17th February 2010
EMA/CAT/106109/2010
Committee for Advanced Therapies (CAT)

Overview of comments received on 'Procedural Advice on the Provision of Scientific Recommendation on Classification of Advanced Therapy Medicinal Products in Accordance with Article 17 of Regulation (EC) No. 1394/2007' (EMA/CAT/99623/2009)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	ROCHE
2	The North-East England Stem Cell Institute (NESCI) and Newcastle Clinical Trials Unit (NCTU) Sender: Dr Sebastian Sethe

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

1. General comments – overview

Stakeholder no. *(See cover page)*	General comment (if any)	Outcome (if applicable)
1.	<u>3. Scope</u> It is not fully clear if the procedure can also be used i) to get recommendation on the ATMP subtype (GT, sCT, TEP). ii) to confirm if the product would be a ATMP although it is clearly a medicinal product The current text in the regulation talks about "questions of borderline with other areas such as cosmetics or medical devices". Possibility to get clarification for all issues on classification related to advanced therapy is supported, since the definitions leave room for interpretation. It is important for the sponsor to know the regulatory class/ subcategory of the medicinal product under development, to know which guidelines and registration procedures to follow. <u>Timelines</u> The procedure seems to take in practice at minimum 90 days (plus the extra option of the CAT, in addition to the applicant, to propose a clock stop for consultation).	Agreed Clarification provided in section 3 'Scope' Timelines of the procedure revised: (See revised flowchart for the procedure) Timeline for Pre-submission activities reduced to 15 calendar days. Applicants can submit the letter of intent and the request for ATMP classification directly at Day -15. CAT coordinator will be appointed at Day 0 (same timepoint as start of procedure)
	How is the potential consultation of WPs, competent authorities and NB carried out and how long does it take? Those consultations should not lead to clock stops as a rule as it now looks like under Section 5, day 30. According to the regulation the recommendation should be given within 60 days after receipt of the request.	CLARIFICATION PROVIDED and how the consultation with WPs is foreseen. It is not expected that competent authorities for devices / notified bodies will be consulted during the classification procedure. Comment taken into account: Section 5.2 revised. When additional information is required, the clock will be stopped in consultation with the applicant. When possible, the consultation with WPs will take place during the procedure and will not lead to clock stop as a rule

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	The "Request Form and Briefing Information" template refers to "submission dates listing". However, it is not stated, how frequent are the planned submission dates of the letters of intent. The steps listed above should not lead to unnecessary long procedure.	CLARIFICATION PROVIDED: Dates of submissions are set up on monthly basis.
	ITF, EC, NB, CA and WP view What happens if ITF or EC/NB/CA/WP disagrees with the CAT recommendation? Is the sponsor informed about the divergent views?	WPs are not consulted on the outcome of the ATMP classification for which CAT is responsible. They may provide information/advice at the request of the CAT that will enable the Committee to reach a conclusion on the classification.
	ITF ITF is responsible for peer-review of the classification recommendations and is said to have a broad expertise (Section 4.5. of the guidance). Will the list of the members of the ITF be public?	The ITF provides regulatory, legal procedural and scientific support to the CAT during the procedure. The European Commission should be consulted in accordance with the provisions of Article 17 of Regulation (EC) No 1394/2007 and the comments from the EC are taken into account by the EMEA and CAT coordinator when finalising the scientific recommendation, integrating all comments received. The CAT will thereafter adopt the scientific recommendation which is then provided to the applicant. There might be situations where the Commission is also consulted to seek legal and regulatory clarification before CAT adopts its draft recommendation at Day 30. This is also reflected in the updated text.
	Reference to definitions Because of complexity of the current and amended legislation on definitions of the ATMPs, it would be appreciated if the valid definitions of also GTPM and sCT were described directly in the final classification documents.	The ITF is composed of Agency's staff with scientific, regulatory and legal competence and experience, identified to support diverse aspects of Innovation. The membership is not permanent by appointment from management taking in to account competences needed and workload. The ITF members in charge of supporting specific procedures are made known to the applicants. A list of ITF members is not published. Definition is included in the Request form template.

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2.	A major theme in Advanced Therapies regulation is the difficulty in clearly ascribing the ATMP designator to complex, innovative products. This is recognised by Regulation (EC) No 1394/2007 in its Article 17. As supported by Recital 24 to the Regulation and other evidence, the aim of this provision is to provide innovators with a process that provides them with reliable advice within a clearly defined timespan. It also aims at a situation where innovators and regulators are in frequent, productive dialogue. The draft EMEA procedures go some way in implementing these requirements, and meeting these aims, but risk failure in some respects. Notably, 1. the timelines provided for are stretched to the maximum allowed rather than flexibly adjustable. 2. a pre-evaluation period and ill-defined “Clock-Stop” provision threatens to extend the period of uncertainty originally envisaged to take no more than 60 days to 105 days and beyond. 3. the form that applicants are required to submit demands up-front the kind of detailed interpretation of the law that innovators are seeking clarification on from EMEA . These and other items addressed in the specific comments section need to be addressed if CAT seeks to establish a reputation as a responsive and responsible partner in navigating the regulatory uncertainties in this emerging area. The provision of proactive rather than reactive advice and guidance	1.Timelines of the procedure are revised: (See revised flowchart for the procedure) Timeline for Pre-submission activities reduced to 15 calendar days. Applicants can submit the letter of intent and the request for ATMP classification directly at Day -15. CAT coordinator will be appointed at Day 0 (same timepoint as start of procedure) 2. The comment has been taken into account: Section 5.2 revised. When additional information is required, the clock will be stopped in consultation with the applicant. The maximum clock stop is 1 month (See revised flowchart for the procedure). The possibility to stop the clock is still maintained for the benefit of the Applicant when after the discussion at CAT at Day 30, important additional information is needed to conclude on the classification. 3. The procedure is implemented in such a way to be sure that it ‘allows the applicant to be heard’. It is their opportunity to put forward their position with respect to their proposed classification, and it would be up to the CAT to justify why they cannot agree with the applicant, allowing eventually an oral explanation (would not be possible if the applicant did not provide any opinion). In the applicant’s interest, they need to prepare their position in a structured way and need to reflect on the very same

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	including 'thought experiments' would also be of great assistance especially while case studies as per Art.17(2) are still unavailable. In general, the fact that EMEA is consulting stakeholders on this process is a welcome sign that the regulator is alive to the necessity to shape this emerging regulatory landscape responsibly. This remains a critical time in the process as CAT has only recently been convened and 'first impressions' are formed. Dialogue between the Agency and innovators will be frustrated where institutional structures and procedures signal an unresponsive 'structure over substance' approach. This would be especially detrimental in Art.17-type enquiries that are intended to be providing assurance and clarity to individual innovators and the sector and where safety considerations are not yet at the forefront.	points that the CAT will be discussing the classification. This adds to the transparency of the process and gives guidance to the applicant on how to identify the difficult areas of interpretation. Also, the applicant would also need to understand the definitions in order to provide the relevant supportive scientific data for each elements considered. Not considering the definitions when applying would lead to lenghtening the procedures by increasing the number of non-validated request due to insufficient data needed for the CAT to make a conclusion, as seen in the previous classifications.

2. Specific comments on text

*A note on line numbers: as the consultation document does not give line numbers, and indeed the text is not always formatted in lines, Section and page numbers are given for the avoidance of doubt.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
Sect. 1, pg 3	2	**Timing of other EMEA interactions** (Sect.1, page 3) **Comments:** It is not clear why ATMP designation should impact on the considerations relevant to a paediatric investigation plan (or waiver) or orphan drugs designation. In fact, clarity about the need for a PIP or orphan drug status in the pre-submission stage may be useful just as early in the development process as clarity about ATMP designation. Consequently, it would be helpful to clarify, that the recommended order is not a strict requirement. **Proposed change (if any):** "This procedure is recommended, but not required, to be done before scientific advice, Paediatric Investigation Plan (PIP), certification, orphan drug designation and submission of a Marketing Authorisation."	Agreed. Text revised as follows: "The ATMP classification allows applicants to clarify, in case of doubt, the classification of their product and, if needed, it is recommended that this is done before submission of request for scientific advice/protocol assistance, Paediatric Investigation Plan (PIP) evaluation, certification of quality and non-clinical data for SMEs developing ATMPs, orphan drug designation and Marketing Authorisation Application (MAA)."
Sect. 3, pg 3	2	**Statement on scope** (Sect 3, page 3.) **Comments:** The intention of this statement is presumably to ward off unnecessary or frivolous applications, however in practice this provision may lead to confusion at this point in the guidance because of its perceived circularity. **Proposed change (if any):**	Agreed. Text amended as per 'Alternative option'.

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		<u>Preferred</u> "The request for scientific recommendation on classification procedure is available only for products for which there are doubts as to whether or not they fall with the definition of ATMP." <u>Alternative (less preferred)</u> "The request for scientific recommendation on classification procedure is available only for products based on genes, cells or tissues, as starting material, active substance or finished product including when combined with medical devices, bio-materials, scaffolds or matrices, and for which there are doubts as to whether or not they fall with the definition of ATMP." In both cases, this would be an opportune place to link to further advice and guidance on this matter.	Agreed. Section on definitions inserted in the document and cross reference to the relevant definitions inserted in section 3.
Sect 4.1, pg 4	2	**<u>The responsibility of CAT vs. EMEA at large</u>** (Sect 4.1 page 4) **Comments:** This provision points to a potential mis-interpretation of the legal basis. Art.17 states that the applicant may request "(…) scientific recommendation of the Agency (…) " and that "The Agency shall deliver this recommendation (…)" Recital 24 confirms that "The Committee for Advanced Therapies, with its unique expertise, should have a prominent role in the provision of such advice" Consequently, the intended framework is that CAT provides advice to the Agency but that the final recommendation is issued by EMEA entire, rather than just by CAT. This has implications for positioning the recommendation in its legal context, e.g. in a Judicial Review.	All scientific committees are part of EMEA The legal status of the Recommendation is not different if is an 'EMEA recommendation' or a 'CAT recommendation'.

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		Proposed change (if any): The CAT is the committee responsible for the provision of scientific advice on classification.	Not accepted: Scientific Advice is a specific procedure involving the Scientific Advice Working Party (SAWP) different from the ATMP classification. According to Regulation (EC) No 726/2004 the SAWP is established as a standing working party of the CHMP with the sole remit of providing scientific advice, particularly regarding the development of new therapies.
Sect.4.5, pg. 4	2	**<u>"Peer review" by the Innovation Task Force</u>** (Sect. 4.5, pg. 4) **Comments:** Innovation Task Force is a non-statutory body whose existence or remit is not defined in legislation. Of particular interest is the statement that ITF activities are to be considered "peer-review". Presumably, in this context, this is to mean that ITF will act as a 'peer' to CAT. However this form of words has a particular typical connotation in ATMP-related research usually including recruitment from academia and often voluntariness and anonymity. The words "peer review" are not mentioned once in the statement on mandate (EMEA/20220/06) or in the SOP on briefing meetings and regulatory advice (SOP/H/3044/ SOP/H/3138) regarding the ITF. If ITF were to employ mechanisms of peer review in order to assist CAT in their advice or EMEA in their recommendation, these processes should be made more transparent including a remit for the applicant to exclude competitors from the review process and to ensure confidentiality. **Proposed change (if any):** <u>Preferred</u> RE-consider and clarify the role of IFT and provide more information than just a weblink.	Following clarification has been included in the Procedural Advice: "The Innovation Task Force provides operational, scientific, regulatory and legal support to the CAT, contributing to the preparation of the draft classifications in the light of previous experience and newly emerging scientific aspects." The specific tasks of the ITF have been described.

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		<u>Alternative (less preferred)</u> The Innovation Task Force provides further advice (including scientific, regulatory and legal competences) to CAT of the draft scientific recommendation.	
(1) Sect.5 pg.5 para "Day -30" (2) Sect.5 pg.5 para "Day -Day -15" points 2 and 3 (3) Sect.5 pg.5 para "Day -Day -15" point 4 (4) Sect.5 (5) Sect.5 pg.5 para "Day -Day -15" point 3 Sect.5 pg.5 para "Day -Day -15" point 4	2	**<u>Pre- evaluation checks</u>** **Comments:** The regulation prescribes a period of "*<u>within</u>* 60 days" from the request for clarification to the issuance of a recommendation. Time limitations for regulators are typically included in legislation to ensure that there are no undue bureaucratic delays and to give a clear indication of the time (and time related cost) implications of the regulatory process. It is legitimate to establish certain administrative requirements that enable regulators to meet these timelines, but it is not legitimate to install administrative barriers that effectively extend the maximum deadline. Consequently: 1. The requirement of submitting a letter of intent "at least one month before the start of the procedure" is a potential breach of Regulations 1394/2007 letter and spirit. It is completely unclear from the documentation provided in the consultation document why a period of 30 days is required to appoint EMEA and CAT coordinators. Instead, EMEA could designate a coordinator immediately upon receipt, and a CAT coordinator could be nominated either on a fixed schedule or via in-between-meetings-communication. 2. Stakeholders need to be better informed about what a "checking step" entails – does this relate only to whether administratively essential information such as the applicant's address is	1. See revised flowchart for the procedure. Letter of intent could come together with the submission of the request. But leave the possibility for letter of intent to come earlier. 2. Clarification provided.

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		provided? If not, what other considerations apply? 3. preparation of a briefing note is not a legitimate part of the 'pre-evaluation' period. 4. it is very unclear why a "check" must always take a fixed period of 15 days. **Proposed change (if any):** (1) "Wherever possible, a letter of intent should be sent to the CAT Secretariat ideally some weeks ahead of the request, so that the request can be processed more effectively." (2) "The EMEA Coordinator checks the adequacy of the request, such as (…) If major additional information such as (…) is needed, the procedure is initiated at the next starting date, provided that the required information is made available." (3) Delete the following and copy to "Evaluation by CAT": "The EMEA Coordinator prepares a briefing note on the points for consideration by the CAT Coordinator (e.g. regulatory, legal and scientific issues, proposal to consult a Working Parties/Competent Authorities/Notified Body if needed)". (4) State "up to 15 days" throughout in relation to the "Checking Step".	3. Not accepted: briefing note is part of the validation and support to CAT coordinator. 4. This is a minimum time needed for EMEA and CAT to received the request, to inform the CAT (premail) and to appoint the EMEA and CAT coordinators. Additionally, this 2 week timeline will allow to establish a dialogue with the applicant and facilitate a successful validation and outcome of the ATMP classification 1. Agree in principle. 2. Agreed in principle. Section 5.1 has been amended. 3. Not accepted: briefing note is part of the validation and support to CAT coordinator. 4. Not accepted: see explanation above.

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(2) Sect.5 pg.5 para "Day -Day -15" points 4 and Sect. 5 entire	2	**<u>Submission Dates and CAT meetings schedule</u>** **Comments:** The procedure references a "start date" and "submission dates" – but it is quite unclear what this list comprises, who determines what dates should be made available, how many submission dates there will be per month/year and what the statutory justification of having a limited range of submission dates is. All references to time points are presumably aimed at CAT meeting dates. However, that is not clear from the text, and not endorsed in the Regulation. It is apparently the intention that there will be three CAT meetings regarding any particular request. However, it not obvious why this should be necessary or required. In theory, a single meeting could suffice, where the CAT opinion is noted and then collated with other views such as the EC and the ITF. The first, 'receiving meeting' is apparently not set up to review the request in any substantial way. If detailed instructions were to emerge from that meeting, it is unclear why a period of 30 days would need to elapse for a follow up. If in fact the first meeting were meant to be more substantial, it could be identified at that juncture if further information from the applicant was required. Also, the 'final meeting' of CAT is scheduled on day 60. However, "the Agency" (not CAT) "shall <u>deliver</u> this recommendation (…) <u>within</u> 60 days after receipt of the request ". "Delivery" strongly implies that notification of the applicant is required on the same day. It is not clear	Clarification has been provided in the text: See responses above and revised timelines for the procedure.

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		why a final meeting should be necessary given that CAT has next to no remit or time to introduce further changes to recommendation on Day 60. **Proposed change (if any):** And adjust the timetabling so that 60 days is not the minimum time and that only one or two rather than three CAT meetings are required. e.g. Delete “at the next start date” Delete “The procedure starts according to the list of submission dates.”	See responses above and revised timelines for the procedure.
Sect 5, Page 7, Textbox titled “Day 30” / “Day 40” respectively	2	**<u>Timing of Consultation with the EC</u>** **Comments:** Regulations proscribe that EMEA shall deliver its recommendation “after consultation with the Commission” – however, European Law does not establish that the EC must be consulted on a final draft in this matter. Also, presumably feedback from the EC is likely to focus on slightly different aspects, so any advice it gives could be incorporated at early stages **Proposed change (if any):** It may be expedient for timing purposes to consult the EC earlier in the process.	See responses above and revised timelines for the procedure. Proposed change is not agreed: the consultation of EC (in line with art 17§2) can only be on basis of the draft recommendation agreed by CAT at Day 30. However, it is proposed that the recommendation is already adoped at Day 30 pending consultation with EC. This will allow, when possible, to conclude the procedure already at Day 40. In exceptional cases, legal/regulatory clarification can be sought from EC before the D30 adoption of the recommendation. This will not abolish the need the EC consultation on the draft scientific recommendation.
Sect 5, Page 7, Textbox titled “Day 30: Request for	2	**<u>Clock Stop and the involvement of third parties</u>** **Comments:** There is no ‘Clock Stop’ provided in legislation, but such	

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additional information"		a provision seems sensible if (and only if) the pre-procedural checks can be kept to a minimum as outlined above. However, 'Clock Stop' must be related to seeking further clarification from the applicant, they cannot involve the delegation of scrutiny to some other body. The guidance in the flow chart is potentially confusing in this regard. **Proposed change (if any):** "Consultation of a Competent Authorities/Notified Bodies and /or Working Parties (no Clock Stop)."	Partially agreed. Flow-chart revised and explanatory text included. When possible, the consultation with WPs and NBs will take place during the procedure and will not lead to clock stop as a rule
Sect.5, Page 7, in Paragraph "Day 60"	2	**<u>Confining applicants to "companies"</u>** **Comments:** Art.17 speaks of "Any applicant developing a product". ATMP innovators may be 'companies', but may also include charities, NGO's, clinical consortia and others. Confining the remit of applicants to 'companies' is not appropriate. **Proposed change (if any):** "Once adopted, the final CAT Scientific recommendation on classification of ATMP is sent to the applicant and represent the final position of the CAT. "	Agreed.
Sect.6 relating to the Request Form Template*	2	**<u>Request form</u>** ***Please note:** The document referenced in our copy of the consultation form does currently exist on the EMEA website	The request form will be included as an attachment

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(A) Sect.1.1, page 2, (B) Sect. 1.4 pg 2 (C) Sect. 2 Pg.2-3		(http://www.emea.europa.eu/pdfs/human/genetherapy/Request_Form.pdf) The following comments are in reference to the document "Request Form and briefing information" available at http://www.emea.europa.eu/pdfs/human/cat/ATMP_class_requestform.doc **Comments:** A. Art.17 speaks of "Any applicant developing a product". ATMP innovators may be 'companies', but may also include charities, NGO's, clinical consortia and others. Confining the remit of applicants to 'companies' is not appropriate. B. It is unclear why the information relating to development stages is necessary and required to determine whether a product can be classified as ATMP. C. The entire section 2 is a grave flaw in the way it is presented. The point of an Art.17 request is to obtain clarity from the Agency regarding the classification of the product. Where such a product can be subsumed into the definition of an ATMP category without any doubt by the applicant him/herself, the entire request would be moot in the first place. The area of classifying ATMP is difficult, a fact clearly recognised by legislators and the motivation for instituting the Art.17 procedures. Asking the applicant to 'do the Agency's work for them' completely misses the point of why applicants would seek an Art.17 recommendation, alienates stakeholders and reinforces a stereotype of medical regulatory agencies being bureaucratic, inefficient and nor ready to	Agreed. To B: section 6 has been update stating '.. relevant for the ATMP classification'. For example, manufacturing data might be necessary to understand that the cells are manipulated / engineered ; non-clinical/clinical information can be helpful to justify the medical claim/indication To C: see explanation above (General comments, point 3)

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		engage positively and helpfully with stakeholders by providing genuine advice. **Proposed change (if any):** (A) "Entity developing the product (applicant)" (B) Delete section 1.4 (C) Revise the entire Section 2 of the request form in a manner that does not require the applicant to answer questions that are the task of the Agency to advise on.	
Section 6, p. 8/9	1	Comments: The link to the "Request form Template" does not work	Link modified in the text
Sect.7	2	**Comments:** The intention of the Art.17(2) provision, is not to establish a register for scientific, safety or market monitoring purposes, but to provide a register of case studies so as to better inform the community about when and why products would be considered ATMP. Case studies have great signalling power in indicating how the regulator interprets the law in this relatively untested area. However, at this point in time such a 'stock' of cases is not yet available. The most efficient way of reducing uncertainty is to provide information proactively rather than purely in a reactive fashion. Such information should not simply be a restatement of the law, but provide tangible-real world explanations. These efforts would very quickly pay off by reducing the amount of redundant queries and by providing a clear sense of regulatory direction.	

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		Proposed change (if any): 1. CAT should supplement, wherever possible the information provided through Art.17(2) disclosures with other relevant advice and guidance. 2. Until a great remit of applications is available, fictitious case studies would be of great benefit to the community.	1. The ATMP Regulation provide specific provisions on what can be published. EMEA will review what additional information can be made public. 2. EMEA will consider ways of providing additional guidance.