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Consultation document

**Definition of Investigational Medicinal Products (IMPs) and
use of Auxiliary Medicinal Products (AMPs)**

**Recommendations of the expert group on clinical trials for the implementation
of Regulation (EU) No 536/2014 on clinical trials on medicinal products for
human use**

*This document does not necessarily reflect the views of the European Commission and should
not be interpreted as a commitment by the Commission to any official initiative in this area.*

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1. INTRODUCTION

To facilitate the conduct of clinical trials in the Member States of the European Union¹, especially multi-centre clinical trials carried out in more than one Member State, it is necessary to have a common understanding of the definition of an investigational medicinal product (IMP).

This document intends to clarify and provide additional guidance on the definition of IMPs and to provide recommendations about the use of auxiliary medicinal products (AMPs), in accordance with applicable EU legislation.

2. MEDICINAL PRODUCTS INTENDED FOR RESEARCH AND CLINICAL TRIALS AND INVESTIGATIONAL MEDICINAL PRODUCTS (IMPs)

The Community Code relating to medicinal products for human use excludes, in Article 3(3) of Directive 2001/83/EC, "*medicinal products intended for research and development trials*" from its scope of application.

Regulation (EU) No 536/2014 Article 2 (5) defines an IMP as "*a medicinal product which is being tested or used as a reference, including as a placebo, in a clinical trial*". Further information on IMPs can be found in "The rules governing medicinal products in the European Union" Volume 10 – Guidance documents applying to clinical trials, Clinical Trials Regulation (EU) No 536/2014 Questions and Answers (currently being updated).

It follows that medicinal products with a marketing authorisation are IMPs too when they are to be used as the test product, reference product or placebo in a clinical trial.

3. AUXILIARY MEDICINAL PRODUCTS (AMPs)

3.1. What is an AMP?

AMPs are medicinal products that fall within Article 3(3) of Directive 2001/83/EC, while not falling within the definition of IMPs as defined in Regulation (EU) No 536/2014 Article 2 (5).

Regulation (EU) No 536/2014 Article 2 (8) defines an AMP as "*a medicinal product used for the needs of a clinical trial as described in the protocol, but not as an investigational medicinal product*".

¹ For the purposes of this document, references to the EU, EU Member States or Member States should be understood to include the EEA or EEA contracting States, unless indicated otherwise.

70 For instance, some clinical trial protocols require the use of medicinal
71 products such as rescue medication, challenge agents, medicinal products
72 used to assess end-points in the clinical trial and background treatment.
73 According to the definition, an AMP must first be a medicinal product.
74 Consequently, not all products used for the needs of a clinical trial are
75 AMPs, e.g. some challenge agents are not defined as AMPs because they
76 are not medicinal products. AMPs should not include concomitant
77 medications; medications unrelated to the clinical trial and not relevant for
78 the design of the clinical trial. A list of types of AMPs, with examples, is
79 included in Annex 1 of this document.

80
81 Regulation (EU) No 536/2014 Article 2 (10) defines an authorised AMP
82 as *“a medicinal product authorised in accordance with Regulation (EC)
83 No 726/2004, or in any Member State concerned in accordance with
84 Directive 2001/83/EC, irrespective of changes to the labelling of the
85 medicinal product, which is used as an auxiliary medicinal product”*.

86
87 Only authorised AMPs may be used in a clinical trial unless an authorised
88 AMP is not available in the Union or where the sponsor cannot reasonably
89 be expected to use an authorised AMP. A justification to this effect shall
90 be included in the protocol.

91
92 Where there are problems with respect to the availability of authorised
93 AMPs, unauthorised AMPs may be used in a clinical trial in justified
94 cases. The price of the authorised AMP should not be considered as
95 having an effect on the availability of such medicinal products. Subjects
96 should not have to pay for IMPs, AMPs, medical devices used for their
97 administration and procedures specifically required by the protocol, unless
98 the law of the Member State concerned provides otherwise. ~~Member
99 States shall ensure that unauthorised AMPs may enter their territories for
100 the purpose of their use in a clinical trial.~~

101
102 Medicinal products that do not have a marketing authorisation, but
103 prepared in accordance with a magistral formula, i.e. prepared in a
104 pharmacy in accordance with a medical prescription for an individual
105 patient, and medicinal products prepared in a pharmacy in accordance
106 with the prescriptions of a pharmacopoeia and intended to be supplied
107 directly to the patients served by the pharmacy in question, i.e. officinal
108 formula, as referred to in Article 61 (5) of the regulation (EU) No
109 536/2014..

Requirements for AMPs

113 Where the AMP is not authorised, or where an authorised AMP is
114 modified while such modification is not covered by a marketing
115 authorisation, it shall be manufactured according to Good Manufacturing
116 Practice (GMP) or to at least an equivalent standard, in order to ensure

It is proposed to change this sentence as it is not the member States responsibility to ensure that unauthorised AMPs can be imported. Proposal : "Sponsors shall ensure that unauthorised AMPs are authorised for importation by Member States where the clinical trial is carried out".

117 appropriate quality. Full GMP equivalent to GMP for IMPs may not be
118 required in these cases but any deviations need to be justified. Appropriate
119 GMP requirements foreseen for the safety of the patients should still be
120 applied and the sponsor should ensure that AMPs are of appropriate
121 quality for the purposes of the trial, taking into account, among other
122 things, the source of the raw materials and any repackaging.

123
124 The sponsor is responsible for implementing a system to ensure that the
125 trial is conducted and data are generated in accordance with the principles
126 of Good Clinical Practice (GCP). To comply with these principles, a trial
127 has to be conducted according to the protocol and all clinical trial
128 information should be recorded, handled and stored in such a way that it
129 can be accurately reported, interpreted and verified. In this context,
130 traceability of medicinal products which allows adequate reconstruction of
131 AMP movements and administration should be ensured taking into
132 account the purpose of the trial and trial subjects' safety. It has at least to
133 include a procedure to record which patients received which AMPs during
134 the trial with an evaluation of the compliance, where necessary.

135
136 AMPs may be supplied by the sponsor or by the investigator site.

137 138 **3.3. Documentation requirements in the application dossier**

139
140 As a general rule, the documentation requirements in the application
141 dossier for IMPs also apply to AMPs irrespective their marketing
142 authorisation Regulation (EU) No 536/2014 Annexes I and II set out the
143 requirements of the application dossier for initial applications and
144 substantial modifications, respectively. It should be left to Member States
145 to establish the language requirements for the application dossier. To
146 ensure that the assessment of the application for authorisation of a clinical
147 trial functions smoothly, Member States should consider accepting a
148 commonly understood language in the medical field as the language for
149 the documentation not destined for the subject.

150
151 Labelling requirements for both authorised and unauthorised AMPs are set
152 out in Chapter X and Annex VI of Regulation (EU) No 536/2014. The
153 language of the information on the label shall be determined by the
154 Member State concerned. The medicinal product may be labelled in
155 several languages.

156 157 **3.4. Adverse reactions related to AMPs**

158
159 Regulation (EU) No 536/2014 Article 46 states, "*Safety reporting with*
160 *regard to AMPs shall be made in accordance with Chapter 3 of Title IX of*
161 *Directive 2001/83/EC*", which cover authorized AMPs.-
162

163 Regarding unauthorised AMPs, sponsors are not legally required to report
164 serious adverse reactions. However, the sponsor is obliged to keep detailed
165 records of all adverse events which occur in the trial setting, unless the
166 protocol provides differently (Article 41 of Regulation EU 536/2014) .
167 This would also include all adverse events where a causal relationship
168 with an AMP not authorized in the EU is suspected.

169
170 Nevertheless, sponsors are highly encouraged to report adverse reactions
171 to the Eudravigilance Database as described in Article 40 (1) of the
172 regulation. While all SAEs and SARs should be included in the annual
173 safety report of the relevant IMP, and non serious adverse events and non
174 serious suspected adverse reactions should be reported in the Clinical
175 Study Report. Further details, also with regard to adverse reactions
176 possible interacting with IMP, please see safety section of the Questions
177 and Answers Paper Version XX.

178
179 In addition according to article 53 the sponsor shall notify Member States
180 of all unexpected events which affect the benefit/risk balance of the
181 clinical trial, but which are not suspected unexpected serious adverse
182 reactions (as referred to in Article 42). **Annex 1 – Types of AMPs with**
183 **examples**

184

185 This section provides guidance on some categories of medicinal products which may be
186 used in clinical trials as auxiliary medicinal products (AMPs).

187

188 **(1) Rescue medication**

189

190 *Description:*

191

192 Rescue medications are medicines identified in the protocol as those that may be
193 administered to the patients when the efficacy of the IMP is not satisfactory, or the effect
194 of the IMP is too great and is likely to cause a hazard to the patient, or to manage an
195 emergency situation.

196

197 Rescue medication allows patients to receive effective treatment, e.g. placebo controlled
198 clinical trials where a standard treatment is available or dose response studies where
199 lower doses might be ineffective. Rescue medications are sometimes called “Escape
200 medications” in protocols. Usually these AMPs are authorised AMPs and are used
201 according to the authorised conditions.

202

203 *Examples:*

204

205 *Ineffective treatment* - A repeat-dose, randomised, double-blind, placebo-controlled,
206 three-parallel group study performed to evaluate the analgesic efficacy and safety of
207 intravenous acetaminophen as compared with its prodrug (propacetamol) and placebo in
208 patients suffering mild to moderate pain after an orthopaedic surgical operation. Patients
209 were allowed "rescue" patient-controlled intravenous morphine for pain.

210

211 *Anticipated adverse reactions* - A phase III clinical trial trying to assess the efficacy of a
212 new anti-neoplastic IMP. All patients receive a corticoid/antihistamine treatment in order
213 to minimise the appearance of expected adverse reactions.

214

215 *Anticipated emergency situation* - A clinical trial where a new biotechnology product is
216 to be given for the first time to humans. The protocol requires the availability of
217 appropriate medicinal products needed for the treatment of anaphylactic shock.

218

219

Feedback requested:

You are invited to elaborate further on "early escape" procedures.

220

221

222

223 **(2) Challenge agents**

224

225 *Description:*

226

227 Challenge agents are usually given to trial subjects to produce a physiological response
228 that is necessary before the pharmacological action of the IMP can be assessed.

229

230 *Examples:*

231

232 *Skin prick test* – Skin prick tests may be used to identify subjects with allergic responses
233 to specific allergens. Dilute solutions are manufactured from extracts of allergens such as
234 pollens, house dust, animal dander and foods. In the skin prick test, a drop of each
235 solution is placed on the person's skin, which is then pricked with a needle. If the person
236 is allergic to one or more substances, he/she has a wheal and flare reaction. This test may
237 be used as part of the inclusion criteria for a clinical trial of a new medicine to control or
238 prevent symptoms from allergic reactions.

239

240 *Blood pressure* – Open-label sensitivity test of blood pressure response to oral tyramine
241 following treatment with an IMP (new MAO inhibitor) in healthy volunteers.

242

243 **(3) Medicinal products used to assess end-points in the clinical trial**

244

245 *Description:*

246

247 This type of AMP is given to the subject as a tool to assess a relevant clinical trial end-
248 point; it is not being tested or used as a reference in the clinical trial.

249

250 *Examples:*

251

252 *Organ function* – PET radiopharmaceuticals are administered to a clinical trial population
253 to measure the function of a certain organ before and after the subject has been given an
254 IMP whose effects in this organ are the primary end-point of the clinical trial.

255

256 *Arterial wall function* – Acetylcholine is administered directly in coronary arteries to
257 evaluate coronary endothelium dysfunction. The test is performed at baseline – before the
258 first administration of an IMP – and at the end of the study, after the treatment period.

259

260 **(4) Background treatment**

261

262 *Description:*

263

264 This type of medicinal product is administered to each of the clinical trial subjects,
265 regardless of randomisation group, to treat the indication which is the object of the study.
266 Background treatment is generally considered to be the current standard of care or part
267 thereof for the particular indication. In these trials, the IMP is given in addition to the
268 background treatment and safety/efficacy is assessed. The protocol may require that the
269 IMP plus the background treatment is compared to an active comparator or to placebo
270 plus background treatment.

271

272 The timing of the start of standard of care as a background treatment may be different.
273 For instance:

274

- 275 • Subjects may already be taking the standard of care medicine(s) when entered into the
276 study, and this treatment would be one of the inclusion criteria; or
277 • Newly diagnosed subjects may be assigned to the standard of care medicines at the
278 same time as they are assigned to the IMP.
279

280 The nature of the background medicine(s) will be specified in the protocol, e.g. as the
281 standard treatment given according to local clinical practice, by the name of active
282 substances or medicinal products prescribed depending on patient needs and according to
283 the doctor's judgement.
284

285 The standard of care medicine(s) for a specific indication (recognised standard of care),
286 or a component of the standard of care for a particular medical indication, is based on a
287 consensus of Member States concerned.
288

289 *Examples:*
290

291 Development of a new medicinal product for HIV patients is likely to include patients on
292 standard of care medicine(s) for their primary disease (e.g. antiretroviral medicinal
293 products). In this case the new medicinal product for HIV would be the IMP and the
294 standard antiretroviral treatment would be background treatment.
295

296 In oncology, patients often receive combination treatments. These may all be approved
297 for the treatment of the disease to be investigated but may not be completely defined in
298 the protocol. For example the development of a new indication for a medicine used in
299 women with breast cancer recently compared that medicine versus observation in patients
300 who had received, regardless of trial, at least four cycles of neoadjuvant or adjuvant
301 chemotherapy and were allowed concurrent hormonal adjuvant therapy. In this case that
302 medicine would be considered an IMP and the neoadjuvant or adjuvant chemotherapy
303 and hormonal therapy products would be AMPs.