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4 **Guideline on the responsibilities of the sponsor with**  
5 **regard to handling and shipping of investigational**  
6 **medicinal products for human use in accordance with**  
7 **Good Clinical Practice and Good Manufacturing Practice**  
8 **Draft**

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| <b>Related content</b> | <p><b><i>The clinical trial regulation (EU) No 536/2014</i></b><br/><a href="http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000629.jsp">http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000629.jsp</a></p> <p><b><i>Detailed Commission guidelines No C(2017) 8179 on GMP for investigational medicinal products for human use</i></b><br/><a href="https://ec.europa.eu/health/human-use/good_manufacturing_distribution_practices/gmp_developements_en">https://ec.europa.eu/health/human-use/good_manufacturing_distribution_practices/gmp_developements_en</a></p> |
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## 21 **Introduction**

22 This guideline complements the Delegated Regulation (EU) No 2017/1569 of 23 May 2017, on good  
23 manufacturing practice (GMP) for investigational medicinal products (IMP) and arrangements for  
24 inspections, that has as legal basis the first subparagraph of Article 63(1) of Regulation (EU) No  
25 536/2014 on clinical trials on medicinal products for human use, and the detailed Commission  
26 guidelines No C(2017) 8179 on good manufacturing practice for investigational medicinal products for  
27 human use, pursuant to the second subparagraph of Article 63(1) of Regulation (EU) No 536/2014.

28 The guideline lays down the principles for management of the investigational medicinal products by the  
29 sponsor for use in a clinical trial and in accordance with Good Clinical Practice (GCP) which are at the  
30 interface with, and complementary to, Good Manufacturing Practice.

## 31 **1. Two-step release procedure**

32 A clinical trial in the EU can only start after a clinical trial authorisation has been granted by the EU  
33 member states concerned, following fulfilment of the requirements of Chapter II (Authorisation  
34 procedure for a clinical trial) of Regulation (EU) No 536/2014.

35 Investigational medicinal products should remain under the control of the sponsor until after  
36 completion of the two-step procedure, consisting of the batch certification by the Qualified Person (QP)  
37 and the regulatory release by the sponsor for use in a clinical trial. Both steps should be recorded and  
38 retained in the clinical trial master file held by, or on behalf of, the sponsor.

39 The certification of each batch by the QP of the manufacturer ensures, in line with Article 62(1) of  
40 Regulation (EU) No 536/2014, that the provisions of 63(1) and 63(3) of Regulation (EU) No 536/2014  
41 and those set out in Article 12 of the Commission Delegated Regulation (EU) No 2017/1569, have been  
42 complied with and documented.

43 It should be noted that regulatory release of the IMP can be given for some countries at one time  
44 point, and for others at a later stage.

45 The regulatory release by the sponsor will also need to verify that any aspects required for compliance  
46 with the Regulation are in place before IMPs are shipped to the clinical investigator sites. These checks  
47 will vary depending on the trial, but may cover for example:

- 48 • Contracts with investigators and applicable service providers.
- 49 • If the authorisation of the clinical trial is subject to conditions, that these conditions are met.
- 50 • Any local/national approvals.
- 51 • Where applicable, de-coding arrangements are in place.

52 De-coding arrangements should be available to the appropriate responsible investigator site personnel  
53 before, or at the same time, IMPs are received at the investigator site. The sponsor is responsible for  
54 ensuring that the investigator has appropriate access to systems for immediate un-blinding prior to the  
55 start of the trial.

56 The sponsor should have standard operating procedures (SOPs) in place that describe the regulatory  
57 release process within the organisation.

58 The regulatory release should be documented and approved prior to the shipment of IMPs to the  
59 clinical investigator sites or pharmacy where applicable, to ensure that a trial does not start without  
60 the necessary arrangements and approvals in place.

## 61 **2. Shipping**

62 It should be ensured that the shipping of the IMPs minimises any risk while ensuring that the quality of  
63 the product is maintained and the applicable elements of guidelines on Good Distribution Practice  
64 (GDP) of medicinal products for human use are taken into consideration.

65 Shipping of IMPs to the clinical investigator site or pharmacy, where applicable, should be conducted  
66 according to instructions given by, or on behalf of, the sponsor in the shipping order. Records including  
67 timing to support the supply chain should be maintained. Unless the IMP does not require any special  
68 storage conditions, temperature control and monitoring of the storage conditions are necessary and  
69 these records should also be maintained. Deviations from the specified conditions during shipment  
70 should be formally investigated. Responsibility for the control of the IMPs shipment remains with the  
71 sponsor (or representative) until it has been received and accepted by the clinical investigator site or  
72 pharmacy, where applicable.

73 A detailed inventory of the shipments made should be maintained. It should particularly mention the  
74 addressees' identification.

75 Transfers of IMPs from one trial site to another should remain the exception. Such transfers should be  
76 covered by standard operating procedures. The product history while outside of the control of the  
77 manufacturer, through for example, trial monitoring reports and records of storage conditions at the  
78 original trial site, should be reviewed as part of the assessment of the product's suitability for transfer  
79 and the advice of the certifying QP should be sought. The product should be returned to the  
80 manufacturer, or another authorised manufacturer, for re-labelling, if necessary, and certification by a  
81 QP. Records should be retained and full traceability ensured.

## 82 **3. Contractual arrangements**

83 Responsibilities of the manufacturer and sponsor should be appropriately defined, agreed and  
84 controlled in a written contract, mentioned in recital 4 to the Commission Delegated Regulation (EU)  
85 No 2017/1569 specifying principles and guidelines for good manufacturing practice for investigational  
86 medicinal products for human use and arrangements for inspections, which clearly establishes the  
87 duties of each party, taking into account EudraLex, Volume 4, Part I, Chapter 7, as applicable.

88 The detailed Commission guidelines No C(2017) 8179 on good manufacturing practice for  
89 investigational medicinal products for human use further mentions certain issues which could be  
90 covered by technical agreements. Examples of such responsibilities include:

- 91 • Ensure that re-labelling responsibilities are defined.
- 92 • Ensure that where applicable comparators are sourced from an authorized vendor and that  
93 arrangements for recall are in place.
- 94 • Ensure that the most up to date information is provided to the QP for consideration during the  
95 batch certification process in accordance with the documents set out in the clinical trial applications  
96 authorised by EU member states<sup>1</sup>.
- 97 • Ensure that any proposed revision of manufacturing and control methods are appropriately  
98 communicated between the manufacturer and the sponsor as this may require submission of a  
99 substantial modification to the clinical trial application.

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<sup>1</sup> As described in chapters II, for initial applications, and chapter III, for substantial modifications, of the Regulation (EU) No 536/2014

- 100 • Ensure that decoding arrangements and the respective responsibilities of each party are  
101 appropriately defined.
- 102 • Ensure that any agreed responsibilities are not subcontracted to a third party without prior  
103 evaluation and approval from the contract giver.
- 104 • Ensure that the responsibilities for recall, return and destruction of IMPs are appropriately defined  
105 and documented.
- 106 • Ensure that the documentation required in the clinical trial master file (e.g. batch documentation,  
107 documentation related to assembly and packaging of IMPs) remains available to the sponsor after  
108 the retention periods as defined in Article 8 of the Delegated Regulation on GMP for IMPs expires.
- 109 • Define the storage retention of samples.
- 110 • Define arrangements for destruction of investigational medicinal products.
- 111 • If applicable, clarify the manufacturer responsibility for the regulatory release.
- 112 • In case a sponsor is not a manufacturer and relies on chain of contracted manufacturers, specify  
113 the exact role of manufacturer (e.g. specific tasks and GMP related responsibilities) in the chain of  
114 manufacturers.
- 115 • Responsibilities on the handling of deviations during shipment to investigators where applicable.
- 116 • The process of transferring IMPs from one investigator site to another when applicable should also  
117 be addressed.