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Reflection paper on classification of advanced therapy medicinal products

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1. Executive summary

Further to the implementation of Article 17 of Regulation (EC) No 1394/2007ⁱ (hereinafter referred as to 'the Advanced Therapy Medicinal Products (ATMPs) Regulation'), applicants have access to an optional procedure which is the CAT (Committee for Advanced Therapies) scientific recommendation for the classification of ATMPs, hereafter referred to as "ATMP classification". It is underpinned by the ATMP Regulation which enables the European Medicines Agency (EMA) in close collaboration with the European Commission to determine whether or not a given product meets the scientific criteria, which define ATMPsⁱⁱ. The ATMP classification procedure can be used in order to clarify the status of a product which may fall under different legislation (e.g. medical devices, transplants and cosmetics, etc...).

The CAT issues scientific recommendations determining whether or not the referred product falls, within the definition of an ATMP in the European Union.

The ATMP Regulation and the Directive 2001/83/EC Annex I Part IVⁱⁱ provide precise legal definitions for ATMPs. As a prerequisite to any further ATMP classification, the product under development has first to be qualified as a biological medicinal product for human use, according to the definitions in the Directive 2001/83/ECⁱⁱⁱ

The ATMP classification is based on the evaluation of whether a given product fulfils one of the definitions of gene therapy medicinal product (GTMP), somatic cell therapy medicinal product (sCTMP) or tissue engineered product (TEP) and whether the product fulfils the definition of a combined ATMP or not. However, it is also acknowledged that, due to the complex nature of these therapeutic products, the limited data package at an early stage of product development and the rapid evolution of science and technology, questions of borderline may arise^{iv}.

The ATMP classification is a non-mandatory, free of charge, legally non-binding procedure that helps developers to clarify the applicable regulatory framework. It also provides clarity on the development path and scientific-regulatory guidance to be followed. The ATMP classification may sometimes also be a useful tool for applicants to initiate a tailored dialogue on the product development with regulators. Indeed, due to its easy and fast process, the ATMP classification, along with other tools (e.g. ITF briefing meetings¹), should be seen as a first opportunity to engage with regulators. Once the candidate ATMP classification has been clarified and confirmed, the dialogue can continue with the use of other regulatory procedures such as scientific advice and ATMP certification, the latter exclusively set up under the auspices of the dedicated committee (CAT). In addition, and depending on the type of product under development, liaison with other committees such as Committee for Orphan Medicinal Products (COMP) and/or Paediatric Committee (PDCO) may be recommended to the applicant. The ATMP classification may also help developers to gain access to all relevant services and incentives offered by the EMA.

Although clinical trials are under the responsibility of the National Competent Authorities, it is important to stress that the classification recommendation made by the CAT may help when submitting a clinical trial dossier, as the applicant and the concerned competent authorities will be made aware of a European classification position which can clarify and facilitate identification of the most relevant criteria and procedure to be applied.

Moreover, the ATMP classification can be applied for at any stage of the product development, even at a very early stage when non-clinical and clinical data are not available. It should be noted that scientific recommendations given by the CAT are always related to a defined product. It is thus not possible to classify scientific 'concepts' where a clear description of the product cannot be provided.

¹ See EMA website: [European Medicines Agency - Human medicines - Innovation Task Force \(ITF\)](#)

44 As of January 2012, more than 50 products have been evaluated for classification by the CAT.²

45 **Scope**

46 The aim of this reflection paper is to introduce the ATMP classification procedure by means of:

- 47 • clarifying the legal basis for ATMP classification;
- 48 • providing clarification on the grounds applied for the classification of ATMPs;
- 49 • providing further clarification on the information to be submitted by applicants for the purpose of
50 the ATMP classification;
- 51 • communicating the current status of discussions on some borderline cases and on selected areas
52 where scientific knowledge is fast evolving or experience is limited.

53 **2. Discussion**

54 **2.1. Legal basis of ATMP classification**

55 According to Article 1(a) of Regulation (EC) No.1394/2007, an 'advanced therapy medicinal product'
56 means any of the following medicinal products for human use:

- 57 • a gene therapy medicinal product as defined in Part IV of Annex I to Directive 2001/83/EC, as
58 amended
- 59 • a somatic cell therapy medicinal product as defined in Part IV of Annex I to Directive 2001/83/EC,
60 as amended
- 61 • a tissue engineered product as defined in Article 1(b) of Regulation (EC) No. 1394/2007.

62 The ATMP Regulation also gives a definition of 'Combined ATMP' which contain as an integral part of
63 the product a medical Device (see below)

64 The definitions of a gene therapy medicinal product and a somatic cell therapy medicinal product
65 according to Directive 2001/83/EC, Annex I, Part IV, as amended (implementing Directive
66 2009/120/EC) are as follows:

67 **Gene therapy medicinal product**

68 Gene therapy medicinal product means a biological medicinal product which fulfils the following two
69 characteristics:

70 (a) it contains an active substance which contains or consists of a recombinant nucleic acid used in or
71 administered to human beings with a view to regulating, repairing, replacing, adding or deleting a
72 genetic sequence;

73 (b) its therapeutic, prophylactic or diagnostic effect relates directly to the recombinant nucleic acid
74 sequence it contains, or to the product of genetic expression of this sequence.

75 Gene therapy medicinal products shall not include vaccines against infectious diseases.

76 **Somatic cell therapy medicinal product**

77 Somatic cell therapy medicinal product means a biological medicinal product which fulfils the following
78 two characteristics:

79 (a) contains or consists of cells or tissues that have been subject to substantial manipulation so that
80 biological characteristics, physiological functions or structural properties relevant for the intended
81 clinical use have been altered, or of cells or tissues that are not intended to be used for the same
82 essential function(s) in the recipient and the donor;

83 (b) is presented as having properties for, or is used in or administered to human beings with a view to
84 treating, preventing or diagnosing a disease through the pharmacological, immunological or metabolic
85 action of its cells or tissues.

86 For the purposes of point (a), the manipulations listed in Annex I to Regulation (EC) No 1394/2007, in
87 particular, shall not be considered as substantial manipulations: cutting, grinding, shaping,
88 centrifugation, soaking in antibiotic or antimicrobial solutions, sterilization, irradiation, cell separation,
89 concentration or purification, filtering, lyophilization, freezing, cryopreservation, and vitrification. It
90 should be pointed out that this list is non-exhaustive. Thus, based on scientific considerations, the CAT
91 can also consider any other manipulation as "non substantial". This has already been done by the CAT
92 for the radiolabelling of leukocytes. This technique, which has been used in clinical practice in a
93 hospital setting since many years, should not be considered a substantial manipulation. Therefore the
94 CAT has concluded that radioactively labelled leukocytes should mainly not be considered as ATMPs.

95 Further, a '**Tissue engineered product**' according to Article 1(b) of Regulation (EC) No. 1394/2007
96 means a product that:

97 "*- contains or consists of engineered cells or tissues, and*

98 *- is presented as having properties for, or is used in or administered to human beings with a view*
99 *to regenerating, repairing or replacing a human tissue.*

100 *A tissue engineered product may contain cells or tissues of human or animal origin, or both. The*
101 *cells or tissues may be viable or non-viable. It may also contain additional substances, such as*
102 *cellular products, bio-molecules, biomaterials, chemical substances, scaffolds or matrices.*

103 *Products containing or consisting exclusively of non-viable human or animal cells and/or tissues,*
104 *which do not contain any viable cells or tissues and which do not act principally by*
105 *pharmacological, immunological or metabolic action, are excluded from this definition."*

106 Article 1(c) of Regulation (EC) No. 1394/2007 also states that:

107 "*Cells or tissues shall be considered 'engineered' if they fulfil at least one of the following*
108 *conditions:*

109 *- the cells or tissues have been subject to substantial manipulation, so that biological*
110 *characteristics, physiological functions or structural properties relevant for the intended*
111 *regeneration, repair or replacement are achieved. The manipulations listed in Annex I, in*
112 *particular, shall not be considered as substantial manipulations,*

113 *- the cells or tissues are not intended to be used for the same essential function or functions in*
114 *the recipient as in the donor."*

115 According to Article 1(d) of Regulation (EC) No. 1394/2007, a '**Combined advanced therapy**
116 **medicinal product**' means an advanced therapy medicinal product that fulfils the following conditions:

117 *- it must incorporate, as an integral part of the product, one or more medical devices within the*
118 *meaning of Article 1(2)(a) of Directive 93/42/EEC or one or more active implantable medical*
119 *devices within the meaning of Article 1(2)(c) of Directive 90/385/EEC, and*

120 *- its cellular or tissue part must contain viable cells or tissues, or*

121 *- its cellular or tissue part containing non-viable cells or tissues must be liable to act upon the*
122 *human body with action that can be considered as primary to that of the devices referred to.*

123 Article 1(2) of Regulation (EC) No. 1394/2007 states that:

124 "Where a product contains viable cells or tissues, the pharmacological, immunological or
125 metabolic action of those cells or tissues shall be considered as the principal mode of action of
126 the product."

127 Furthermore, an advanced therapy medicinal product containing both autologous and allogeneic
128 cells or tissues shall be considered to be for allogeneic use.

129 Finally Article 1(5) of Regulation (EC) No. 1394/2007 states that:

130 "A product which may fall within the definition of a tissue engineered product and within the definition
131 of a somatic cell therapy medicinal product shall be considered as a tissue engineered product. A
132 product which may fall within the definition of a somatic cell therapy medicinal product or a tissue
133 engineered product, and a gene therapy medicinal product, shall be considered as a gene therapy
134 medicinal product."

135 **2.2. Scientific grounds applied to the classification of ATMPs**

136 According to Article 17 of the ATMP Regulation, products are classified according to the respective
137 definitions of gene therapy medicinal product, somatic cell therapy medicinal products, tissue
138 engineered product and combined ATMP, on the basis of scientific information provided by the
139 applicant.

140 This section elucidates the scientific criteria applied for the classification of ATMPs. The following list of
141 criteria is based largely on the experience gained by the CAT through recommendations on ATMP
142 classification issued so far². These should not be considered as exhaustive and might be subject to
143 change as science evolves.

144 **2.2.1. Claim on the mode of action (MoA)**

145 In this context, the information on the claimed MoA is particularly important in order to ascertain
146 whether the product is for treatment, prevention or diagnosis of a disease, and exerts its activity via a
147 pharmacological, immunological or metabolic action or whether the intended MoA of the product is
148 regeneration, repair or replacement of cells/tissues.

149 For example, if mesenchymal stem cells are used to treat a diseased organ, this could act via a
150 combination of mechanisms which can include metabolic, immunological, pharmacological,
151 regeneration and repair. In such a case, the predominant mode of action claimed will affect whether
152 this will be classified as somatic cell therapy or tissue-engineered product.

153 The claim can be based either on data and/or on current scientific knowledge, but it has to be
154 sufficiently substantiated in each case. Otherwise, the CAT may only conclude that a product is an
155 ATMP, but not yet if it is, for example, a tissue engineered product or a somatic cell therapy medicinal
156 product.

157 **2.2.2. Criteria for GTMP**

158 The definition of gene therapy medicinal product according to Annex I, part IV, section 2.1 of Directive
159 2001/83/EC, as amended, is articulated into two conditions that have both to be fulfilled
160 simultaneously: 1) the product has to be of biological origin and contains recombinant nucleic acid(s)

² The complete list of scientific recommendations on classification of ATMPs can be found at:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000301.jsp&mid=WC0b01ac05800862c0

161 and 2) the recombinant nucleic acid(s) should be directly involved in the therapeutic action of the
162 product. In this respect the following observations can be made:

163 • Indent (a) of the definition of Gene therapy medicinal product :

164 the recombinant nucleic acids should be of biological origin independently from the origin of the
165 vector system used (e.g. viral/bacterial vectors or micellar and liposomal formulations, etc.)

166 • Indent (b) of the definition of Gene therapy medicinal product on the notion of "*its therapeutic,*
167 *prophylactic or diagnostic effect relates directly to the recombinant nucleic acid sequence it*
168 *contains, or to the product of genetic expression of this sequence*":

169 pending fulfilment of the indent (a) of the definition, the MoA and proposed indication, as claimed
170 by the applicant for the defined products, are of importance when considering the "direct"
171 relationship of the effect to the delivered genetic sequence or the expressed product. As an
172 illustration, the CAT provided two scientific recommendations for classifications for genetically
173 modified T cells encoding an exogenous thymidine kinase gene. The T cell preparations were
174 intended for immune reconstitution as adjunct treatment in haematopoietic stem cell
175 transplantation.

176 These T cell preparations have been classified as somatic cell therapy medicinal products
177 considering that the treatment was adjunctive T-cell therapy supporting immune reconstitution of
178 leukaemia patients who underwent bone marrow transplantation after myeloablative conditioning
179 regime. In both cases, the genetic modification leading to the expression of the exogenous gene
180 herpes simplex virus thymidine kinase - by the addition of the corresponding genetic sequence -
181 relates to the treatment (with ganciclovir administration) of a potential graft versus host disease
182 that may occur in some patients undergoing Haematopoietic Stem Cell Therapy (HSCT). The
183 recommendation on the classification as somatic cell therapy considered the primary role of the
184 cells intended for the "immune reconstitution" of the patients while the genetic modification was
185 restricted to a second role of controlling the potential risk of graft versus host disease. However, it
186 should be stressed that being considered as a genetically modified somatic cell therapy product,
187 most of the principles and requirements that normally apply to gene therapy medicinal products,
188 may also apply for these products (i.e. the classification does not necessarily exempt from the
189 relevant and applicable regulatory requirements of GTMP).

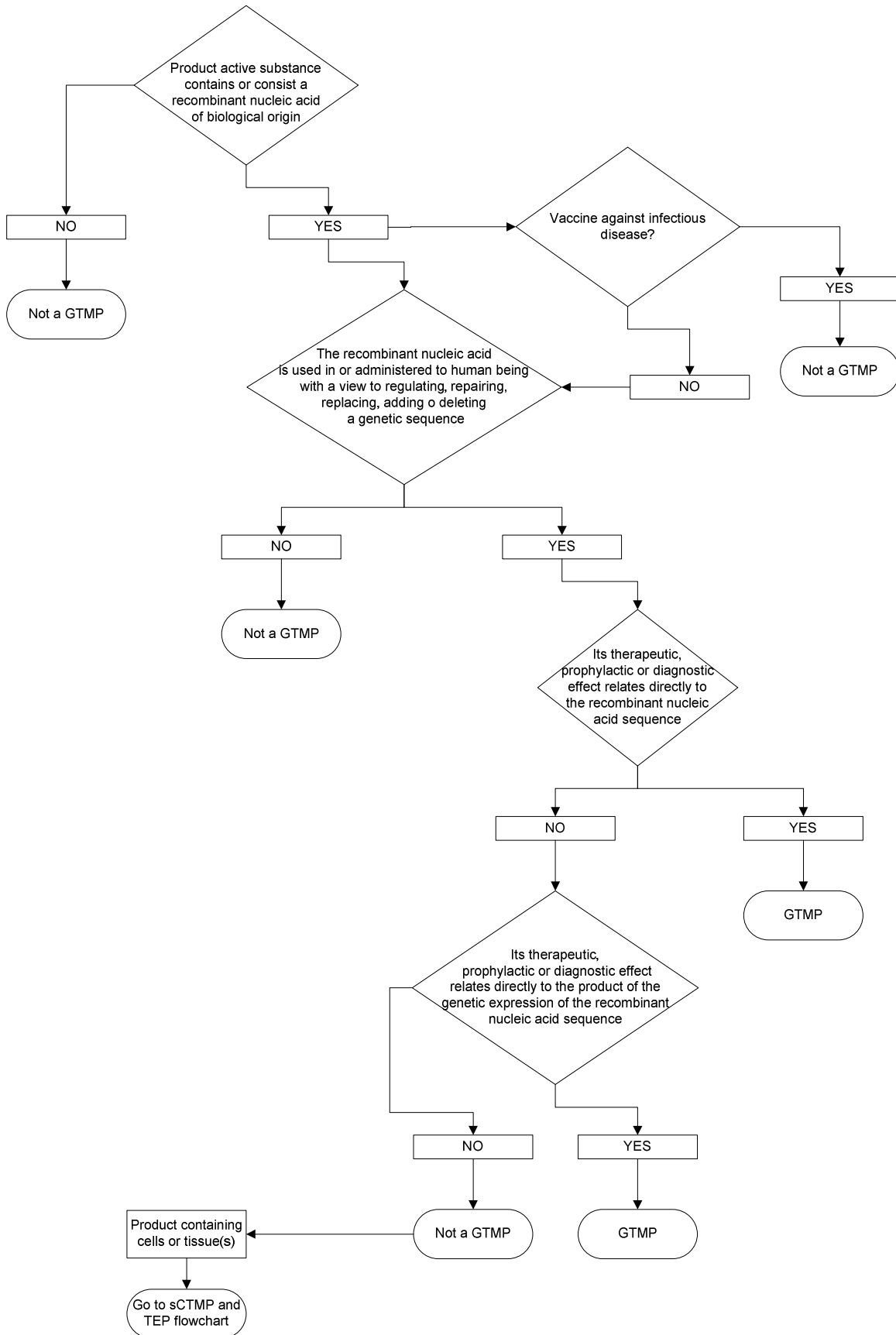
190 • The gene transfer does not necessarily have to take place in the human body, since for example
191 the product encoding <.....> for ex-vivo transduction of corneal tissue has also been classified as a
192 gene therapy medicinal product

193 • The legislation also foresaw that "*Gene therapy medicinal products shall not include vaccines*
194 *against infectious diseases*". Live recombinant viral vectors (delivering genes encoding specific
195 antigen sequences into human somatic cells) could fulfil the definition of Gene Therapy Medicinal
196 Products (GTMP) when administered for example in oncology, but similar products would not be
197 classified GTMPs when intended as prophylactic or therapeutic against infectious disease, based on
198 this legal exemption. This is, on a scientific level, also stressed by the fact that the term "cancer
199 vaccine" is considered obsolete and should be replaced by "cancer immunotherapy product".

200 As example, CAT has classified a live recombinant lentiviral vector encoding viral epitopes for
201 therapeutic vaccination against that virus as not being an ATMP in application of the above-
202 mentioned exception.

203 **Figure 1. DECISION TREE FOR GTMP**

204 The following questions can help applicants to classify their product:



205

206 **2.2.3. Criteria for somatic cell therapy medicinal products (sCTMP) and**
207 **tissue engineered products (TEP):**

208 sCTMP and TEP both contain or consist of engineered cells or tissues (see definition in section 2.1
209 above). To be considered 'engineered', cells or tissue(s) should fulfil at least one of the following
210 criteria:

211 1. Substantial manipulation: during the manufacturing process the cells or tissue(s) have been
212 manipulated so that their biological characteristics, physiological functions or structural properties
213 have been modified to achieve their intended function. Examples of substantial manipulations
214 include cell expansion (culture), genetic modification of cells, differentiation with growth factors,
215 etc.

216 Cell enrichment and expansion by culturing is currently by default considered substantial
217 manipulation. Although it may not necessarily lead to apparent changes in cell behavior of the gross
218 phenotype of the cells before and after culture, it is possible that the biological characteristics,
219 physiological function(s) or structural properties of the cells are changed by cell culture. Most
220 adherent cells, for example, are impacted by the repeated attachment and detachment cycles. It
221 has been demonstrated that even the techniques applied for cell detachment might lead to different
222 permanent phenotypic changes especially on cell surface proteins. Another example is primary cells,
223 where genotypic changes leading to senescence which begin to appear during in vitro cell culture.
224 Some cell types are shown to be especially sensitive to culture conditions and prone to genotypic
225 alterations.

226 2. Non-homologous use: the cells or tissues are not intended to be used for the same essential
227 function or functions in the recipient as in the donor. A relevant example is represented by
228 autologous bone-marrow derived cells which are only minimally manipulated (e.g. bone-marrow
229 aspirate) but injected in the patient's heart for regeneration of the myocardium. In this context it is
230 important to mention that only the function and mechanism of action of the cells is crucial with
231 regard to the non-homologous use regardless of the anatomical region where they are applied.

232 The main difference between sCTMP and TEP is determined on the basis of the intended function of the
233 product as claimed by the Applicant. The sCTMPs are intended for the prevention, diagnosis and/or
234 treatment of diseases via pharmacological, metabolic actions, whereas TEPs are used in or
235 administered to human beings with a view to regenerating, repairing or replacing a human tissue. The
236 decision, whether a product fulfils the requirements of a sCTMP or a TEP, is taken on the basis of the
237 claimed mode of action in association with its associated claimed intended function.

238 The therapeutic action of the product i.e. "regeneration- repair - replacement" is an important
239 component in determining the classification as TEP. These may be interlinked processes that cannot be
240 defined separately but have to be considered together. The three processes may occur concomitantly
241 or sequentially (e.g. implantation of chondrocytes to replace missing cartilage followed by repair and
242 induction of regeneration).

243 Isolated pancreatic beta cells embedded in an alginate matrix may serve as example for the
244 delineation between somatic cell therapy and tissue engineering: This product is administered to
245 patients with a view to restoring, correcting or modifying physiological function via a metabolic action
246 of the cells it contains (secretion of insulin). The intended function is not to regenerate, repair or
247 replace an organ or tissue. This decision was driven by the fact that the claimed MoA of the product
248 was the transient restoration of beta cell activity (the "replacement of the function"), but not the
249 regeneration, repair nor the replacement of the human tissue itself. In line with this approach, human
250 liver-derived progenitor cells were also classified as somatic cell therapy, since the cells serve to

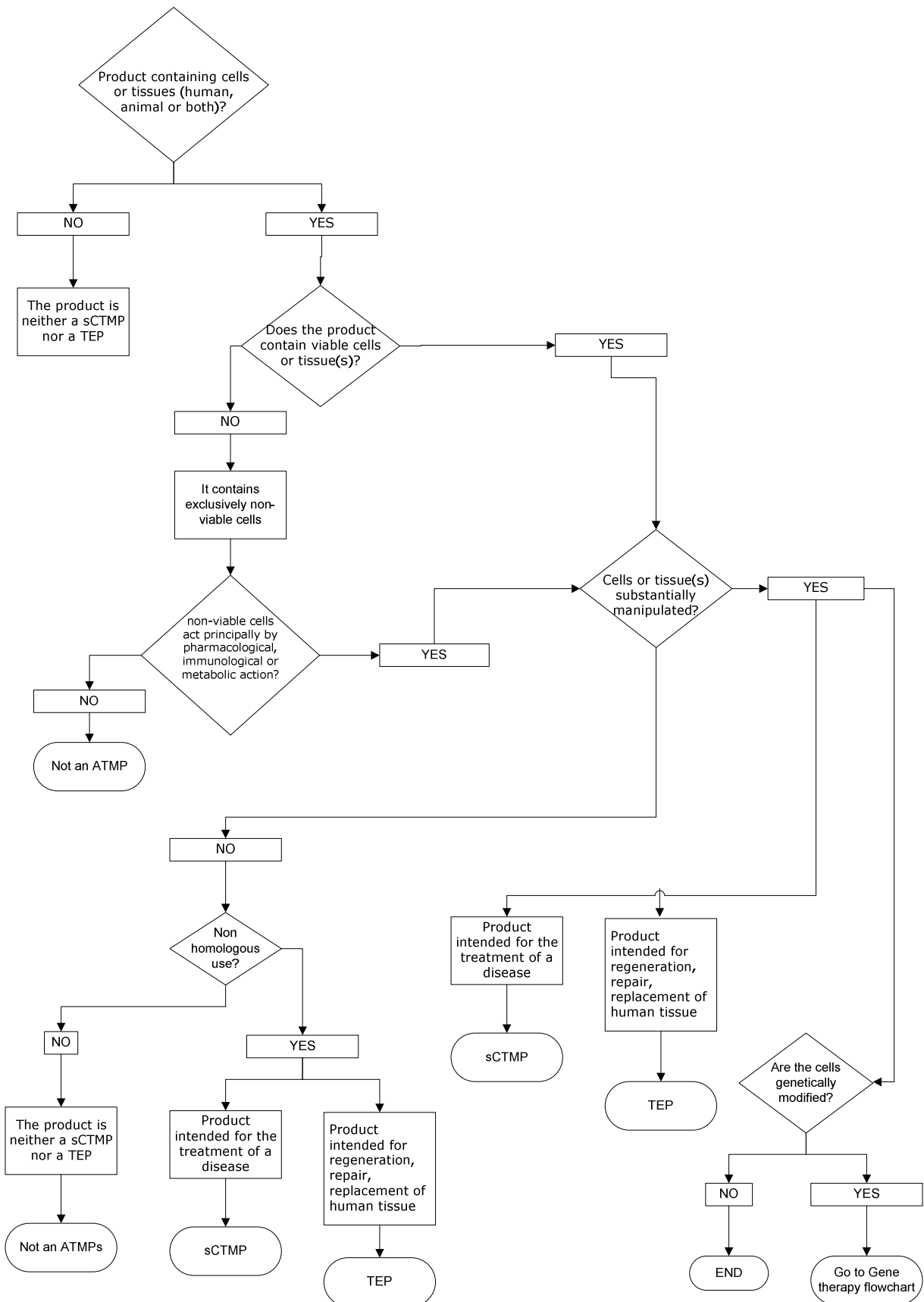
251 primarily replace a function (treatment of inborn errors of liver metabolism) rather than the tissue
252 itself.

253 In contrast, a preparation of cells derived from adult skeletal muscle tissue, intended for the treatment
254 of stress urinary incontinence, was classified as a TEP. Here, the cells are administered primarily with a
255 view to regenerating, repairing or replacing a human tissue, in this case the replacement of urethral
256 sphincter muscle cells, or to repair respective injured tissue.

257 It should be noted that the effect of a tissue engineered product can be transient, e.g. autologous
258 human keratinocytes intended for the treatment of acute burns may only transiently repair the
259 underlying structure and later be replaced.

260 **Figure 2. DECISION TREE FOR sCTMP and TEP**

261 The following questions can help applicants to classify their product:



262

263 **2.2.4. Criteria for combined ATMPs**

264 A product is classified as a combined ATMP when it fulfils the definitions provided in Article 2(1)(d) of
265 the ATMP Regulation (EC) 1394/2007 (See Section 2.1 above).

266 Combined ATMPs incorporate a cellular part consisting of viable or non-viable cells or tissues and of
267 one or more medical devices or one or more active implantable medical devices as an integral part of
268 the product. If cells or tissues are not viable these must exert the primary action of the combined
269 product.

270 Examples of combined ATMPs:

271 Autologous chondrocytes are put in culture medium in order to proliferate until the appropriate number
272 of cells is reached. The expanded cells are thereafter seeded onto a collagen membrane and
273 administered into the cartilage lesion in a joint fixed on this membrane. The primary action of the
274 combined product is given by the viable cells that repair the damaged tissue, while the medical device
275 part is a tool that is needed to retain the cells physically to the cartilage defect and guide their local
276 distribution.

277 Autologous osteoprogenitor cells, isolated from bone marrow, are cultured together with a
278 bioresorbable scaffold, which is CE marked for surgical use. During cell culture, the cells expand and
279 grow within and around the scaffold that acts as physical support. The finished combined product is an
280 integrated product consisting of a cellular component and a matrix. The repairing/replacing effect on
281 the bone defect is accomplished by the living cells that continue to grow within the lesion while the
282 biodegradable matrix is gradually eliminated. However, like in the first example, the matrix still has its
283 intended function at the time of implantation.

284 It should be noted that normally the medical device should retain its original form and function to be
285 considered as being "integral part" of the final product and thus qualify this product as a combined
286 product. CAT has, for example, classified a product containing pancreatic beta cells in an alginate
287 matrix as non-combined ATMP (somatic cell therapy), as the function of the matrix was no longer
288 considered to be linked to its structural properties (see also discussion on borderline cases further
289 below).

290 Examples of non-combined ATMP:

291 Human endothelial cells are cultured in a gelatin matrix and used to treat vascular injury. The applicant
292 claims that the product reduces the intimal thickening of vessels injured by the frequent procedures of
293 artero-venous grafts and fistula placements in patients that undergo hemodialysis. The underlying
294 mechanism of action is based on the concept that the allogeneic endothelial cells release biological
295 factors that inhibit the intimal hyperplasia, reduce the graft thrombosis, and repair the vascular injury.
296 The gel matrix is a CE marked medical device indicated in surgical procedures as an adjunct to
297 haemostasis. In combination with the endothelial cells, the gel is seeded with the cells as starting
298 material and becomes an integrated part of the final product. The applicant is supposing that the gel
299 matrix has the function to keep the cells around the vascular injury site to release the therapeutic
300 factors, but that it is also contributing in some way to provide the correct signals to the cells. The
301 matrix is therefore acting as an active substance of the final product that is therefore considered to be
302 a somatic cell therapy medicinal product and not a combined advanced therapy product.

303 **2.3. Evolving and borderlines areas**

304 The ATMP classification procedure will also have to clarify borderline cases between ATMPs versus non-
305 ATMPs as well as between the different product categories within the ATMP sphere. Below are given
306 examples where assigning ATMPs to their respective categories have been subject to debate.

307 **2.3.1. Advanced therapies versus transplant/transfusion**

308 Products consisting of cells or tissues may scientifically be at the border between Tissues and Cells
309 directive (Directive 2004/23/EC) and the ATMP regulation. One example is the recommendation of the
310 CAT that a preparation of human pancreatic Langerhans' islets should not be classified as an ATMP.
311 CAT considered that, for this preparation, the described process steps do not constitute substantial
312 manipulations so that there is no change in the biological characteristics of the islets. In addition, the
313 product was intended to be used for the same essential function in the recipients, be it in the
314 allogeneic or autologous conditions described. This conclusion is, however, not directly applicable to
315 any other pancreatic beta cell products which may be submitted for classification, as they may be
316 derived from very different and more complex process and substantial manipulations, as discussed
317 elsewhere also in this paper.

318 In contrast, some products initially considered as non-ATMP because of an essentially minimal
319 manipulation or maintenance of the initial biological properties and autologous origin have been
320 classified by the CAT as ATMP due to their intended heterologous use. For example, autologous bone
321 marrow-derived progenitor cells intended for treatment of patients with myocardial infarction, or other
322 vascular diseases would be considered non-homologous use and therefore ATMPs (in this case tissue
323 engineering products).

324 **2.3.2. Gene therapy medicinal product versus biologicals containing or** 325 **consisting of GMOs (genetically modified organisms)**

326 CAT discussed several examples of genetically modified bacteria which express a human gene
327 sequence. The decisive factor for classification was to determine whether the medicinal product is
328 administered to human beings with a view to regulating, repairing, replacing adding or deleting a
329 genetic sequence. One could in this case argue that the genetic sequence is not "added" to human
330 cells, but remains in the bacteria, and equally also the protein it expresses. On the other hand,
331 although there is no integration of the genetic sequence into human cells, it may still be claimed that
332 the medicinal product is adding a genetic sequence into humans to elicit a pharmacological effect. It
333 was clarified that the legal definition "*it contains an active substance which contains or consists of a*
334 *recombinant nucleic acid used in or administered to human beings with a view to regulating, repairing,*
335 *replacing, adding or deleting a genetic sequence*" should be read "as is", that is, without adding for
336 example "to the human body" when interpreting it. Accordingly, the CAT classified this medicinal
337 product as a gene therapy medicinal product, since a genetic sequence is added.

338 **2.3.3. Gene therapy medicinal product versus cell therapy medicinal** 339 **product**

340 Another borderline scenario is products that are modified by adding a mRNA sequence, for example
341 dendritic cells (DC) electroporated with mRNA in vitro and administrated to the patient to elicit a
342 specific immune response. One could argue that the claimed mechanism of action is directly related to
343 the expression of the mRNA encoded antigens to stimulate e.g. tumour specific immune responses.
344 However, due to its relatively short half life there may be little or no residual mRNA at the time of re-
345 administration of the dendritic cells to the patient. Thus, it can be claimed that a recombinant nucleic
346 acid is not administered to human beings with a view to adding a genetic sequence, but rather the
347 mRNA electroporated DCs could be seen as an intermediate in the manufacturing process where the
348 phenotype is finally altered without alteration of the genotype of the cells. Therefore, the product was
349 considered not to comply with the definition of a gene therapy medicinal product. Instead CAT
350 considered that the product was a somatic cell therapy product as it consists of cells which were

351 administered to human beings with a view to treating a disease through the immunological action of
352 the modified cell populations.

353 **2.3.4. Combined products versus TEP non-combined (device acting as** 354 **excipient or no longer acting as device)**

355 The border between combined or non-combined ATMPs is often discussed in classification procedures.
356 Two situations have to be taken into account: first, the medical device is an active integral part of the
357 final product (combined) and, secondly, the combined component is not a medical device but
358 considered as an excipient in the final formulation of the drug (and therefore not combined).

359 Human aortic endothelial cells cultured in a matrix and intended for the treatment of vascular injury
360 were classified as sCTMP, not combined. The matrix alone has been approved as medical device in the
361 EU but the CAT considered that the matrix, as a component of this medicinal product, is remodelled by
362 the cells contributing to product efficacy. Thus, the manufacturing process uses the medical device in a
363 way that it was not intended to be used. As an active integral part of the final product it was not
364 considered to be a medical device any more.

365 A similar situation applies to another example, already discussed, which is the mixture of pancreatic
366 beta cells and their accompanying endocrine cell populations embedded in an alginate matrix for the
367 treatment of diabetes. The CAT was of the opinion that the inert alginate matrix is reworked by the
368 cells during culture and becomes an active integral part of the product that supports to
369 contain/preserve the biological characteristics and functional activities of the cells. The CAT therefore
370 classified the product as a sCTMP, not combined.

371 In contrast, human fibroblasts cultured onto a biodegradable matrix were classified as a combined TEP.
372 Here, the matrix is an integral but not an active part of the product, but it fulfils its function as CE
373 marked medical device when administered to patients.

374 **2.4. Clarifications on procedural aspects information to be submitted by** 375 **the applicant**

376 In order to facilitate the access to the ATMP classification, the CAT has published the procedural
377 advice for the ATMP classification³, which describes the procedure and gives guidance for the steps
378 to be followed by the applicant for the submission of an ATMP classification.

379 Upon receipt of a valid request⁴, the CAT delivers a scientific recommendation on an ATMP
380 classification after consultation with the European Commission within 60 days.

381 The following **scientific information** is deemed as minimal and necessary to be submitted, in
382 order for the CAT to classify a product:

- 383 • Active substance: description of active substance (including starting materials, when relevant), any
384 additional substances (e.g. when applicable: structural component such as scaffolds, matrices,
385 biomaterials, biomolecules and/or other components), medical device or active implantable medical

³ [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](#)

⁴ For the submission of an ATMP classification, applicants should complete a [Pre-submission request form](#) (selecting in the drop-down menu ATMP-ATMP classification) and the [ATMP Classification Request form and briefing information](#) and return both to: AdvancedTherapies@ema.europa.eu

386 device (including information on the classification status of the Medical Device from a Medical
387 Device Competent Authority when applicable).

388 • Finished Product: qualitative & quantitative composition, mode of administration, pharmaceutical
389 form and description of the finished product ready for clinical use.

390 • Mechanism of Action/ Proposed use: claimed mechanism of action, properties (including
391 pharmacological, immunological or metabolic, if applicable), proposed use / indication (including
392 therapeutic, prophylactic, diagnostic). See also section 2.2.1. above. Applicants should provide an
393 in-depth discussion on how the product works and what data are there to support the mechanism
394 of action. This is essential, since the outcome of the classification will depend on the claim the
395 Applicant provides and how strong the evidence is to support it. For example, CAT was for one
396 product not able to classify it as tissue engineered product or somatic cell therapy medicinal
397 product, since the claim for the mechanism of action was not sufficiently defined, and not enough
398 data (be it data with the product or what is published for that given product class) was presented
399 to support the Applicant's claims.

400 • Summary of the status of the development of the product: key elements of manufacturing, quality
401 aspects (including description and level of manipulations on cells and tissues, when applicable).
402 Outline of Non-Clinical development and Clinical development relevant for the ATMP classification.

403 Depending on the stage of development at which the classification advice is sought, some of the
404 parameters or information requested above may not be finalised. In this case, the target profile
405 and intended product description may suffice.

406 In addition to the qualitative and quantitative description of the product to be classified, applicants are
407 encouraged to present their understanding of the regulatory definition of the product under
408 development. They should discuss any aspects supporting or not the applicability of the pharmaceutical
409 framework for the development and evaluation of the product. Overlapping aspects relevant to medical
410 devices, cosmetics, human tissues and cells, blood products, borderline medical use or other issues
411 should also be highlighted if appropriate.

412 Details of the regulatory status of the product (including medical device/active implantable device,
413 when applicable), marketing history in EU and non EU countries and information on the current
414 medical use worldwide are requested to complement the overall understanding on the regulatory
415 status of the candidate ATMP.

416 Applicants can include in the request any additional information or bibliographic references to further
417 substantiate their positions on the classification of their product on the light of legal definitions in force.

ⁱ Article 17(1) Any applicant developing a product based on genes, cells or tissues may request a scientific recommendation of the Agency with a view to determining whether the referred product falls, on scientific grounds, within the definition of an advanced therapy medicinal product. The Agency shall deliver this recommendation after consultation with the Commission and within 60 days after receipt of the request.

(2). The Agency shall publish summaries of the recommendations delivered in accordance with paragraph 1, after deletion of all information of commercial confidential nature.

ii Directive 2001/83/EC Annex I Part IV as amended by Directive 2009/120/EC:

Web link to Directive 2009/120/EC:

<http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2009:242:0003:0012:EN:PDF>

iii A medicinal product as defined in Article 1(2) of Directive 2001/83/EC, as amended, is:

(a) Any substance or combination of substances presented as having properties for treating or preventing disease in human beings;

or

(b) Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis"

^{iv} Recital 24 of ATMP Regulation: *The Agency should be empowered to give scientific recommendations on whether a given product based on genes, cells or tissues meets the scientific criteria which define advanced therapy medicinal products, in order to address, as early as possible, questions of borderline with other areas such as cosmetics or medical devices, which may arise as science develops. The Committee for Advanced Therapies, with its unique expertise, should have a prominent role in the provision of such advice.*