, in the interest of patients, whether there is a need to give an opinion.*~~ - The applicant has been consulted and agrees that appropriate supply is not foreseen to be of concern."	Before starting an assessment, the CHMP will consider whether this assessment and an opinion would be of public interest. In proposing this approach the CHMP does not believe that this can be equated with the concept of a forced referral, as it is not consistent with the intention of the legislation provision. CHMP opinions on compassionate use are not binding on the Member States and should not delay any parallel national decisions. Considering the comments received, the CHMP have re-discussed the criteria and confirmed the appropriateness of the approach proposed in the draft guideline.
43	A Member State may notify the CHMP without first making its own assessment of the request for compassionate use. The CHMP may also request additional data from the applicant. The process described leaves open the possibility of much variability, both in terms of the procedure to be followed (Member State's assessment or not) and data to be provided. As it appears that the CHMP will not appoint Rapporteurs for assessment of the compassionate use, it seems preferable that the notifying Member State(s) should conduct their own evaluation before approaching the CHMP, to avoid unnecessary prolongation of the CHMP assessment. There should also be greater clarity around the additional information that may be requested from the applicant, to ensure consistency of assessments. Consider additional wording recommending that the notifying Member States makes a preliminary assessment and to clarify the meaning of "additional information".	Recommending that the notifying Member States makes a preliminary assessment is not appropriate as the MS legislations defer and this might not be compatible with the national handling of compassionate use in practice. The data reviewed by the CHMP should be sufficient to define the conditions of use and the target population for the product. The review of data and the request for relevant information will be done on the case by case basis. More details will be included in the paper on procedural aspects.
	Documentation to be supplied	
44	**EFPIA:** It appears from the text that "any available data" will be provided to the EMEA by the Member State(s). However, to clarify the roles and responsibilities, this could be made more explicit. Change to: "*If*	See amended wording of the guideline.

	a CHMP opinion is to be adopted, the CHMP should use any ~~available~~ relevant *data* that can be provided by the Member State(s) *and ~~the~~* any *existing Member State's assessment ~~if available~~, on the quality, ~~the~~ safety and ~~the~~ efficacy".*	
45	**EFPIA:** Could the request involve an "oral explanation"?	See question 40. Procedural aspects will be part of a separate document. This guideline focuses on the main principles only.
46	**EFPIA / EuropaBio:** In our view, the data requirements outlined should not exceed the data required by MS under existing CU programmes. It must be more clearly stated that there is no expectation on an applicant who is currently preparing or has submitted a MAA to have to initiate the preparation of a separate submission. To aid this it would be helpful to detail the types of documentation, which are commonly available at different times in the development process. A proposal is made in the opposite column for these documents that could reasonably be assumed to be available at defined time points in development: *"(...) the comprehensiveness of which will depend of the stage of development of the product* (see below for list of documents expected to be made available in a submission)*. The CHMP may request additional data to the applicant.* **Documentation Expected to be Readily Available at Certain Development Stages** **After Phase II, Prior to Completion of Phase III** • Investigator Brochure including summaries of completed clinical trials and a review of the safety information and dose justification. • Clinical trial application including the IMPD and the rationale for the Phase III trial for the indication similar to that being considered for compassionate use **Prior to Submission of a marketing authorisation application, Post Completion of Phase III** As above for after Phase II with the addition of preliminary analyses from the Phase III trial if available. Detailed justifications should be provided to support the claim that the medicinal product meets the criteria listed in Article 83(2), in accordance with the definitions provided in this guideline."	This comment will be considered in a separate paper on procedural aspects.
	Update of opinion	
47	**EFPIA / EuropaBio:** - Editorial comment to help clarify that MS do not trigger an Opinion update but a request from a MS may mean an update is needed: *"Updates may be* necessary following a *Member State(s) request,*	The current wording is considered appropriate and reflect the idea that no update can be made unless required by a MS, as per the interpretation of the EC.

	or whenever appropriate, based on available data and/or data provided by the Member State(s) or applicant." - Add new sentence to clarify the CHMP's role in managing multiple Member States' requests: *"The CHMP shall manage multiple, parallel or serial Member State requests in order to avoid excessive numbers of CHMP Opinion updates*."	Comment endorsed.
48	**BIA:** It is our view that the company should be given the opportunity to comment on the opinion prior to its issue and provide supplemental information if necessary to ensure that the most accurate and appropriate information is considered. The guideline does not provide for any appeal by the company if the CHMP opinion is unfavourable. It should be clarified whether this will be available for a request for compassionate use. Additionally, the guideline should cover the situation in which a company may wish to initiate an amendment/update to an opinion. It would be helpful to clarify when it would be considered appropriate to update the CHMP opinion.	See question 40.
49	**BIA:** This section implies that MS will at some point collect and assess data on compassionate use on the product. However it is unclear to us if and how many MS actually do this. We would welcome clarification with regard to the data that an applicant would be expected to provide and the format in which to be provided. The data package supplied should not constitute a "mini marketing authorisation application", as this would place unnecessary burden on both the applicant and the CHMP and could delay the adoption of an opinion.	It is assumed that when they notify the EMEA, MS may have already collected and assessed data following a request for compassionate use, or in other situations, MS(s) may not have yet collected and/or assessed any data based on national legislations. The CHMP would use any relevant data provided by the member state(s) or available in the public domain, and any existing MS(s)' assessment(s) on the quality, the safety and the efficacy of the product. The CHMP may request, after consultation with the company, additional data from the company to allow the evaluation of the conditions of use of the medicinal product, for the intended target population, in the context of compassionate use.
	Pharmacovigilance	
50	**ECPC**: 1/ We recommend that all such CHMP assessments and updates for compassionate use are published and publicly available in a Register. 2/ Valuable pharmacovigilance data can be gathered during the compassionate use phase to supplement the Clinical Trials data.	1/ See question 54. 2/ In accordance with Article 83(6), the pharmacovigilance rules and responsibilities are those defined in Articles 24(1) and 25, which are the provisions that apply for centrally authorised medicinal products. There are no additional requirements for product under compassionate use.
	6. FROM OPINIONS ON CONDITIONS OF COMPASSIONATE USE TO OPINIONS ON MARKETING AUTHORISATIONS	
51	**ECPC:** The continuous supply during the period between granting of the centralised MA and placing the product on the market is critical. It would	The need and responsibilities for continuous supply during the period between granting of the centralised and placing the product on the market are stated in the

	be unethical to deny the patient access to the product because of administrative or pricing and reimbursement delays.	guideline.
52	**BIA:** We would welcome clarification regarding the expectations of patients for continued access to the product under a compassionate use programme should an MAA be withdrawn or rejected or if an MAA is not filed with the EMEA.	These aspects will be further detailed in a separate document on procedural aspects.
53	**EFPIA:** In order to avoid any confusion it is proposed to clarify when referring to Compassionate use Opinions as opposed to a marketing authorisation Opinion: *"Once a medicinal product has been authorised, updates of* compassionate use *opinions are no more required."*	This comment has been included in the revised guideline.
54	**MSD:** MSD believes that the updating of an opinion on the conditions for CU after the CHMP opinion for a MA has been adopted is over administrative. It takes now at the maximum 67 days to issue the binding CD. We fear that the timeframe for updating the compassionate use opinion, which is not defined here, will increase the administrative burden and tie valuable Agency resources without patient benefit. Please delete the requirement to update the compassionate use CHMP opinion after adoption of the MA CHMP opinion.	Updates of CU opinions may be triggered by MS(s) on their request, or whenever considered appropriate by the Committee based on available data and/or data provided by the MS(s) or companies (e.g. new safety data). ▪ Art 83 concerns making medicinal product belonging to the categories referred to in Art 3(1) and (2) of the regulation available for compassionate use to patients "who can not be treated satisfactorily by an authorised product". ▪ Before the Commission Decision is granted, the recommendations of the CHMP opinion (i.e. SPC, EPAR) are not published and therefore only a cross reference to the summary of opinion (limited information) can be made. ▪ The target population of the CU opinion and the indication of the MA opinion are likely to be different. For the three reasons mentioned above, the CU opinion cannot be superseded by the MA opinion. - However, once a medicinal product for which a CHMP opinion on the conditions for compassionate use exists, has received a CHMP opinion for a marketing authorisation, its opinion for compassionate use may be updated taking into account the MA opinion, where appropriate (e.g. safety recommendations). - Finally, once a medicinal product has been authorised updates of compassionate use opinions are no longer required and reference is made to the relevant information published on the EMEA website about the authorised product.
	7. TRANSPARENCY	
55	**EFPIA / EuropaBio:** - The confidentiality of data assessed must be fully respected and the published opinion must be limited to the final recommendations for compassionate use without detailing commercially sensitive information.	The final recommendation will be published in a form of summary of opinion and/or summary of product characteristics. Extensive EPARs will not be published and companies will be consulted to ensure that commercially sensitive information is removed before publications.

	- The procedure only applies CU for groups of patients (e.g. "cohort") and not to use on a named patient basis. A number of MS only allow CU on a named patient basis, so opinions adopted by the CHMP will have no relevance in those MS. Consideration should be given to whether the distinction should be made more explicit. Concretely, MS in which only named patient use is allowed could be listed for each of the CU opinions published by CHMP (but also in the accompanying Q&A document). This could help to avoid creating any false hopes.	This approach seams complex based on the number of various legislation and possible changing legislation. It might not be accurate to state in writing, on the EMEA website, which country can legally implement or not the CHMP recommendations, which could be misleading and suggest that these country have decided, based on scientific grounds, to follow the CHMP recommendation and initiate a programme. The decision of the MSs to follow CHMP opinion for compassionate use is left to their discretion.
	8 . FEES FOR COMPASSIONATE USE	
56	**BIA:** It is unclear to us as to why should the sponsor of a MAA pay for a CHMP compassionate use opinion when it is the Member State that initiates the request for such an opinion. Moreover, this requirement discriminates against "development only companies", as they are unlikely to be the MAA applicant. The product will have been licensed out to another company, which will apply for marketing authorisation. It would be helpful to clarify whether the SME fee reduction apply to Compassionate Use opinions.	- Fees shall be paid by companies. Licensing arrangements between companies are not relevant to this guideline. See also question 57. - Companies that have been assigned SME status by the Agency are eligible for a 90% reduction in the scientific service fee (which includes opinions on medicinal products for compassionate use), see Commission Regulation (EC) No 2049/2005 which lays down the rules regarding the payment of fees to, and the receipt of administrative assistance from, the EMEA by SMEs. The specific provision is in Article 7.1(c). A link is attached to the Commission Regulation http://europa.eu.int/eur-lex/lex/LexUriServ/site/en/oj/2005/l_329/l_32920051216en00040007.pdf
57	**EFPIA / EuropaBio:** We would as a matter of principle question the legitimacy of a fee levied to a company for a CHMP opinion, which has been requested by a National Competent Authority. Further procedural information is requested regarding the payment of this fee. Will the fee be payable up front (or just recouped by EMEA at the time of payment of the MAA fee) and will further fee's be requested for updates of opinion? Furthermore clarification is requested regarding the reimbursement if, • following the generation of additional safety and efficacy data the applicant company decides not to file a centralised MAA or, • If the applicant decides to file the MAA via a route other than centralised is also requested (i.e. products falling under the optional scope of the centralised procedure). It is stated the CU use fee will be deducted from the MAA fee "where such application is submitted **by the same applicant**".	See question 56. Fees will be payable on receipt of the invoice sent by the EMEA 45 days after the start of the procedure. It is not foreseen in the legislation that fees are payable for updates of opinions No reimbursements are foreseen in the legislation. For medicinal products belonging to the categories referred to in Article 3(2) of Regulation (EC) No 726/2004 (the so-called "optional scope"), the EMEA (and the company) shall only be notified when the eligibility to the centralised procedure has been already confirmed by the CHMP.

	We understand that this wording is taken from Council Regulation 297/95 as amended, however, such a requirement is inappropriate and both the Regulation and Guideline need to be amended to remove this wording. It is also proposed to amend Council Regulation 297/95 as amended, in a similar way. The requirement is inappropriate as it is possible that due to pharmaceutical company mergers, commercial contracts, etc. the initial compassionate use applicant may not be the same as the marketing authorisation application applicant and we need to avoid a situation where the compassionate use fees are unable to be deducted from the initial marketing authorisation application.	Polices and Procedural aspects to facilitate the deduction of the fee for compassionate use from the fee payable to the EMEA for a MAA for the same medicinal product will be further detailed in a separate document.

QUESTIONS AND ANSWERS DOCUMENT		
Line no. + para no.	**Comment and Rationale**	**Outcome**
General	**EFPIA**: General comment: This brief document is poorly written and an odd mixture of legally oriented explanations (e.g. Questions 2, 5) and patient-oriented, lay language communication (e.g. Question 4). Unfit for its purpose, we would recommend it be thoroughly revised.	The Q&A has been reviewed in line with the comments received and the revised guideline.
Question 1	**EFPIA**: The first sentence is meaningless and incorrect. The second sentence '…at the level of Member States…" is probably incomprehensible to a lay person. Revise as follows: *"*The EU legislation requires medicinal products to be authorised by either the European Commission (centralised procedure) or relevant national Competent Authorities before they are marketed in the Community." (…) "Compassionate use is another option, whereby under certain conditions promising medicinal products may be made available to patients before they become commercially available. The actual rules and conditions for compassionate use, however, vary between the European Member States*"*	The Q&A has been reviewed in line with the comments received and the revised guideline.
Question 3	**EFPIA**: To avoid any confusion with marketing authorisation procedures, we would recommend to clarify that what is being described is EMEA's role in assessment of conditions for compassionate use. Only products for life-threatening disease are mentioned. Reword question as follows: *"What are the medicinal products that can be reviewed by the EMEA* in view of compassionate use recommendations?" Revise 1st sentence: *"*The EMEA can only perform a compassionate use review of medicinal	The Q&A has been reviewed in line with the comments received and the revised guideline.

	products that are *(…)"* Proposed to change last sentence to: "(…) *aiming at treating a group of patients suffering from a life threatening disease* or a chronically or seriously debilitating disease". …or possibly: *"(…)* a chronic or seriously handicapping disease*…"*	
Question 4	**EFPIA**: Lacks in clarity. Change to: *"If appropriate, your doctor may contact the health authority that supervises compassionate use programmes in your country."*	The Q&A has been reviewed in line with the comments received and the revised guideline.
Question 5	**EFPIA**: It is unclear whom this Q&A is addressed to. In any event, we doubt that it can as written be understood by the majority of patients. If the intention is to redirect the patient/physician to the national health authority, the Q&A must be clearer on this point. Reword title: **"Are compassionate use programmes available in all the European Member States?"** Replace the two sentences by: *"*No, compassionate use programmes are currently not available in all Member States and the recommendations made by the EMEA are no legal obligations for the Member States. Your doctor can verify with your national health authority if a compassionate use program is possible*."*	The Q&A has been reviewed in line with the comments received and the revised guideline.
Question 6	**EFPIA**: Avoid any possible confusion with CHMP opinions. Change 1st sentence to: *"*The name of the product which has undergone an EMEA compassionate use review will be published on the EMEA website*."*	The Q&A has been reviewed in line with the comments received and the revised guideline.