05 December 2018
EMA/CAT/857624/2018
Inspections, Human Medicines Pharmacovigilance and Committees Division

Committee for Advanced Therapies (CAT)

Agenda for the meeting on 05-07 December 2018

Chair: Martina Schüßler-Lenz; Vice-Chair: Ilona Reischl

05 December 2018, 14:00 – 18:00, room 03-F

06 December 2018, 09:00 – 18:00, room 03-F

07 December 2018, 09:00 – 12:00, room 03-F

Health and safety information

In accordance with the Agency's health and safety policy, delegates are to be briefed on health, safety and emergency information and procedures prior to the start of the meeting.

Disclaimers

Some of the information contained in this agenda is considered commercially confidential or sensitive and therefore not disclosed. With regard to intended therapeutic indications or procedure scopes listed against products, it must be noted that these may not reflect the full wording proposed by applicants and may also vary during the course of the review. Additional details on some of these procedures will be published in the CAT meeting reports once the procedures are finalised.

Of note, this agenda is a working document primarily designed for CAT members and the work the Committee undertakes.

Note on access to documents

Some documents mentioned in the agenda cannot be released at present following a request for access to documents within the framework of Regulation (EC) No 1049/2001 as they are subject to on-going procedures for which a final decision has not yet been adopted. They will become public when adopted or considered public according to the principles stated in the Agency policy on access to documents (EMA/127362/2006).

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Table of contents

1. Introduction

1.1. Welcome and declarations of interest of members, alternates and experts

Pre-meeting list of participants and restrictions in relation to declarations of interests applicable to the items of the agenda for the CAT plenary session to be held 05-07 December 2018. See December 2018 CAT minutes (to be published post-January 2019 CAT meeting).

1.2. Adoption of agenda

CAT agenda for 05-07 December 2018 meeting

1.3. Adoption of the minutes

CAT minutes for 07-09 November 2018 meeting

1.4. Technical information

2. Evaluation of ATMPs

2.1. Opinions

No items

2.2. Oral explanations

No items

2.3. Day 180 list of outstanding issues

No items

2.4. Day 120 list of questions

No items

2.5. Day 80 assessment reports

No items

2.6. Update on ongoing initial applications

No items

2.7. New applications

No items

2.8. Withdrawal of initial marking authorisation application

No items

2.9. Re-examination of initial application procedures under Article 9(2) of Regulation No. 726/2004

No items

2.10. GMP and GCP inspections requests

No items

2.11. Type II variations - variation of therapeutic indication procedure according to Commission Regulation (EC) No 1234/2008

2.11.1. Imlygic - talimogene laherparepvec - EMEA/H/C/002771/II/0027

Amgen Europe B.V.

Rapporteur: Olli Tenhunen, CHMP Coordinator: Tuomo Lapveteläinen

Scope: Opinion: Safety
Update of section 4.8 of the SmPC in order to add granulomatous dermatitis as new adverse drug reaction with an uncommon frequency and to update the adverse reaction dyspnoea from dyspnoea exertional to dyspnoea under common frequency.

Action: for adoption

2.11.2. Imlygic - talimogene laherparepvec - EMEA/H/C/002771/II/0028

Amgen Europe B.V.

Rapporteur: Olli Tenhunen; CHMP Coordinator: Tuomo Lapveteläinen; PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: RSI
Submission of an updated RMP version 4.0 in order to align the important identified and potential risks and missing information with the revised guideline Good Pharmacovigilance Practices Module V (Revision 2), resulting in the reclassification and removal of a number of identified and potential risks and missing information.

Action: for adoption

2.11.3. Kymriah - tisagenlecleucel - Orphan - EMEA/H/C/004090/II/0001

Novartis Europharm Limited

Rapporteur: Rune Kjeken; CHMP Coordinator: Bjorg Bolstad

Scope: Opinion. Quality

Action: for adoption

2.12. GMP and GCP inspections requests

No items

2.13. Other Post-Authorisation Activities

2.13.1. Alofisel - darvadstrocel - Orphan - EMEA/H/C/004258/REC/004

Takeda Pharma A/S

Rapporteur: Lisbeth Barkholt, CHMP Coordinator: Kristina Dunder

Scope: Quality

Action: for adoption

2.13.2. Kymriah - tisagenlecleucel - Orphan - EMEA/H/C/004090/REC/001

Novartis Europharm Limited

Rapporteur: Rune Kjeken; CHMP Coordinator: Bjorg Bolstad

Scope: Quality

Action: for information

Note: conclusion adopted by CHMP at its November 2018 meeting

3. Certification of ATMPs

Information related to this section cannot be released at the present time as it is deemed to contain commercially confidential information.

3.1. Opinion

No items

3.2. Day 60 Evaluation Reports

No items

3.3. New Applications

No items

4. Scientific Recommendation on Classification of ATMPs

4.1. New requests – Appointment of CAT Coordinator

4.1.1. Recombinant adeno-associated virus (serotype 5) containing the human retinal guanylate cyclase 1 (GUCY2D) gene – H0005261

Intended for the treatment of inherited retinal disease caused by biallelic mutations in GUCY2D, including Leber congenital amaurosis type 1 (GUCY2D-LCA)

Scope: appointment of CAT Coordinator and adoption of timetable

Action: for adoption

4.1.2. Autologous cord blood nucleated cells – H0005260

Intended for the treatment of paediatric brain damage, hypoxic-ischemic encephalopathy, cerebral palsy

Scope: appointment of CAT Coordinator and adoption of timetable

Action: for adoption

4.1.3. Recombinant adeno-associated virus (serotype 0) containing the human α-L-iduronidase (hIDUA) gene - H0005258

Intended for the treatment of mucopolysaccharidosis type I

Scope: appointment of CAT Coordinator and adoption of timetable

Action: for adoption

4.1.4. Cultured autologous adipose-derived stem cells - H0005257

Intended for the treatment of urinary diversion in patients requiring radical cystectomy for the treatment of bladder cancer

Scope: appointment of CAT Coordinator and adoption of timetable

Action: for adoption

4.1.5. Adeno-associated virus serotype rh10 (AAVrh10) containing a transgene that encodes a microRNA (miRNA) targeting superoxide dismutase 1 (SOD1) messenger RNA (mRNA) - H0005259

Intended for the treatment of amyotrophic lateral sclerosis (ALS) due to mutations in SOD1 gene

Scope: appointment of CAT Coordinator and adoption of timetable

Action: for adoption

4.2. Day 30 ATMP scientific recommendation

4.2.1. Bacteriophage capsid containing deoxyribonucleic acid (DNA) encoding a ribonucleic acid (RNA)-guided nuclease and associated RNA guides, targeting shiga-toxin genes - H0005237

Intended for the treatment of Shiga-toxin producing *E. coli* (STEC) infection

Scope: ATMP scientific recommendation

Action: for adoption

4.2.2. Allogeneic expanded natural killer (NK) cells – H0005241

Intended for the treatment of multiple myeloma

Scope: ATMP scientific recommendation

Action: for adoption

4.2.3. Autologous modified CD34+ haematopoietic cells transduced with a lentiviral vector encoding for the CD18 β-subunit of human β2 integrin - H0005238

Intended for the treatment of severe leukocyte adhesion deficiency type I (LAD-I)

Scope: ATMP scientific recommendation

Action: for adoption

4.2.4. Allogeneic cultured postnatal thymus tissue-derived product - H0005239

Intended for immune reconstitution in patients with congenital athymia

Scope: ATMP scientific recommendation

Action: for adoption

4.2.5. Autologous dendritic cell, electroporated with messenger ribonucleic acid (mRNA) encoding tumour antigen Wilms tumor (WT)-1 – H0005240

Intended for the treatment of lung cancer

Scope: request for supplementary information

Action: for adoption

4.3. Day 60 revised scientific recommendation (following list of questions)

4.3.1. Whole lipoaspirate containing viable autologous adipose-derived regenerative cells - H0005212

Intended for the treatment of progressive hemifacial atrophy (Parry-Romberg syndrome)

Scope: assessment of the responses from the applicant. Revised ATMP scientific recommendation

Action: for adoption

4.3.2. Viable autologous adipose-derived regenerative cells combined with whole lipoaspirate - H0005213

Intended for the treatment of progressive hemifacial atrophy (Parry-Romberg syndrome)

Scope: assessment of the responses from the applicant. Revised ATMP scientific recommendation

Action: for information

4.3.3. Viable autologous adipose-derived regenerative cells combined with whole lipoaspirate - H0005214

Intended for the treatment of progressive hemifacial atrophy (Parry-Romberg syndrome)

Scope: assessment of the responses from the applicant. Revised ATMP scientific recommendation

Action: for information

4.3.4. Whole lipoaspirate containing viable autologous adipose-derived regenerative cells - H0005215

Intended for the treatment of burn scars

Scope: assessment of the responses from the applicant. Revised ATMP scientific recommendation

Action: for information

4.3.5. Viable autologous adipose-derived regenerative cells - H0005216

Intended for the treatment of burn scars

Scope: assessment of the responses from the applicant. Revised ATMP scientific recommendation

Action: for information

4.3.6. Viable autologous adipose-derived regenerative cells - H0005217

Intended for the treatment of burn scars

Scope: assessment of the responses from the applicant. Revised ATMP scientific recommendation

Action: for information

4.4. Finalisation of procedure

4.4.1. Allogeneic Wharton's jelly mesenchymal stem cells (MSCs) on dermal scaffold - H0005198

Intended for the treatment of epidermolysis bullosa

Scope: the European Commission raised no comments. Final ATMP scientific recommendation

Action: for information

4.4.2. Genetically modified bone marrow derived allogeneic mesenchymal stem cells (MSCs) expressing human alpha-1 antitrypsin (AAT) - H0005206

Intended for the treatment of steroid refractory acute graft-versus-host-disease (GvHD), grades II-IV

Scope: the European Commission raised no comments. Final ATMP scientific recommendation

Action: for information

4.4.3. Suspension of human olfactory ensheathing cells (OECs) and olfactory nerve fibroblasts (ONFs) – H0005197

Indicated for the treatment of complete and incomplete spinal cord injuries in human patients, aiming to support neuroregeneration

Scope: the European Commission raised no comments. Final ATMP scientific recommendation

Action: for information

4.4.4. Human donor haematopoietic stem cells treated *ex vivo* - H0005195

Intended for the treatment of severe combined immunodeficiency

Scope: the European Commission raised no comments. Final ATMP scientific recommendation

Action: for information

4.4.5. Recombinant adeno-associated virus serotype 1 (AAV1) containing a transgene that encodes a microRNA (miRNA) targeting huntingtin - H0005196

Intended for the treatment of Huntington's disease

Scope: the European Commission raised no comments. Final ATMP scientific recommendation

Action: for information

5. Scientific Advice

Information related to this section cannot be released at the present time as it is deemed to contain commercially confidential information.

5.1. New requests – appointment of CAT Rapporteurs

Timetable:

-Final Briefing Package:	09.01.2019
-Start of the procedure at SAWP:	17.01.2019
-CAT report due by:	17.01.2019
-CAT recommendation:	25.01.2019

5.2. CAT reports

5.3. List of Issues

5.4. Finalisation of SA procedures

5.5. Follow-up on SA procedures

6. Pre-Authorisation Activities

Information related to this section cannot be released at the present time as it is deemed to contain commercially confidential information.

6.1. Paediatric investigation plans

6.2. ITF briefing meetings in the field of ATMPs

6.3. Priority Medicines (PRIME) – Eligibility requests

6.3.1. Month 0 - Start of the procedure

No items

6.3.2. Month 1 – Discussion of eligibility

No items

6.3.3. Month 2 – Recommendation of eligibility

7. Organisational, regulatory and methodological matters

7.1. Mandate and organisation of the CAT

No items

7.2. Coordination with EMA Scientific Committees

7.2.1. Committee for Medicinal Products for Human Use (CHMP)

Scope: Summary of Outcomes (SoO) for the November 2018 meeting

Action: for information

7.2.1. Scientific Coordination Board (SciCoBo) – meeting of 22 November 2018

CAT: Martina Schüßler-Lenz

Scope: feedback on the outcome of the SciCoBo meeting that took place on 22 November 2018

Action: for information

7.3. Coordination with EMA Working Parties / Working Groups / Drafting Groups

7.3.1. Guideline on requirements for investigational ATMPs

Drafting group: Ilona Reischl (Rapporteur), Tiina Palomäki (Rapporteur), Martina Schüßler-Lenz, Simona Badoi, Tomáš Boráň, Violaine Closson-Carella, Paolo Gasparini, Carla Herberts, Metoda Lipnik-Stangelj, Margarida Menezes Ferreira, Christiane Niederlaender, Maura O'Donovan, Olli Tenhunen, Heli Suila, Barbara Bonamassa, Giuseppa Pistritto, Marcel Hoefnagel

Scope: updated guideline following feedback from the Guideline Consistency Group (GCG)

Action: for adoption

Note: break-out meeting of the DG on Wednesday 06.12.2018.

7.3.2. Working Party with Patients' and Consumers' Organisations (PCWP) and Working Party with Healthcare Professionals' Organisations (HCPWP)

Scope:
-Meeting summary PCWP plenary meeting 25 September 2018
-Meeting summary PCWP/HCPWP joint meeting 25 September 2018

Action: for information

7.3.3. CAT contribution to the Scientific Advice Working Party (SAWP)

CAT: Martina Schüßler-Lenz

Scope: feedback from the November 2018 discussion

Action: for discussion

7.4. Cooperation within the EU regulatory network

7.4.1. Evaluation of the EU legislation on blood, tissues and cells

Scope: questionnaire to the Member States on the interface between the blood, tissue / cell and pharmaceutical legislation

Action: for information

7.5. Cooperation with international regulators

7.5.1. International pharmaceutical regulators programme – cell therapy group

EMA: Patrick Celis

Scope: feedback from the international teleconference call of 13 November 2018; proposal from PMDA to develop a reflection paper on tumourigenicity evaluation of pluripotent stem cells.

Action: for discussion

7.6. CAT work plan

7.6.1. Genome editing technologies on drug development editing – regulatory considerations

Scope: feedback from the drafting group discussion of 27.11.2018.

Action: for discussion

7.7. Planning and reporting

7.7.1. Planning estimates of forthcoming ATMP MAAs

Scope: Q4/2018 update of the business pipeline report for the human scientific committees

Action: for information

7.8. Others

7.8.1. Request from the European Commission for EMA's opinion on the definitions of pharmacological, immunological, metabolic and medical diagnosis

Scope: definitions of pharmacological, immunological, metabolic and medical diagnosis

Action: for appointment of sponsors

Note: this topic was first introduced to CAT in July 2018

7.8.2. Relocation of EMA to The Netherlands

Action: for information

7.8.3. Discussion paper *'Use of patient disease registries for regulatory purposes - methodological and operational considerations'*

Scope: the discussion paper has been published on the EMA website. Comments and suggestions by 30 June 2019 https://www.ema.europa.eu/en/human-regulatory/post-authorisation/patient-registries

Action: for information

Note: you will see on the document that comments and suggestions are welcome before 30 June 2019 by sending the Form for submission of comments https://www.ema.europa.eu/documents/other/form-submission-comments_en.doc or an annotated version of the document (mentioning on the first page your name, affiliation and contact details) to: EMAregistries@ema.europa.eu.

7.8.4. Marketing authorisation applications of ATMPs according to Article 10a of Directive 2001/83/EC

Scope: Proposal: feedback and next steps

Action: for information

7.8.5. Tumourigenicity assays for cell therapy products

CAT: Carla Herberts

Scope: feedback from the Health and Environmental Sciences Institute Cell Therapy-TRAcking, Circulation & Safety (ILSI-HESI CT-TRACS) Committee: activity of Forum for Innovative Regenerative Medicine-Committee for Non-Clinical Safety Evaluation of Pluripotent Stem Cell-derived ProducT (FIRM-CoNCEPT) on the design and validation of in vitro and in vivo tumourigenicity assays for cell therapy and work. CAT input is sought on the design of *in vitro* tumourigenicity assays

Action: for discussion

7.8.6. 24th Pharmaceutical Inspection Co-operation Scheme (PIC/S) expert circle meeting on human blood, tissues, cells and ATMPs: *'How to conduct inspections of human blood, tissues, cells and ATMPs'*

CAT: Dariusz Śladowski

Scope: feedback from the teleconference that took place on 22-26 October 2018, Warsaw, Poland

Action: for information

8. Any other business

No items

Date of next CAT meeting:

23-25/01/2019

9. Explanatory notes

The Notes give a brief explanation of relevant agenda items and should be read in conjunction with the agenda.

Abbreviations / Acronyms

AAV: Adeno-Associated Virus

AR: Assessment Report

ATMP: Advanced Therapy Medicinal Product

BWP: Biologics Working Party

CAT: Committee for Advanced Therapies

CHMP: Committee for Medicinal Product for Human Use

COMP: Committee for Orphan Medicinal Products

CTFG: Clinical Trial Facilitation Group

DG: Drafting Group

EC: European Commission

ERA: Environmental Risk Assessment

FDA: Food and Drug Administration

FL: Final Letter

GCG: Guideline Consistency Group

GCP: Good Clinical Practice

GLP: Good Laboratory Practice

GMO: Genetically-modified organism

GMP: Good Manufacturing Practice

GTMP: Gene Therapy Medicinal Product

HTA: Health Technology Assessment Bodies

HSPC: Hematopoietic Stem and Progenitor Cells

ITF: Innovative Task Force

JR: Joint Report

LoOI: List of outstanding issues

LoQ: List of questions

MA: Marketing Authorisation

MAA: Marketing Authorisation Application

MAH: Marketing Authorisation Holder

MSC: Mesenchymal stem cells

PDCO: Paediatric Committee

PMDA: Pharmaceuticals and Medical Devices Agency (Japan)

PIP: Paediatric Investigation Plan

PL: Package leaflet

PRAC: Pharmacovigilance and Risk Assessment Committee #

PRIME: Priority Medicines

RMP: Risk Management Plan

RP: Reflection paper

RSI: Request for supplementary information

SAs: Scientific Advices

SAG-O: Scientific Advisory Group Oncology

SAWP: Scientific Advice Working Party

SR: Summary Report

SWP: Scientific Working Party

SME: Small and medium size enterprises

SmPC: Summary of Products Characteristics

TT: Timetable

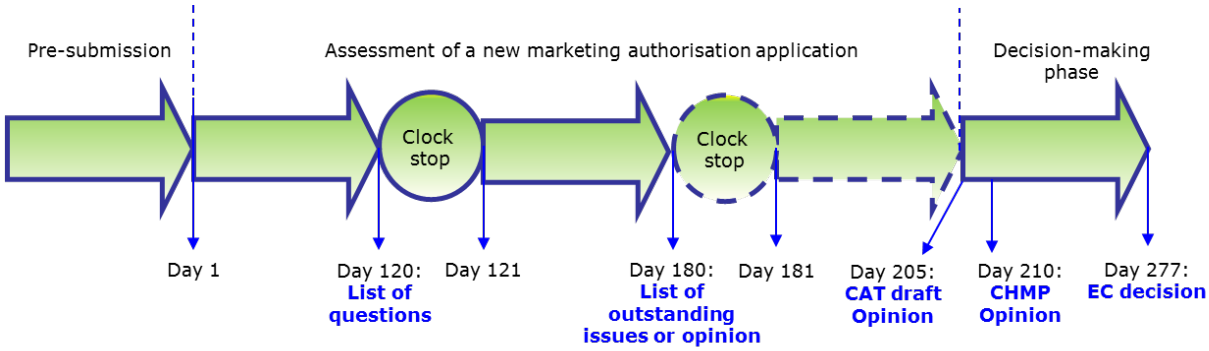
Evaluation of ATMPs (section 2)

This section lists applications for marketing authorisations of new Advanced Therapy Medicinal Products (ATMPs) that are to be discussed by the Committee. It also lists any ATMP related inspection requests (section 2.9) and Post-authorisation activities (section 2.10).

New applications (sections 2.1. to 2.12.)

Section 2.1 is for ATMPs nearing the end of the evaluation and for which the CAT is expected to adopt a draft **opinion** at this meeting on whether marketing authorisation should be granted. Once adopted, the CAT opinion is transmitted to the CHMP for final adoption. The CHMP opinion will be forwarded to the European Commission for a final legally binding decision valid throughout the EU. More information on the evaluation of ATMPs can be found here.

The other items in the section are listed depending on the stage of the evaluation, which is shown graphically below:



The assessment of an application for a new medicine takes up to 210 'active' days. This active evaluation time is interrupted by at least one 'clock-stop' during which time the applicant prepares the answers to questions from the CAT. The clock stop happens after day 120 and may also happen after day 180, when the CAT has adopted respectively a **Day 120 list of questions** (section 2.3) or a List of outstanding issues to be addressed by the company, which is listed in the agenda under sections 2.7 (**Ongoing evaluation procedures**). Section 2.7 also includes the CAT discussions at any other timepoint of the evaluation procedure of new applications.

Oral explanation (section 2.2.)

Prior to adoption of the CAT opinion, marketing authorisation applicants are normally invited to the CAT plenary meeting to address questions raised by the Committee.

Oral explanations normally relate to ongoing applications, but they can also relate to any other issue for which the CAT would like to discuss with company representatives in person.

Re-examination procedures (new applications) under article 9(2) of regulation no 726/2004 (section 2.6.)

This section lists applications for new marketing authorisation for ATMPs for which the applicant has requested a re-examination of the opinion previously issued by the CHMP. Similar to the initial evaluation of a marketing authorisation of an ATMP, CAT will adopt a draft re-examination opinion, which is transmitted to the CHMP for final adoption.

Withdrawal of applications (section 2.7.)

This section includes information on marketing authorisation applications that are withdrawn by the applicant. Applicants may decide to withdraw applications at any stage during the assessment and a CAT opinion will therefore not be issued. Withdrawals are included in the agenda for information or discussion, as necessary.

New applications (section 2.9.)

In this section, information is included on upcoming marketing authorisation applications for ATMPs, as well as information on appointment of Rapporteurs for new ATMP applications.

GMP and GCP Inspections Issues (section 2.10.)

This section lists inspections that are undertaken for ATMPs. Inspections are carried out by regulatory agencies to ensure that marketing authorisation holders comply with their obligations. Inspection can relate to good manufacturing practice (GMP), good clinical practice (GCP), good laboratory practice (GLP) or good pharmacovigilance practice (GVP).

Post-authorisation activities (section 2.12.)

This section lists type II variations, extension application according to Annex I of Reg. 1234/2008, re-examination procedures for type II variations (including extension of indication applications) for which the applicant has requested re-examination of the opinion previously issued by the CHMP and other issues concerning authorised medicines that are not covered elsewhere in the agenda such as annual reassessments, 5-year renewals, supply shortages, qualify defects. Issues that have been discussed at the previous meeting of the PRAC, the EMA's committee responsible for evaluating and monitoring safety issues for medicines, will also be included here.

Certification of ATMPs (section 3)

This section includes the scientific evaluation by the CAT of quality and non-clinical data that small and medium-sized enterprises have generated at any stage of the ATMP development process. More information on the ATMP certification procedure can be found here.

Scientific Recommendation on Classification of ATMPs (Section 4)

This section includes the scientific recommendation by the CAT on whether medicines based on genes, cells or tissues meet the scientific criteria that define ATMPs. More information on the ATMP classification procedure, including the outcomes of finalised classifications, can be found here.

Scientific Advice (section 5)

This section includes all scientific advice given to companies during the development of an ATMP. Information related to the number of ATMP related scientific advices discussed by CAT can be found in the CAT Monthly reports. Further information on SAWP can be found here.

Pre-Authorisation (section 6)

Paediatric Investigation Plan (PIP)

This section includes the discussion of an ATMP before a formal application for marketing authorisation is submitted. These cases refer for example to requests for an accelerated assessment for medicines that

are of major interest for public health or can be considered a therapeutic innovation: in case of an accelerated assessment the assessment timetable is reduced from 210 to 150 days.

CAT contributes to the evaluation of a Paediatric Investigation Plan (PIPs) for ATMPs by the Paediatric Committee. These PIPs are included in this section of the Agenda.

ITF Briefing meeting in the field of ATMPs

This section refers to briefing meetings of the Innovation Task Force and International co-operations activities of the CAT

The Innovation Task Force (ITF) is a body set up to encourage early dialogue with applicants developing innovative medicines. Minutes of meetings with applicants developing ATMPs and of other ITF meetings of interest to the CAT are included in this section of the agenda. Further information on the ITF can be found here.

Priority Medicines (PRIME)

This section includes the new requests for eligibility to PRIME for ATMPs under development, the discussions in CAT of these eligibility requests and the final recommendations for eligibility of ATMPs adopted by CHMP.

CAT will appoint one of its members as the CAT sponsor for each new ATMP eligibility request who will lead the CAT discussion based on the recommendation from the SAWP.

Organisational, regulatory and methodological matters (section 7)

This section includes topics related to regulatory and procedural guidance, CAT workplan, CAT meeting organisation (including CAT membership), planning and reporting, co-ordination with other committees, working parties and scientific advisory groups.

Furthermore, this section refers to the activities of the CAT drafting groups developing scientific guidelines for gene therapy medicinal products and for cell-based medicinal products, cooperation within the EU regulatory network and international regulators as well as direct interaction with interested parties. It also includes topics of scientific interest for the Committee that are not directly related to the work of the CAT drafting groups or CAT associated working parties.

Any other business (section 8)

This section is populated with miscellaneous topics not suitable under the previous headings.

More detailed information on the above terms can be found on the EMA website: www.ema.europa.eu/