20 February 2019
EMA/CAT/92832/2019
Inspections, Human Medicines Pharmacovigilance and Committees Division

# Committee for Advanced Therapies (CAT)

## Agenda for the meeting on 20-22 February 2019

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

20 February 2019, 14:00 – 18:30, room NL 2-A

21 February 2019, 09:00 – 18:30, room NL 2-A

22 February 2019, 09:00 – 12:00, room NL 2-A

**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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# 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 20-22 February 2019. See February 2019 CAT minutes (to be published post-March 2019 CAT meeting).

## 1.2. Adoption of agenda

CAT agenda for 20-22 February 2019 meeting

## 1.3. Adoption of the minutes

CAT minutes for 23-24 January 2019 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

### 2.4.1. Onasemnogene abeparvovec - Orphan - EMEA/H/C/004750

**Accelerated assessment**

AveXis Netherlands B.V.; treatment of spinal muscular atrophy (SMA)

Scope: Day 120 list of questions

**Action:** for adoption

## 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/0029

Amgen Europe B.V.

Scope: safety: Opinion
Update of section 5.2 of the SmPC in order to update the pharmacokinetic properties information based on the final results from study 20120324, a phase 2, multicenter, single-arm trial to evaluate the biodistribution and shedding of talimogene laherparepvec in subjects with unresected, stage IIIB to IVM1c melanoma. This submission fulfils MEA 006.1. In addition, the Marketing authorisation holder (MAH) took the opportunity to update Annex II as per the already assessed EMEA/H/C/002771/ANX/001 procedure.

**Action:** for adoption

## 2.12. Other Post-Authorisation Activities

### 2.12.1. Kymriah - tisagenlecleucel - Orphan - EMEA/H/C/004090/REC/004

Novartis Europharm Limited

Scope: Quality

**Action:** for adoption

### 2.12.2. Kymriah - tisagenlecleucel - Orphan - EMEA/H/C/004090/ANX/003

Novartis Europharm Limited

Rapporteur: Rune Kjeken, CHMP Coordinator: Bjorg Bolstad

Scope: Clinical: the Statistical Analysis Plan from CTL019B2401 has been submitted to address the post-authorisation measures for Kymriah (INN: tisagenlecleucel) described below (also in AnnexII of SmPC and in RMP): In order to further evaluate the efficacy of Kymriah in patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL), the applicant will conduct and submit a prospective, observational study in patients with r/r DLBCL based on data from registry with efficacy outcome measures in line with study C2201, including details of the manufacturing turnaround time (i.e., time from last relapse or confirmed refractory status, time from decision to treat, and time from leukapheresis to infusion). Pre-specified subgroup analysis will be conducted to evaluate the effectiveness of Kymriah.

**Action:** for adoption

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

Novartis Europharm Limited

Rapporteur: Rune Kjeken; CHMP Coordinator: Bjorg Bolstad

Scope: Quality

**Action:** for discussion

## 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

### 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 viral vector serotype 8 (AAV8) encoding a codon optimised cDNA encoding human Retinitis Pigmentosa GTPase Regulator (coRPGR) – H0005315

Intended for the treatment of X-linked retinitis pigmentosa (XLRP)

Scope: appointment of CAT Coordinator and adoption of timetable

**Action:** for adoption

#### 4.1.2. Heterogeneous mixture of human milk-derived nutritional and viable non-nutritional ingredients

Human milk substitute/supplementation of premature infants and children of mothers with milk shortage

Scope: letter to the applicant **Action:** for discussion

#### 4.1.3. Allogeneic adult bone-marrow-derived stem cells transiently transfected with a plasmid construct encoding the intracellular domain of human Notch-1 – H0005313

Intended for the treatment of motor deficits arising from acquired brain injury, including traumatic brain injury, ischaemic stroke and haemorrhagic stroke

Scope: appointment of CAT Coordinator and adoption of timetable

**Action:** for adoption

### 4.1.4. Autologous T cells transduced with a T cell receptor (TCR) targeting human Telomerase Reverse Transcriptase (hTERT) – H0005314

Intended for the treatment of various cancer types expressing hTERT

Scope: appointment of CAT Coordinator and adoption of timetable

**Action:** for adoption

## 4.2. Day 30 ATMP scientific recommendation

### 4.2.1. Recombinant adeno-associated viral vector serotype-5 expressing human 21-hydroxylase gene – H0005295

Treatment of congenital adrenal hyperplasia

Scope: ATMP scientific recommendation

**Action:** for adoption

### 4.2.2. Autologous skeletal muscle derived cells attached to biodegradable poly(DL-lactide-co-glycolide) microparticles combined with skeletal muscle derived cells – H0005289

Treatment of faecal incontinence and anorectal malformation

Scope: ATMP scientific recommendation

**Action:** for adoption

### 4.2.3. Allogeneic, *ex vivo* expanded, umbilical cord (UC) blood-derived, haematopoietic CD34+ progenitor cells and allogeneic, non-expanded, UC blood-derived, haematopoietic mature myeloid and lymphoid cells - H0005288

Haematopoietic reconstitution of patients who are medically indicated for allogeneic haematopoietic stem cell transplantation

Scope: ATMP scientific recommendation

**Action:** for adoption

### 4.2.4. *In vitro* transcribed single-stranded messenger RNA (mRNA) molecules encoding human interferon-α2b, interleukin-12, interleukin-15sushi, and Granulocyte-macrophage colony-stimulating factor – H0005291

Treatment of solid tumors

Scope: ATMP scientific recommendation

**Action:** for adoption

### 4.2.5. Allogeneic cord blood mononuclear cells - H0005292

Treatment of neurological disorders, autism spectrum disorders, cerebral palsy

Scope: ATMP scientific recommendation

**Action:** for adoption

### 4.2.6. Recombinant adeno-associated viral vector (AAV) containing a human micro-dystrophin gene drug substance – H0005293

Treatment of patients with Duchene muscular dystrophy (DMD)

Scope: ATMP scientific recommendation

**Action:** for adoption

### 4.2.7. Plasmid vector expressing interleukin-12 gene – H0005294

Treatment of advanced melanoma

Scope: ATMP scientific recommendation

**Action:** for adoption

### 4.2.8. *Ex vivo* expanded allogeneic bone marrow derived mesenchymal stromal cells – H0005290

Treatment of graft-*versus*-host disease

Scope: ATMP scientific recommendation

**Action:** for adoption

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

No items

## 4.4. Finalisation of procedure

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

Treatment of progressive hemifacial atrophy (Parry-Romberg syndrome)

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

**Action:** for information

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

Treatment of progressive hemifacial atrophy (Parry-Romberg syndrome)

Scope: comments raised by the European Commission. Revised final ATMP scientific recommendation

**Action:** for adoption

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

Treatment of progressive hemifacial atrophy (Parry-Romberg syndrome)

Scope: comments raised by the European Commission. Revised final ATMP scientific recommendation

**Action:** for adoption

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

Treatment of burn scars

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

**Action:** for information

### 4.4.5. Viable autologous adipose-derived regenerative cells - H0005216

Treatment of burn scars

Scope: comments raised by the European Commission. Revised final ATMP scientific recommendation

**Action:** for adoption

### 4.4.6. Viable autologous adipose-derived regenerative cells - H0005217

Treatment of burn scars

Scope: comments raised by the European Commission. Revised final ATMP scientific recommendation

**Action:** for adoption

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

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

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

**Action:** for information

### 4.4.8. Autologous cord blood nucleated cells – H0005260

Treatment of paediatric brain damage, hypoxic-ischemic encephalopathy, cerebral palsy

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

**Action:** for information

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

Treatment of mucopolysaccharidosis type I

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

**Action:** for information

### 4.4.10. Cultured autologous adipose-derived stem cells - H0005257

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

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

recommendation

**Action:** for information

### 4.4.11. Recombinant adeno-associated virus serotype rh10 (AAVrh10) containing a transgene that encodes a micro ribonucleic acid (miRNA) targeting superoxide dismutase 1 (SOD1) messenger RNA (mRNA) - H0005259

Treatment of amyotrophic lateral sclerosis (ALS) due to mutations in SOD1 gene

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

**Action:** for information

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

Postponed

Treatment of lung cancer

Scope: comments raised by the European Commission. Revised final ATMP scientific recommendation

**Action:** for adoption

## 4.5. Follow-up and guidance

# 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

## 5.2. CAT reports

## 5.3. List of Issues

## 5.4. Finalisation of 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

No items

## 6.2. ITF briefing meetings in the field of ATMPs

## 6.3. Priority Medicines (PRIME) – Eligibility requests

### 6.3.1. Month 1 – Discussion of eligibility

### 6.3.2. Month 2 – Recommendation of eligibility

### 6.3.3. Ongoing support

### 6.3.4. Follow-up

# 7. Organisational, regulatory and methodological matters

## 7.1. Mandate and organisation of the CAT

### 7.1.1. CAT membership

UK: John Johnston – new alternate. New membership mandate from 30 January 2019

UK: James McBlane – membership ended on 29 January 2019

Croatia: Nenad Medic – membership ended on 06 February 2019

**Action:** for information

### 7.1.2. Strategic Review & Learning meeting – joint CAT/Clinical trial facilitation group (CTFG), Bucharest, Romania, 13-14 June 2019

CAT resources: Simona Badoi

Scope: initial topics for the agenda

**Action**: for discussion

## 7.2. Coordination with EMA Scientific Committees

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

Scope: Summary of Outcomes (SoO) of the January 2019 meeting

**Action:** for information

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

None

## 7.4. Cooperation within the EU regulatory network

### 7.4.1. EDQM/Council of Europe – 4th edition of the guide to the quality and safety of tissues and cells for human application

CAT: Martina Schüssler-Lenz

Scope: invitation to participate in the consultation of the 4th edition of the guide to the quality and safety of tissues and cells for human application. Deadline: 8 March 2019.

**Action**: for discussion

Note: weblink to the consultation:
http://extranet.edqm.eu/dropboxout/045FeTCbK9YidCaHofWneRjQuVeHi7oxxUtyyN0mqeK/4th%20ed%20of%20TC%20Guide%20for%20open%20consultation-TO%2019%201_.zip

### 7.4.2. New EU initiative to optimize the interplay between the pharma and the GMO framework

Scope: update of discussions with GMO authorities

**Action:** for information

## 7.5. Cooperation with international regulators

### 7.5.1. ATMP cluster teleconference with FDA, Health Canada and PMDA

The teleconference will take place

CAT: Martina Schüßler-Lenz

Scope: draft agenda

**Action:** for discussion

## 7.6. CAT work plan

None

## 7.7. Planning and reporting

None

## 7.8. Others

### 7.8.1. EMA implementation of the new medical device and *in vitro* diagnostic regulation

CAT: Ilona Reischl

Scope: follow-up from presentation at the July 2018 CAT meeting and updates on the various work streams.

**Action:** for discussion

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

CAT Sponsor: Margarida Menezes Ferreira: pharmacologicalCAT Sponsors: Jan Mueller-Berghaus, Ilona Reischl: immunologicalCAT Sponsor: Claire Beuneu: metabolicCAT Sponsors: Paolo Gasparini, Giulio Pompilio: medical diagnosis

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

**Action:** for adoption

Note: the EMA coordinators and CAT sponsors presented the draft definitions of pharmacological, immunological, metabolic and medical diagnosis to the CAT in January 2019.

## 8. Any other business

### 8.1. 22nd annual meeting of the American Society of Gene and Cell Therapy (ASGCT), Washington, DC, USA, 28 April – 02 May 2019

Scope: Workshop on 'Pre-approval commercialization' to take place on Sunday 28th April 2019.

**Action:** for agreement of participation of the CAT Chair

Note: the pre-approval commercialisation workshop covers industry perspectives on chemistry, manufacturing and control (CMC) challenges for cell and gene modified cell therapy products, updates from global regulatory bodies, manufacturing challenges in late phase development of gene therapy products, and discussions on the difficulties in commercialising adeno-associated viral (AAV) product candidates

Date of next CAT meeting:

20-22/03/2019

## 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

EDQM: European Directory for the Quality of Medicines

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

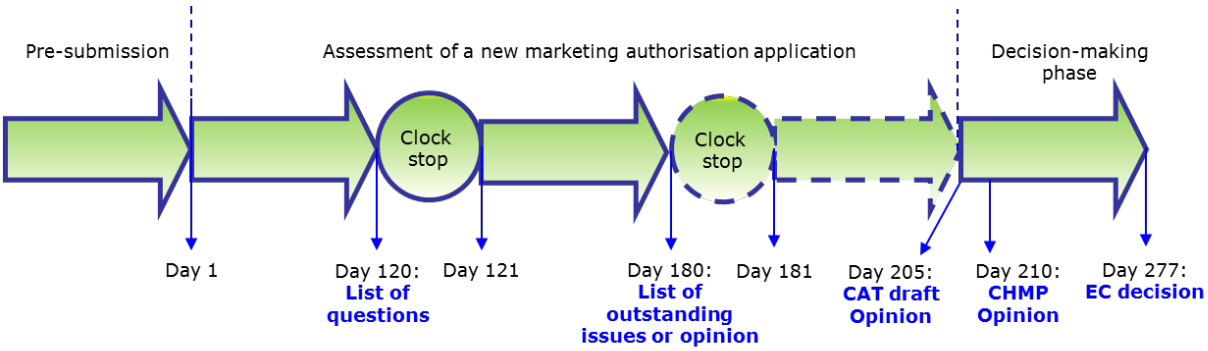
## Evaluation of ATMPs (section 2)

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/