



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

10 November 2016
EMA/CHMP/QWP/BWP/661488/2016
Committee for Human Medicinal Products (CHMP)

Concept paper on developing a guideline on Quality requirements of medicinal products containing a device component for delivery or use of the medicinal product

Agreed by Quality Working Party	September 2016
Agreed by Biologics Working Party	October 2016
Adopted by CHMP for release for consultation	10 November 2016
Start of public consultation	16 February 2017
End of consultation (deadline for comments)	16 May 2017

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Keywords	Drug-device combination products, drug-delivery medical devices, device verification and validation studies, quality management systems of medical devices
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1. Introduction

This concept paper addresses the need for development of a guideline on dossier requirements for medical devices that are supplied along with medicinal products where a device is necessary for administration or localisation (site-specific delivery) of the medicinal product.

2. Problem statement

Annex 1 of the Directive 2001/83/EC, requires that details are provided for the medical devices with which the medicinal product will be used or administered and which will be provided or supplied along with the medicinal product. However, given the wide diversity of devices supplied with medicinal products and continuous technological developments, together with the differences in medical device and medicinal product legislation, the data supplied in the dossiers of the marketing authorisation applications has found to be inconsistent and often incomplete.

It should be noted that there is also no simple, legal terminology to help describe the different situations in which a medical device is either used to deliver a medicinal product or is used with the medicinal product.

The medical device may be supplied as an integral component of the medicinal product (e.g. pre-filled syringe, auto-injector), or separately (co-packaged; e.g. oral syringe, pen-injector), as a non-integral combination with the medicinal product, or independently marketed (in cases where the device meets the requirements for the necessary delivery system stated in the Summary of Product Characteristics (SmPC) for the medicinal product). These are all referred to as drug-device combination products (DDC) within the context of this concept paper (see glossary).

There has been an increase in the number of marketing authorisation applications (MAAs) and requests for scientific advice for medical devices for delivery or localisation of the medicinal product. In particular, the number of commercially available novel devices with automated functions is increasing. These devices may prove potentially useful for patients with regular and long-term dosing requirements. DDCs increasingly allow patients to administer medicinal products in the home environment themselves or with the support of a professional or lay caregiver, therewith replacing administration by health-care professionals in hospitals. Due to technological advancements in the area of electronics and computing, medicines 'systems' are being developed and marketed, including medical devices that are being used to calculate dosages or monitor adherence of medicinal products.

Medical devices supplied as integral to a medicinal product, such as pre-filled syringes, inhalers, and auto-injectors, are more complex than container-closure systems, due to the associated delivery and measuring or metering function. Inappropriate use of these devices may compromise the safety and efficacy of the medicinal product and result in adverse drug reactions (ADRs) or medication errors. Complex DDCs have the highest risk of inappropriate usage. DDC fitness for the intended purpose (e.g. administration of a medicinal product) needs to take into account the Quality aspects of the device in itself and its use with the particular medicinal product, as well as the complexity of the device component, the patient characteristics, the caregiver characteristics where relevant and the clinical-situation in which the DDC is to be used.

It is therefore appropriate to provide guidance on Quality data requirements for medicinal products incorporating, or used with, medical devices i.e. DDCs to assessors and pharmaceutical industry.

41 **3. Discussion**

42 The historical clear delineation between regulatory pathways for medicinal products and medical
43 devices is acknowledged. The level of data provided to medicines competent authorities should be in
44 line with the applicable legislation and regulatory guidance and should commensurate with the
45 complexity of the medical device's intended use.

46 The CE marking process for medical devices provides confirmation of conformity with Annex 1 of the
47 Medical Devices Directive (Directive 93/42/EEC, MDD). For CE marked medical devices provided
48 separately but sometimes co-packaged with the medicinal product, the assessment performed by the
49 Notified Body may not fully take into account the characteristics of the specific medicinal product that
50 the device is to be used with. This could have an impact on the overall quality, safety or efficacy of the
51 medicinal product when used along with the specified medical device. This specific aspect is to be
52 addressed in the context of the assessment of the application for marketing authorisation and there is
53 no intention on duplication of assessment performed during assignment of CE mark for the medical
54 device. In contrast, in situations where the device and the medicinal product form a single integral
55 product which is intended exclusively for use in the given combination and which is not reusable, the
56 medical device is not assessed by a Notified Body and assessment of all of the above aspects, including
57 compliance with Annex 1 to the MDD, is conducted as part of the assessment of the application for
58 marketing authorisation.

59 The guideline will consider the data requirements with respect to quality aspects in relation to safety
60 and performance of the medical device, whether it is an integral component of the medicinal product or
61 a stand-alone device, including usability studies in target patient population with the relevant clinical
62 conditions, to show that it can be used satisfactorily by the target patient group.

63 Information on managing the DDC related changes during the product lifecycle will also be considered.
64 This will include the data requirements for variations for quality related changes of device component.

65 **4. Recommendation**

66 The Quality Working Party and Biologics Working Party recommend developing a guideline on quality
67 aspects of the dossier requirements for DDCs for marketing authorisation applications, line extension
68 applications and variations to show that the combination has been appropriately designed and
69 controlled and can be used correctly in the intended clinical situations.

70 The scope of the guideline will only include human medicinal products.

71 The guideline should consider the information to be included in product literature (SmPC, Patient
72 information leaflet and labelling) to ensure the safe and effective use of the medicinal product. It
73 should also include the necessary considerations for cases where there is a specific requirement for
74 medical devices for use with the medicinal product (such as nebulisers or anaesthetic delivery
75 equipment) but where these are available separately, often from a different manufacturer.

76 The guidance will not specifically address issues related to integral device as part of combined
77 advanced therapy medicinal products (cATMPs as per Regulation (EC) No 1394/2007) but it is expected
78 that the same principles will apply. However, quality issues related to devices when used for a delivery
79 function in cATMP products will be covered.

80 **5. Proposed timetable**

81 The Concept Paper will be released for a 3-month external consultation.

82 Following the receipt of Concept Paper comments, the draft Guideline will be prepared and released for
83 a 6-month external consultation.

84 The draft Guideline will be revised in light of comments received, finalised and published.

85 **6. Resource requirements for preparation**

86 The preparation will mainly involve the Quality Working Party (QWP) and Biologicals Working Party
87 (BWP), with support from other Working Parties and expertise from Medical Devices competent
88 authorities, as necessary.

89 **7. Impact assessment (anticipated)**

90 The new guideline will provide guidance for pharmaceutical industry, medical device industry and
91 regulatory authorities.

92 **8. Interested parties**

93 Academia, international scientific societies, pharmaceutical industry, medical devices industry and
94 notified bodies, healthcare professionals.

95 **9. Glossary**

96 1. **Medicinal product:** The definition of a medicinal product is given in Article 1(2) of Directive
97 2001/83/EC:

98 a. 'Any substance or combination of substances presented as having properties for treating or
99 preventing disease in human beings;

100 or

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

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105 2. **Medical Device:** The definition of medical device is given in Article 1(2)(a) of Directive 93/42/EEC:
106 'medical device' means any instrument, apparatus, appliance, software, material or other article,
107 whether used alone or in combination, including the software intended by its manufacturer to be
108 used specifically for diagnostic and/or therapeutic purposes and necessary for its proper
109 application, intended by the manufacturer to be used for human beings for the purpose of:

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- diagnosis, prevention, monitoring, treatment or alleviation of disease;
 - 111 • diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap;
 - 112 • investigation, replacement or modification of the anatomy or of a physiological process;
 - 113 • control of conception;

114 and which does not achieve its principal intended action in or on the human body by
115 pharmacological, immunological or metabolic means, but which may be assisted in its function by
116 such means."

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118 3. **Drug device combination (DDC) product:** In the EU, there is no legal definition for a product
119 where a medicinal product and a medical device are presented together either as an integral
120 combination or presented separately for use together. The terminology in the context to this
121 concept paper is restricted to medicinal product as defined by Directive 2001/83/EC.

122 **10. References to guidelines**

- 123 1. Guideline Q8 (R2) on Pharmaceutical Development, EMA/CHMP/ICH/167068/2004
- 124 2. Notes for Guidance on Developmental Pharmaceuticals, CPMP/QWP/155/96
- 125 3. Guideline on plastic immediate packaging materials, CPMP/QWP/4359/03
- 126 4. Advanced Therapy Medicinal Products, REGULATION (EC) No 1394/2007
- 127 5. Good practice guide on risk minimisation and prevention of medication errors,
128 Pharmacovigilance Risk Assessment Committee (PRAC), EMA/606103/2014