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4 Reflection paper on classification of advanced therapy 5 medicinal products

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Keywords	<i>ATMP classification, Gene therapy, Somatic cell therapy, Tissue engineered Products, Combined ATMPs</i>
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11 Introductory statement on the changes introduced during the revision of this Reflection Paper

12 CAT is now operating the ATMP classification procedure for more than 5 year and has classified over
13 100 products based on genes, cells and tissues.

14 The Reflection Paper on classification of ATMPs has been updated to reflect the current thinking of the
15 CAT on substantial manipulation and non-homologous use (see section 2.2.3).

16 Additional changes have been implemented throughout the text to clarify the existing concepts, e.g.
17 the demarcation between vaccines against infectious diseases and gene therapy medicinal products
18 (see section 2.2.2) and the Criteria for combined ATMPs (see section 2.2.4).



19 Reflection paper on classification of Advanced Therapy
20 Medicinal Products

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40 **1. Executive summary**

41 Further to the implementation of Article 17 of Regulation (EC) No 1394/2007ⁱ (hereinafter referred as
42 to 'the Advanced Therapy Medicinal Products (ATMPs) Regulation'), applicants have access to an
43 optional procedure which is the CAT (Committee for Advanced Therapies) scientific recommendation
44 for the classification of ATMPs, hereafter referred to as "ATMP classification". It is underpinned by the
45 ATMP Regulation which enables the European Medicines Agency (EMA) in close collaboration with the
46 European Commission to determine whether or not a given product meets the scientific criteria, which
47 define ATMPsⁱⁱ. The ATMP classification procedure has been established in order to address, as early as
48 possible, questions of borderline with other areas such as cosmetics or medical devices, transplants
49 etc.

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

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

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

62 The ATMP classification procedure is voluntary and free of charge. While the recommendation on
63 classification provided by the Agency is not binding, the procedure can help developers to clarify the
64 applicable regulatory framework. It also provides clarity on the development path and scientific-
65 regulatory guidance to be followed. The ATMP classification may sometimes also be a useful tool for
66 applicants to initiate a tailored dialogue on the product development with regulators. Indeed, the ATMP
67 classification, along with other tools (e.g. ITF briefing meetings¹), should be seen as a first opportunity
68 to engage with regulators. Once the candidate ATMP classification has been clarified and confirmed,
69 the dialogue can continue with the use of other regulatory procedures such as scientific advice and
70 ATMP certification, the latter exclusively set up under the auspices of the dedicated committee (CAT).
71 The ATMP classification may also help developers to gain access to all relevant services and incentives
72 offered by the EMA.

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

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

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

82 In addition, the ATMP classification procedure is only applicable when a product is based on genes,
83 cells or tissues.²

84 If additional scientific information becomes available during the product development which could
85 impact on the previously submitted ATMP classification, the applicant can submit a follow-up request.

86 The summary outcome ATMP classifications assessed so far by the CAT is available on the EMA
87 website³. This information is updated on a monthly basis.
88

89 **Scope**

90 The aim of this reflection paper is to provide guidance on the ATMP classification procedure, as well as
91 on the interpretation of key concepts of the definition of gene therapy medicinal product, somatic cell
92 therapy medicinal product, tissue engineered product, and combined advanced therapy medicinal
93 product. The guidance reflects the experience gained in the application of the classification procedure..

94 **2. Discussion**

95 **2.1. Legal basis of ATMP classification**

96 According to Article 2(1)(a) of Regulation (EC) No.1394/2007, an 'advanced therapy medicinal product'
97 means any of the following medicinal products for human use:

- 98 • a gene therapy medicinal product as defined in Part IV of Annex I to Directive 2001/83/EC, as
99 amended
- 100 • a somatic cell therapy medicinal product as defined in Part IV of Annex I to Directive 2001/83/EC,
101 as amended
- 102 • a tissue engineered product as defined in Article 2(1)(b) of Regulation (EC) No. 1394/2007.

103 Article (2)(1)(d) of the ATMP Regulation also gives a definition of 'Combined ATMP'. These products
104 contain as an integral part of the product a medical Device (see below).

105 The definitions of a gene therapy medicinal product and a somatic cell therapy medicinal product
106 according to Directive 2001/83/EC, Annex I, Part IV, as amended (implementing Directive
107 2009/120/EC) are as follows:

108 **2.1.1. Gene therapy medicinal product**

109 Gene therapy medicinal product means a biological medicinal product which fulfils the following two
110 characteristics:

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

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

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

117 **2.1.2. Somatic cell therapy medicinal product**

² Taking into account the remit of the European Medicines Agency, as stated in Article 17 of Regulation 1394/2007 i.e. "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"

³ 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

118 Somatic cell therapy medicinal product means a biological medicinal product which fulfils the following
119 two characteristics:

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

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

127 For the purposes of point (a), the manipulations listed in Annex I to Regulation (EC) No 1394/2007, in
128 particular, shall not be considered as substantial manipulations: cutting, grinding, shaping,
129 centrifugation, soaking in antibiotic or antimicrobial solutions, sterilization, irradiation, cell separation,
130 concentration or purification, filtering, lyophilization, freezing, cryopreservation, and vitrification. It
131 should be pointed out that this list is non-exhaustive.

132 **2.1.3. Tissue engineered products**

133 Tissue engineered products, according to Article 2(1)(b) of Regulation (EC) No. 1394/2007, means a
134 product that:

135 *- contains or consists of engineered cells or tissues, and*

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

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

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

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

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

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

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

154 **2.1.4. Combined Advanced Therapy Medicinal Products**

155 According to Article 2(1)(d) of Regulation (EC) No. 1394/2007, a '**Combined advanced therapy**
156 **medicinal product**' means an advanced therapy medicinal product that fulfils the following conditions:

157 *- it must incorporate, as an integral part of the product, one or more medical devices*
158 *within the meaning of Article 1(2)(a) of Directive 93/42/EEC or one or more active*

159 *implantable medical devices within the meaning of Article 1(2)(c) of Directive*
160 *90/385/EEC, and*

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

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

165 For requirements for medical devices and implantable medical devices please consult the relevant
166 European Commission guidelines and Medical Device Legislation, as appropriate.

167 **2.1.5 Additional legal clarifications in Regulation (EC) No. 1394/2007**

168 • With regards to **products containing cells or tissues**, Article 2(1)(2) states that:

169 *"Where a product contains viable cells or tissues, the pharmacological, immunological or*
170 *metabolic action of those cells or tissues shall be considered as the principal mode of*
171 *action of the product."*

172 For Tissue Engineered products their Mode of Action is linked to regeneration, repair or
173 replacement a human tissue, as described in Article 2(1)(b).

174 • In accordance with Article 2(3), an **advanced therapy medicinal product containing both**
175 **autologous and allogeneic cells or tissues** shall be considered to be for allogeneic use.

176 • Demarcation rule between ATMPs:

177 Article 2(4) and 2(5) states that:

178 *"A product which may fall within the definition of a tissue engineered product and within the*
179 *definition of a somatic cell therapy medicinal product shall be considered as a tissue*
180 *engineered product. A product which may fall within the definition of a somatic cell therapy*
181 *medicinal product or a tissue engineered product, and a gene therapy medicinal product, shall*
182 *be considered as a gene therapy medicinal product."*

183 **2.2. Scientific principles applied to the classification of ATMPs**

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

188 This section elucidates the scientific criteria applied for the classification of ATMPs. The following list of
189 criteria is based largely on the experience gained by the CAT through recommendations on ATMP
190 classification issued so far³. These should not be considered as exhaustive and might be subject to
191 change as science evolves.

192 **2.2.1. Claimed mode of action (MoA)**

193 Information on the claimed MoA is particularly important to ascertain whether the product is for
194 treatment, prevention or diagnosis of a disease, and exerts its activity via a pharmacological,
195 immunological or metabolic action, or whether the product is intended for regeneration, repair or
196 replacement of cells/tissues.

197 For example, if mesenchymal stem cells are used to treat a diseased organ, this could act via a
198 combination of mechanisms which can include metabolic, immunological, pharmacological,

199 regeneration and repair. In such a case, the predominant mode of action claimed will affect whether
200 this will be classified as somatic cell therapy or tissue-engineered product.

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

205 **2.2.2. Criteria for GTMP**

206 The definition of gene therapy medicinal product according to Annex I, part IV, section 2.1 of Directive
207 2001/83/EC, as amended, is articulated into two conditions that have both to be fulfilled
208 simultaneously: 1) the product has to be of biological origin and contains recombinant nucleic acid(s)
209 and 2) the recombinant nucleic acid(s) should be directly involved in the mechanism of action (and
210 hence therapeutic action of the product. In this respect the following observations can be made:

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

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

- 214 • Indent (b) of the definition of Gene therapy medicinal product :

215 *"its therapeutic, prophylactic or diagnostic effect relates directly to the recombinant nucleic acid*
216 *sequence it contains, or to the product of genetic expression of this sequence"*: the MoA and
217 proposed indication, as claimed by the applicant are of essential to assess if there is a "direct"
218 relationship between the therapeutic, prophylactic or diagnostic effect of the product and the
219 delivered genetic sequence or the expressed product. As an illustration, the CAT provided two
220 scientific recommendations for classifications for genetically modified T cells encoding an
221 exogenous thymidine kinase gene. The T cell preparations were intended for immune reconstitution
222 as adjunct treatment in haematopoietic stem cell transplantation.

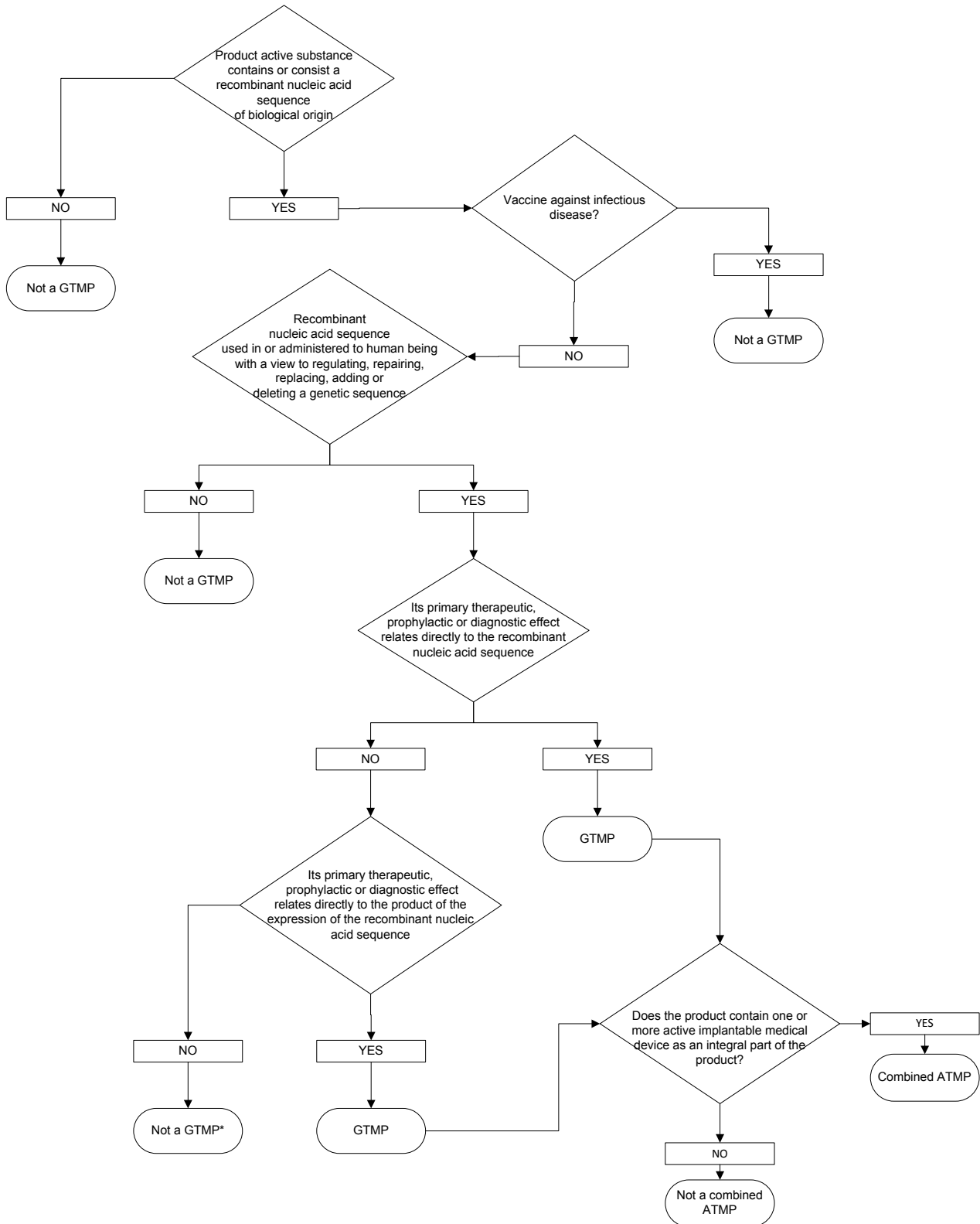
223 These T cell preparations have been classified as somatic cell therapy medicinal products
224 considering that the treatment was adjunctive T-cell therapy supporting immune reconstitution of
225 leukaemia patients who underwent bone marrow transplantation after myeloablative conditioning
226 regime. In both cases, the genetic modification leading to the expression of the exogenous gene
227 herpes simplex virus thymidine kinase - by the addition of the corresponding genetic sequence -
228 relates to the treatment (with ganciclovir administration) of a potential graft versus host disease
229 that may occur in some patients undergoing Haematopoietic Stem Cell Therapy (HSCT). The
230 recommendation on the classification as somatic cell therapy considered that the primary role of
231 the cells was the "immune reconstitution" of the patients, while the genetic modification was
232 limited to a secondary role of controlling the potential risk of graft versus host disease. However, it
233 should be stressed that being considered as a genetically modified somatic cell therapy product,
234 most of the principles and requirements that normally apply to gene therapy medicinal products,
235 may also apply for these products (i.e. the classification does not necessarily exempt from the
236 relevant and applicable regulatory requirements of GTMP).

- 237 • Genetic manipulation does not necessarily have to take place in the human body, since for
238 example products consisting of genetically modified cells generated *ex-vivo* have also been
239 classified as a gene therapy medicinal product (e.g. autologous CD34+ haematopoietic stem cells
240 (HSCs) transduced with lentiviral vector Lenti-D encoding the human ABCD1 cDNA and autologous
241 CD34+ haematopoietic stem cells (HSCs) transduced with lentiviral vector LentiGlobin encoding the
242 human β A-T87Q-globin gene).

- 243 • The legislation provides that "*Gene therapy medicinal products shall not include vaccines against*
244 *infectious diseases*". For classification purposes, vaccines are expected to have prophylactic mode
245 of action, i.e. prevention of an infectious disease in humans. If a product is intended to treat
246 pathologies caused by the infection (e.g. malignancies), it is classified as a GTMP. Live recombinant
247 viral vectors (delivering genes encoding specific antigen sequences into human somatic cells) could
248 fulfil the definition of Gene Therapy Medicinal Products (GTMP) when administered for example in
249 oncology, but similar products would not be classified GTMPs when intended as prophylactic
250 against infectious disease. [In order to enable the](#) classification of borderline products (treatment of
251 infections or premalignancies) the therapeutic indication and target population should be clearly
252 defined.

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

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



255 Explanatory notes: *) The product can contain genetically modified cells for which specific requirements should be followed (see ‘Guideline
 256 on human cell-based medicinal products’ (EMEA/CHMP/410869/2006).
 257

258 **2.2.3. Criteria for somatic cell therapy medicinal products (sCTMP) and**
259 **tissue engineered products (TEP):**

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

263 1. Substantial manipulation

264 The cells or tissue(s) have been manipulated during the manufacturing process so that their
265 biological characteristics, physiological functions or structural properties have been modified to be
266 relevant for their intended function. Examples of substantial manipulations include cell expansion
267 (culture), genetic modification of cells, differentiation/activation with growth factors.

268 Cell culturing leading to expansion is considered substantial manipulation. Although it may not
269 necessarily lead to immediate changes in cell functionality or the phenotype of the cells before and
270 after culture, it cannot be ruled out that the biological characteristics, physiological function(s) or
271 structural properties of the cells are changed by cell culture. Induction of proliferation of cells during
272 cell culture has to be regarded as changes of their biological characteristics and structural
273 properties, at least by increasing cell numbers to augment the desired function of the cells.
274 Furthermore, most adherent cells, for example, are impacted by the repeated attachment and
275 detachment cycles. It has been demonstrated that even the techniques applied for cell detachment
276 might lead to different phenotypic changes especially on cell surface proteins.

277 Enzymatic digestion of tissue to release cells is also considered to be substantial manipulation, when
278 the aim is to dissociate cell-cell contacts. Only when the enzymatic digestion leads to isolation of
279 functionally intact tissue units (e.g. pancreatic islets), the procedure is not considered substantial
280 manipulation.

281 Alternatively, based on scientific considerations, the CAT can also consider other manipulations as
282 "non substantial". One example is the radiolabelling of leukocytes for diagnostic purposes. This
283 technique has no significant impact on the biological properties of the cells and should thus not be
284 considered a substantial manipulation.

285

286 2. Different essential function (non-homologous use).

287 Cells harvested and separated by a simple selection method, and re-administered to fulfil their
288 same essential function will generally be regarded as homologous use. However, depending on
289 whether or not the selection process/method will alter the original characteristics of the cells may
290 result in classification as ATMPs.

291 In case no substantial manipulation of the cells takes place, the classification is based on the
292 essential function of the cells. Such non-substantially manipulated cells used for the same essential
293 function are not considered ATMPs. The same essential function for a cell population means that the
294 cells when removed from their original environment in the human body are used to maintain the
295 original function in the same anatomical or histological environment. An example of this category is
296 bone marrow cells used for haematopoietic reconstitution. All other clinical uses of bone marrow
297 cells are considered to be ATMPs. The same principal applies to other non-substantially manipulated
298 cells from various origins, for example adipose cells transplanted to other than fat tissue are
299 considered to be ATMPs.

300 Similarly, the replacement of an organ or tissue as its whole or functional unit of a tissue (such as
301 cornea or pancreatic islets) is regarded as homologous use. Transplantation of a non-manipulated

302 tissue to another location in the same anatomical or histological environment to achieve the same
303 essential function is also considered as homologous use. This is the case for skin transplantation
304 from one part of the body to another part. Along the same line, subcutaneous implantation of
305 pancreatic islets is considered as homologous use. However, the classification will depend on the
306 manipulation and functional integrity of the pancreatic islets.

307 Animal cells administered to humans will always be considered as ATMPs.

308

309 • Differentiation between sCTMP and TEP

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

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

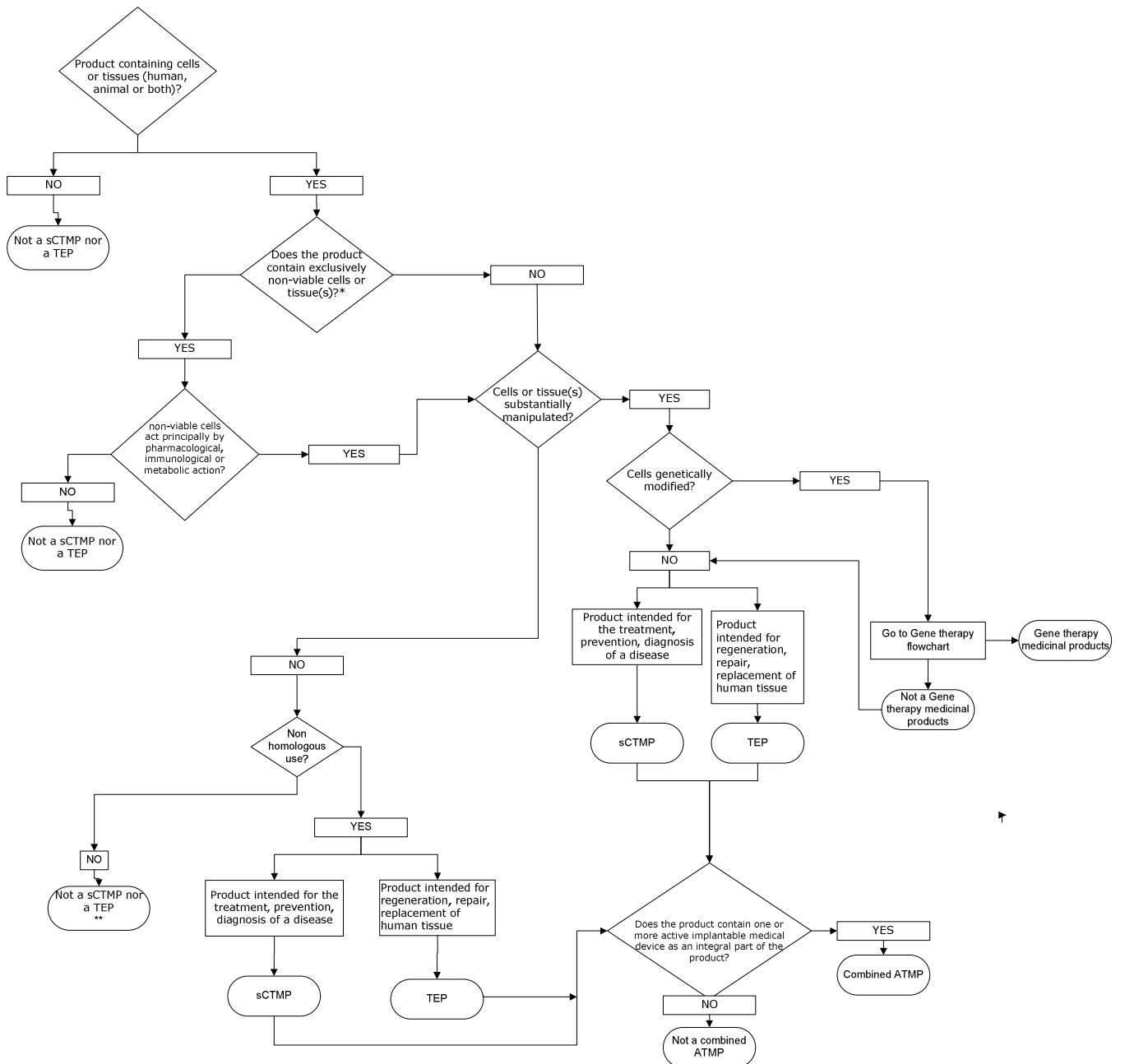
321 Isolated pancreatic beta cells embedded in an alginate matrix may serve as example for the
322 delineation between somatic cell therapy and tissue engineering: This cell-based product was intended
323 to be administered to patients with a view to restoring, correcting or modifying physiological function
324 via a metabolic action of the cells it contains (secretion of insulin). As the claimed MoA of the product
325 was the transient restoration of beta cell activity (the "replacement of the function"), but not the
326 regeneration, repair nor the replacement of the human tissue itself, it was concluded that the product
327 was a somatic cell therapy product. In line with this approach, human liver-derived progenitor cells
328 were also classified as somatic cell therapy, since the cells serve to primarily replace a function
329 (treatment of inborn errors of liver metabolism) rather than the tissue itself.

330 In contrast, a preparation of cells derived from adult skeletal muscle tissue, intended for the treatment
331 of stress urinary incontinence, was classified as a TEP because the cells were administered primarily
332 with a view to regenerating, repairing or replacing a human tissue (the replacement of urethral
333 sphincter muscle cells, or to repair respective injured tissue).

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

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

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



339

340 Explanatory notes:

341 *) viable cells in the meaning of the 'Guideline on human cell-based medicinal products'
 342 (EMA/CHMP/410869/2006); i.e.: viable human cells are defined by the European Pharmacopoeia
 343 monograph describing the biological assay for nucleated cell count and viability [Ph. Eur. General
 344 Chapter 2.7.29 (01/2008:20729)]. In particular the concerned method refers to cell staining by
 345 viability dyes and manual or automated analysis, under a light microscope or by flow cytometry, of a
 346 cell suspension in order to determine the percentage of viable cells. The methods provide information
 347 on the cytoplasmic membrane integrity which is an important factor to defining cell viability.

348 **) See section 2.2.3. Criteria for somatic cell therapy medicinal products (sCTMP) and tissue
 349 engineered products (TEP):

350

351 **2.2.4. Criteria for combined ATMPs**

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

354 Combined ATMPs incorporate an active substance, i.e. a recombinant nucleic acid, cellular part
355 consisting of viable or non-viable cells or tissues and of one or more medical devices or one or more
356 active implantable medical devices as an integral part of the product. If cells or tissues are not viable
357 these must exert the primary action of the combined product.

358 Examples of combined ATMPs:

- 359 • The expanded autologous chondrocytes seeded onto a collagen membrane and administered, fixed
360 on this membrane, into the joint cartilage lesion. The primary action of the combined product is
361 given by the viable cells that repair the damaged tissue, while the medical device part is a tool that
362 is needed to retain the cells physically to the cartilage defect.
- 363 • Autologous osteoprogenitor cells, isolated from bone marrow, are grown within and around a
364 bioresorbable scaffold that acts as physical support. The finished combined product is an integrated
365 product consisting of a cellular component and a matrix. The repairing/replacing effect on the bone
366 defect is accomplished by the living cells that continue to grow within the lesion while the
367 biodegradable matrix is gradually eliminated. However, like in the first example, the matrix still has
368 its intended function at the time of implantation.
- 369 • Genetically engineered cells - where a recombinant human gene in a mammalian expression vector
370 is introduced into human cells through transfection and resulting cells are further cultured in vitro -
371 incorporate as an integral part of the product two components, a semipermeable hollow fibre
372 membrane (HFM) capsule and a scaffold of strands of polyethylene terephthalate (PET) yarn. Both
373 components fulfil the definition of medical devices and/or active implantable medical devices as
374 they are required for maintenance of the cells (growth support, delivery of nutrients) and the
375 semipermeable capsule is needed for release of the therapeutic molecule. As the combined product
376 fulfils both definitions of a tissue engineered product and a gene therapy medicinal product, it was
377 classified as a combined gene therapy medicinal product.

378 It should be noted that normally the medical device should retain its intended purpose / mode of action
379 in the combination to be considered as being "integral part" of the final product and thus qualify this
380 product as a combined product. CAT has, for example, classified a product containing pancreatic beta
381 cells in an alginate matrix as non-combined ATMP (somatic cell therapy), as the function of the matrix
382 was no longer considered to be linked to its structural properties (see also discussion on borderline
383 cases further below).

384 Examples of non-combined ATMP:

385 An example of non-combined ATP can be given with the human endothelial cells cultured in a gelatin
386 matrix and used to treat vascular injury. The applicant claimed that the product reduces the intimal
387 thickening of vessels injured by the frequent procedures of artero-venous grafts and fistula placements
388 in patients that undergo haemodialysis. The underlying mechanism of action is based on the concept
389 that the allogeneic endothelial cells release biological factors that inhibit the intimal hyperplasia,
390 reduce the graft thrombosis, and repair the vascular injury. The gel matrix is a CE marked medical
391 device indicated in surgical procedures as an adjunct to haemostasis. The gel, which is seeded with the
392 cells as active substance, contributes to the formulation of the final product. The applicant is supposing
393 that the gel matrix has the function to keep the cells around the vascular injury site to release the

394 therapeutic factors, but that it is also contributing in some way to provide the correct signals to the
395 cells. The matrix is therefore acting as an active substance of the final product that is therefore
396 considered to be a somatic cell therapy medicinal product and not a combined advanced therapy
397 product.

398 **2.3. Evolving and borderlines areas**

399 The ATMP classification procedure will also have to clarify borderline cases between ATMPs versus non-
400 ATMPs as well as between the different product categories within the ATMP sphere. Below are given
401 examples that illustrate the type of issues that are taken into consideration when assessing borderline
402 cases.

403 **2.3.1. Advanced therapies versus transplants/transfusion**

404 Products consisting of cells or tissues may scientifically be at the border between Tissues and Cells
405 directive (Directive 2004/23/EC) and the ATMP regulation. One example is the recommendation of the
406 CAT that a preparation of human pancreatic Langerhans' islets should not be classified as an ATMP.
407 CAT considered that, for this preparation, the described process steps do not constitute substantial
408 manipulations for the intended use so that there is no change in the biological characteristics of the
409 islets. In addition, the product was intended to be used for the same essential function in the
410 recipients, be it in the allogeneic or autologous conditions described. This conclusion is, however, not
411 directly applicable to any other pancreatic beta cell products which may be submitted for classification,
412 as they may be derived from very different and more complex process and substantial manipulations,
413 as discussed also in section 2.2.3 (cell-based product consisting of isolated beta-cells embedded in an
414 alginate matrix).

415 In contrast, some products previously considered as non-ATMP because of an essentially minimal
416 manipulation or maintenance of the initial biological properties have been classified as ATMP due to
417 their intended non-homologous use. For example, autologous bone marrow-derived progenitor cells
418 intended for treatment of patients with myocardial infarction, or other vascular diseases would be
419 considered non-homologous use and therefore ATMPs (in this case tissue engineering products) (see
420 section 2.2.3).

421 It is possible that cell-based products administered in the same anatomical location fall under the
422 definition of ATMP on grounds that it is for non-homologous use. This can be encountered when the
423 mode of action of the cells is not identical to the one attributed to the cells by the scientific knowledge.
424 As an example, injection of concentrated bone marrow at the site of bone injury with the aim of
425 healing a bone lesion can be considered as non-homologous use.

426

427 **2.3.2. Gene therapy medicinal product versus biologicals containing or** 428 **consisting of GMOs (genetically modified organisms)**

429 CAT has discussed several examples of genetically modified bacteria which express a human gene
430 sequence which raised difficult questions about the interpretation of the first indent in the definition of
431 gene therapy medicinal product (i.e. that "*it contains an active substance which contains or consists of*
432 *a recombinant nucleic acid used in or administered to human beings with a view to regulating,*
433 *repairing, replacing, adding or deleting a genetic sequence*"). The following considerations are relevant
434 in this regard: (i) it could be considered that the genetic sequence is not "added" to human cells, but
435 remains in the bacteria, and equally also the protein it expresses; and (ii) it could be considered that
436 the medicinal product is adding a genetic sequence into humans to elicit a pharmacological effect.

437 Given that the first criteria of the definition of gene therapy medicinal product above referred does not
438 provide that the repair, replacement, addition or deletion of the genetic sequence is done “to the
439 human body”, the CAT classified this medicinal product as a gene therapy medicinal product. The
440 consideration that prevailed was therefore that a genetic sequence is administered to humans and that
441 the effect is due to the product expressed from this added genetic sequence.

442 **2.3.3. Gene therapy medicinal product versus cell therapy medicinal** 443 **product**

444 Another borderline scenario relates to products that are modified by adding a mRNA sequence, for
445 example dendritic cells (DC) electroporated with mRNA in vitro and administrated to the patient to
446 elicit a specific immune response. One could argue that the claimed mechanism of action is directly
447 related to the expression of the mRNA encoded antigens to stimulate e.g. tumour specific immune
448 responses. However, due to its relatively short half-life there may be little or no residual mRNA at the
449 time of re-administration of the dendritic cells to the patient. Thus, it can be claimed that a
450 recombinant nucleic acid is not administered to human beings with a view to adding a genetic
451 sequence, but rather the mRNA electroporated DCs could be seen as an intermediate in the
452 manufacturing process where the phenotype is finally altered without alteration of the genotype of the
453 cells. Therefore, the product was considered not to comply with the definition of a gene therapy
454 medicinal product. Instead CAT considered that the product was a somatic cell therapy product as it
455 consists of cells which were administered to human beings with a view to treating a disease through
456 the immunological action of the modified cell populations.

457 **2.3.4. Combined ATMPs versus non-combined cell-based medicinal** 458 **products (device acting as “excipient” or no longer acting as device)**

459 The border between combined or non-combined ATMPs is often discussed in classification procedures.
460 In this regard it is relevant to consider if (i) the medical device is an active integral part of the final
461 product (combined) or (ii) if the combined component (although CE marked) is not used as a medical
462 device but should be considered as an “excipient” in the final formulation of the drug (and therefore
463 not combined).

464 Human aortic endothelial cells cultured in a porcine gelatine matrix and intended for the treatment of
465 vascular injury were classified as sCTMP, not combined. The matrix alone has been made available in
466 the European Union under the status of a medical device but the CAT considered that the porcine
467 gelatine matrix, as a component of this medicinal product, is remodelled by the cells contributing to
468 product efficacy. Thus, the manufacturing process uses the matrix in a different way than its intended
469 use when considered as a medical device. In this formulation (e.g. the porcine gelatine matrix and the
470 human aortic endothelial cells), the matrix was not considered to be a medical device any more. The
471 CAT therefore classified the product as a sCTMP, not combined ATMP.

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

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

481 **2.4. Clarifications on procedural aspects information to be submitted by**
482 **the applicant**

483 In order to facilitate the access to the ATMP classification, the CAT has published the procedural
484 advice for the ATMP classification⁴, which describes the procedure and gives guidance for the steps
485 to be followed by the applicant for the submission of an ATMP classification.

486 Upon receipt of a valid request⁵, the CAT delivers a scientific recommendation on an ATMP
487 classification after consultation with the European Commission within 60 days.

488 Sufficient scientific information relevant to the decision is essential to be submitted in order for the
489 CAT to classify a product, e.g. on following areas:

- 490 • Active substance: description of active substance (including starting materials, when relevant), any
491 additional substances (e.g. when applicable: structural component such as scaffolds, matrices,
492 biomaterials, biomolecules and/or other components), medical device or active implantable medical
493 device (including information on the classification status of the Medical Device from a Medical
494 Device Competent Authority when applicable).
- 495 • Finished Product: qualitative and quantitative (where available) composition, mode of
496 administration, pharmaceutical form and description of the finished product ready for clinical use.
- 497 • Mechanism of Action/ Proposed use: claimed mechanism of action, properties (including
498 pharmacological, immunological or metabolic, if applicable), proposed use / indication (including
499 therapeutic, prophylactic, diagnostic). See also section 2.2.1. above. Applicants should provide an
500 in-depth discussion on how the product works and what data are there to support the mechanism
501 of action. This is essential, since the outcome of the classification will depend on the claim the
502 Applicant provides and how strong the evidence is to support it. For example, CAT was for one
503 product not able to classify it as tissue engineered product or somatic cell therapy medicinal
504 product, since the claim for the mechanism of action was not sufficiently defined, and not enough
505 data (be it data with the product or what is published for that given product class) was presented
506 to support the Applicant's claims.
- 507 • Summary of the status of the development of the product: key elements of manufacturing, quality
508 aspects (including description and level of manipulations on cells and tissues, when applicable).
509 Outline of Non-Clinical development and Clinical development relevant for the ATMP classification.

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

513 In addition to the qualitative and quantitative description of the product to be classified, applicants are
514 encouraged to present their views on the classification of products under development. They should
515 discuss any aspects supporting or not the applicability of the pharmaceutical framework for the
516 development and evaluation of the product. Overlapping aspects relevant to medical devices,
517 cosmetics, human tissues and cells, blood products, borderline medical use or other issues should also
518 be highlighted if appropriate.

⁴ [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](#)

⁵ 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

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

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

525

526

527 **References**

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.*