REG-91 version 3 – Guideline for notified bodies applying for a scientific opinion (consultation) on ancillary medicinal substance that is an integral part of medical device

This guideline supersedes guideline REG-91 version 2 with the effect from 1st February, 2024

The Guideline is issued on the basis and in accordance with the provision of Section 13 paragraph 2, letter a), point 5 of Act no. 378/2007 Coll. and Act No. 375/2022 Coll.
The Guideline is for recommendation.

Related Legislation:
European Union legislation:
Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use ("Directive 2001/83/EC"), as amended.
Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC ("Medical Device Regulation").

National legislation:
Act no. 378/2007 Coll., on Medicinal Products and on Amendments to Some Related Acts, as amended (Act on Medicinal Products).
Act No. 375/2022 Coll., on Medical Devices and on in vitro diagnostic Medical Devices.
Act No. 90/2016 Coll., Act on Conformity Assessment of Specified Products in Their Supply to the Market
Act No. 500/2004 Coll., Administrative Code, as amended.

Guidelines and ISO standards:
MDCG guidance for consultations of authorities on devices incorporating a medicinal product.
EMEA/CHMP/EWP/110540/2007 - Guideline on the clinical and non-clinical evaluation during the consultation procedure on medicinal substances contained in drug-eluting (medicinal substance-eluting) coronary stents.
European Commission guidelines on medical devices.
CHMP/QWP/227/02 Rev 3/Corr. Guideline on Active Substance Master File Procedure.
ISO 10993-1:2018 Biological evaluation of medical devices — Part 1: Evaluation and testing within a risk management process.
ISO 14155:2020 - Clinical investigation of medical devices for human subjects - Good clinical practice.

Introduction

This guideline is intended for notified bodies ("NB") applying for a scientific opinion on an ancillary medicinal substance used as an integral part of a medical device. A medical device for the purposes of this guideline means a medical device according to Article 2(1) of the Regulation on Medical Devices, accessories of a medical device according to Article 2(2) point 2 of the Regulation on medical devices and the product listed in Annex No. XVI of the Regulation on medical devices. The State Institute for Drug Control ("the Institute") is the administrative body competent according to § 13 paragraph 2, letter a), section 5 of the Act on Medicinal Products to issue a scientific opinion on an ancillary medicinal substance used as an integral part of a medical device, upon the application of a notified body under Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC, in conjunction with the Act No. 375/2022 Coll., as amended ("Medical Device Regulation").

The Institute verifies whether the used medicinal product meets the requirements of point 12.1. Annex I of the Medical Devices Regulation, or whether the quality, safety and utility of a substance that would be considered as a medicinal product on its own, within the meaning of Article 1 (2) of Directive 2001/83 / EC, were verified by analogy with the methods listed in Annex I to Directive 2001/83/EC as required in the relevant conformity assessment procedure under this Regulation.

Before submitting an application for a scientific opinion, the applicant (NB) must verify that the product is classified in the correct category determining a regulatory regime, namely that it is a Class III medical device.

I. The reason for and purpose of an application for a scientific opinion

For medical devices (hereinafter referred to as "MD") incorporating, as an integral part, an active substance with ancillary action, the NB must, after having verified the usefulness of the active substance as part of the MD and taking account of the intended purpose of use, seek a scientific opinion from a competent authority of a Member State of the EEC (hereinafter "Member state") on the quality and safety of the active substance, including the clinical benefit/risk profile of the incorporation of the substance into the MD. A competent authority here means an authority of the Member State responsible for approving applications for marketing authorization of medicinal products prior to their launch. It is the NB's choice which competent authority in the European Union is requested for an opinion. In case that the MD contains a blood derivative, it is necessary to request EMA for a scientific opinion. Information for these cases is available at https://www.ema.europa.eu/en/human-regulatory/overview/medical-devices/consultation-procedure-ancillary-medicinal-substances-medical-devices.

The aspect of "usefulness" relates to the rationale for using the medicinal substance in relation to the specific intended purpose of the MD. It refers to the suitability of the medicinal substance to achieve its intended action, and whether the potential inherent risks (aspects of "safety") due to the medicinal substance are justified in relation to the benefit to be obtained within the intended purpose of the MD. The Report on usefulness should address and discuss all these aspects and the notified body should come to a conclusion if incorporation of ancillary medicinal substance to the MD is acceptable in terms of usefulness and safety or not.

Within the scope of the opinion the Institute may make available relevant information concerning the risks related to the use of the active substance (i.e. resulting from pharmacovigilance).
The NB must take into account the opinion of the Institute, and after considering all of the aspects related to the benefit/risk profile, it either issues the certificate or not.

II. Application for a scientific opinion and reimbursement of costs

The application is submitted on the Application Form REG-92. A separate application is submitted for each MD incorporating an active substance as its integral part. Only if the subject of application is a group of MDs (i.e. a range of catheters in different sizes, but made of the same material and incorporating the same medicinal substance at the same nominal concentration), a combined application is acceptable. For each application it is necessary to reimburse the costs referred to under code R-013 in accordance with the guideline *UST-29 Administrative fees, reimbursement of costs for expert activities, compensation for activities associated with the provision of information and compensation for other tasks* in its valid version. Details of payment can be found at http://www.sukl.eu/sukl/uhrada-nahrad-vydaju-za-odborne-ukony-provadene-na-zadost?lang=2.

Before submitting an application, it is possible to request an oral or written consultation. Information on how to request a consultation can be found at http://www.sukl.eu/sukl/advice-provided-by-sukl .

III. Documentation to be provided by the NB with the application for a scientific opinion

The documentation should be submitted in the English, Czech or Slovak language.

- Via CESP portal:

The documentation should be submitted in the form of a single compressed file in the ZIP format. This ZIP file must not contain any other compressed file. It is necessary to compress the eCTD directory including the root directory.

- Via e-mail room:

The documentation should be submitted in the form of a single compressed file in the ZIP format, without the use of a password. This ZIP file must not contain any other compressed file. It is necessary to compress the eCTD or NeeS directory including the root directory.
The e-mailroom may be used only for the sending of documentation the compressed size of which is less than 15 MB. The documentation, signed by a certified electronic signature of the authorised person, should be sent to posta@sukl.cz.

- Via data mailbox:

Documentation in the eCTD format submitted via the data mailbox should not be compressed.
The data mailbox may be used only for the sending of documentation the size of which is less than 10 MB.

- On an electronic data carrier (CD or DVD):

Along with the data carrier it is necessary to submit a cover letter that includes a list of documents in all the media provided within the application, including the total number of attached electronic media and the electronic format used, and a completed application form. The CD or DVD must be labeled with at least the basic identification data (MD name, MD manufacturer, number of electronic data carrier/total number of carriers - e.g. 1/3, 2/3 and 3/3). The application form and cover letter must be submitted both electronically and in printed form with an original signature. Proof of payment of the cost reimbursement must also be provided with the application.

Documentation should be submitted in e CTD format (Common Technical Documentation); instructions can be found at https://ec.europa.eu/health/sites/default/files/files/eudralex/vol-2/b/update_200805/ctd_05-2008_en.pdf.
When compiling documentation it is necessary to take into account the guidelines for applicants published by the European Commission in Eudralex, see https://ec.europa.eu/health/documents/eudralex/vol-3_en .
The Institute cannot guarantee that documentation that is not submitted in the required eCTD format or does not meet the above technical requirements will be assessed according to the time-schedule below.
Before submitting an application for a scientific opinion to the Institute, the NB must verify the usefulness of the active substance in the MD (NB prepares a Report on the usefulness of the active substance in the MD) and check that the documents provided by the MD manufacturer contain a special part of the documentation relating to the active substance incorporated in the MD (please see below for more details). Subsequently the NB should submit the relevant application to the Institute, including documentation, copy of Report on the usefulness and other attachments listed in the application form.

IV. Procedure of the application for a scientific opinion

The NB is informed about the receipt of the application and about the reference number of the application by e-mail (within 14 days of receipt). In case that the required attachments were not submitted along with the application, or it is necessary to submit additional application, because there are several MDs that cannot be assessed under the same reference number, an appeal is sent to the applicant (Notified Body) with a requirement to complete the data and documentation within a 30-day period. In this appeal, the applicant is also informed on possible consequences if the missing information and documents are not submitted within the specified period. In case that within 30 days of sending an appeal, the Institute does not receive the required documentation, a notice of non-compliance with the application will be sent to a notified body.
From the date when the complete documentation is submitted to the Institute, the application is considered valid, and the Institute has 210 days for the assessment and finalization of a scientific opinion. A pharmaceutical assessor, who assesses the quality of the active substance, and a clinical assessor, who assesses the non-clinical documentation, the clinical documentation, and the NB's Report on the usefulness of the active substance in the MD, are both involved in the evaluation. The clinical assessor also evaluates the benefit/risk profile, taking into account the relevant

pharmacovigilance data, if needed.

If the information submitted is not sufficient to issue an opinion, no later than the 90th day of the time-schedule the Institute sends an appeal to complete further documents. The assessment procedure is stopped until the Institute receives the responses. The deadline for submitting the responses is set to a maximum of 90 days.

Within 60 days of the receipt of responses the Institute assesses the documentation and informs the NB of the assessment result, i. e. it issues either a positive or negative scientific opinion, or eventually sends a second appeal for completion with a deadline of max. 60 days. Subsequently, within 60 days of the receipt of the completed documentation, the Institute assesses the responses and issues either a positive or negative scientific opinion. In exceptional cases, if the amendment is not complete, the Institute may repeat the request for amendment with a period of 60 days. The Institute then has 60 days to assess the amendment and issue an opinion.
In justified cases, the NB may, at the request of the MD manufacturer, ask the Institute to extend the deadline for responses before the deadline of 90/60 days has expired. The Institute will confirm its consent to the extension of the deadline by e-mail within 5 days.

In case of extensive complementary documentation (e.g., within the range corresponding to the whole pharmaceutical, non-clinical or clinical documentation, or their major parts) the Institute cannot guarantee compliance with the deadline for the assessment according to the time-schedule above.

The scientific opinion may include recommendations for the NB to demand from the MD manufacturer, for example, a declaration to complete stability studies and in case that results are outside of the specification, to report these to the NB, along with proposed measures. The NB will forward this data to the Institute for assessment.

Time-schedule of the assessment process:
Day -14: receipt of application
Day 0: valid application
Day 90: assessment – a scientific opinion or appeal for completion
Day 150: assessment - a scientific opinion or appeal for completion
Day 210: assessment - a scientific opinion

V. Documentation to be provided to the Institute

The application form with attachments
The completed application form REG-92 should be accompanied by a cover letter, proof of payment of cost reimbursement, a Report on the usefulness of the active substance as a part of the medical device prepared by the NB and other documents listed in the application form. The application form and cover letter must be submitted both electronically and in printed form with an original signature.

Documentation
Documentation regarding the active substance must contain all the relevant chapters prescribed by the CTD format, however, especially in case of well-known active substances, all the original data are usually not required and references to literature are sufficient, however, it is necessary to submit a copy of the full text of articles. The omission of data must always be justified.
For new active substances or substances used in a non-established manner complete data according to Annex 1 of Directive 2001/83/EC are required.
On its website, EMA has published guidelines relating to the quality, safety and efficacy of active substances in medicinal products and these need to be taken into account when drawing up the documentation - see Scientific guidelines at
https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines/quality-guidelines.
These are recommendations that need not be strictly followed, however, if a different approach is

chosen, it must be justified.
For an effective process of handling the application the Institute strongly recommends that only documentation relevant to the active substance be submitted, according to the following points:

1. General Information

General description of the MD, including the manufacturer's requirement regarding purpose of incorporation of the ancillary medicinal substance in the medical device, together with a critical evaluation of results of the risk assessment.

2. Documentation regarding quality

2.1 Documentation on active substance/s itself:

It is necessary to submit CTD Module 2.3. (Quality Overall Summary) and relevant parts of CTD Module 3 (Module 3.2.S).
Module 3.2.S can be submitted in one of three ways (appropriate possibility should be marked in the Application):

- **Full information on the active substance:** information is sent by the manufacturer of the active substance to the MD manufacturer and then it is included in the documentation submitted by the NB to the Institute for assessment, the requirements are set out in guideline https://www.ema.europa.eu/en/chemistry-active-substances-chemistry-new-active-substances
- **Active Substance Master File (ASMF)**, using the Active Substance Master File Procedure, see guideline https://www.ema.europa.eu/en/active-substance-master-file-procedure

The NB should verify whether the ASMF was actually submitted by the ASMF holder directly to the Institute. The application will not be considered valid until the ASMF is available to the Institute, along with a letter by which the ASMF holder authorizes the Institute to assess the ASMF in context of the particular MD (so-called Letter of Access).
For a new application for a scientific opinion, it is necessary to submit the following:
Cover letter, Applicants Part, Restricted Part, Quality Overall Summary, and Letter of Access. The ASMF procedure is not applicable to substances of biological origin.

- **Certificate of compliance with the monograph of the European Pharmacopoeia (CEP)**

It is possible to check at: https://extranet.edqm.eu/publications/recherches_CEP.shtml whether a CEP has been issued for the active substance from its production place.
While preparing documentation for the active substance it is recommended to follow the Guideline on Summary of Requirements for active substance in the quality part of the dossier https://www.ema.europa.eu/en/summary-requirements-active-substances-quality-part-dossier-scientific-guideline

If the active substance has a monograph in the European Pharmacopoeia (Ph.Eur.), a specification of the active substance should comply with the monograph or should be supplemented by further in-house tests - control of impurities, residual solvents, catalysts etc. It is also necessary to submit results of stability studies supporting re-test period or shelf-life. In case of CEP with indicated re-test period no stability studies are required.
For active substances of animal origin, a declaration to minimize the risk of transmission of TSE (transmissible spongiform encephalopathy) is required.

2.2 Documentation on the active substance/s as incorporated into the medical device:

For the active substance incorporated in the medical device, documentation must be submitted according to the following chapters (it is not necessary to follow this documentation structure if it is submitted in CTD format):

1. Qualitative and quantitative composition

Description of the active substance and its quantity in the MD including lower and upper limit, quantity of all other components (stabilizers, polymers ...) should be provided.

2. Description of the production process

Detailed description is given in the part of the documentation for the NB, here only a description

of process relating to the incorporation of the active substance into the MD is required.

3. Control of the active substance:

Specification of the active substance in the MD including tests on identity and content of the active substance, amount of impurities originating from the active substance, description of control methods for the active substance in the MD and their validations.

4. Control tests during the manufacturing process

Information related to incorporation of the active substance into the MD is required. Submission of summary reports on process validation studies to demonstrate that the manufacture results in devices with controlled and consistent quantity of active substance is encouraged.

5. Final specification of the active substance in the MD

Specification of the active substance in the MD including tests on identity and content of the active substance, amount of impurities originating from the active substance, release rate of the active substance, if applicable, description of control methods for the active substance in the MD and their validation should be submitted.

6. Stability studies

Studies demonstrating desired function of the active substance in the MD throughout the proposed shelf-life under recommended storage conditions should be provided. It is necessary to take into account possible interactions with other materials of the MD and degradation of the active substance,

7. Others

In case of human/animal materials it is necessary to submit an evaluation of the potential risk of viral contamination of the MD by viruses and prions.

3. Non-clinical documentation

The submitted documentation regarding non-clinical information on the active substance used as an integral part of the medical device must contain the chapters mentioned below. All of the non-clinical information provided for the assessed MD should be submitted in a separate document Non-clinical Overview:

a) Non-clinical pharmacology

i. Pharmacodynamics:

This section should address the intended effect of the active substance in the context of its incorporation into the medical device. It is necessary to present both the general pharmacodynamic properties of the active substance and the pharmacokinetic data regarding the use of the active substance as an integral part of the MD. It is possible to present both data published in the scientific literature and pharmacodynamic studies performed with the assessed MD, depending on the nature and purpose of use of such a MD.

ii. Pharmacokinetics:

Depending on the type and nature of the MD, all or some of the following areas may need to be addressed, as appropriate:

- Description of the pattern of local and systemic exposure to the active substance.
- Where the level of exposure fluctuates (AUC), the maximum level and duration of exposure should be considered.
- Where it is considered possible that potential levels of systemic exposure may present a safety concern, maximum peak plasma concentration should be established, taking due consideration of individual variability.
- For new active substances it is necessary to provide information on the release from the MD and, if relevant, data on its subsequent absorption, distribution, metabolism and excretion (AUC and eventually metabolites, if relevant).

In justified cases, it is necessary to submit a pharmacokinetic study conducted with the device in question containing the active substance.

b) Biocompatibility

Biocompatibility tests as defined in the European Standard ISO 10993 should be submitted as part of the biological evaluation of the medical device. The extent of the required biological evaluation

depends on the specific category of MD, the nature of contact with the human body and the duration of contact with the body, see Annex A to the European Standard ISO 10993-1.

The following parameters, among others, are evaluated within the biocompatibility tests:

- Toxicity

The following toxicity data should be submitted: acute toxicity, repeated dose toxicity, genotoxicity, carcinogenicity, reproductive and developmental toxicity. If relevant to the use of the MD, sub-chronic and chronic toxicity data must also be submitted. Reference to the known toxicological profile of the active substance may also be provided. In case of new medicinal substances, it is always necessary to provide the results of toxicity tests. These may include information on the toxicity and biocompatibility of the MD obtained from the evaluation in accordance with the European Standard ISO 10993.

- Local tolerance

The assessment of local tolerance is of particular relevance since the route of exposure to the active substance may be different from its conventional application. It is necessary to provide the relevant results of MD testing according to the European standard ISO 10993, or where appropriate, information from scientific literature. The selection of tests, as well as the omission of some tests or evidence of local tolerance based on data published in the scientific literature must be appropriately justified.

4. Clinical documentation

Since Class III MDs are concerned, clinical data are to form part of the documentation provided by notified bodies under Medical Device Regulation. These data should address the requirements for clinical evaluation of MDs incorporating an active substance as required by Annex X of Directive 93/42/EEC. These data should address the safety of the MD in its entirety. The usefulness/efficacy of the active substance in the MD should be addressed by clinical evaluation.

All of the clinical data provided for the assessed MD should be submitted as a separate document Clinical Overview.

The aim of clinical documentation is to verify the usefulness of incorporating the active substance to the medical device. Clinical data may consist either of a critical evaluation of scientific literature where equivalence (essential similarity) of the assessed MD to similar MDs whose safety and efficacy has been confirmed, was demonstrated, and the data demonstrate compliance with Essential Requirements, or of the results of clinical trials performed with the assessed MD, or a combination of both of these options.

References to literature, summaries of non-clinical and clinical experience, the results of clinical trials with the only MD, the only medicinal product or with the MD containing the active substance may also be submitted. The submitted data should explain why the active substance was incorporated to the medical device and identify the patients profiting from the combination of MD and the active substance compared to the MD on its own and should also include a description of the mechanism of action of the MD and of the active substance and the mechanism of action of the combined product.

The appropriate methodology for clinical investigations of medical devices is described in the European Standard ISO 14155: 2020 - Clinical investigation of medical devices for human subjects - Good clinical practice.

For some types of products, i.e. antimicrobial wound dressing, in vitro data must be provided for the demonstration of antimicrobial effects.

Attention should also be paid to any specific guidelines that, among other things, define specific requirements for non-clinical and clinical documentation for certain types of medical devices with an active substance, such as coronary stents releasing the active substance, intra-uterine devices containing copper, etc. see, for example, the guideline Clinical and non-clinical evaluation during the consultation procedure on the medicinal substance contained in drug-eluting (medicinal substance-eluting) coronary stents (EMEA/CHMP/EWP/110540/2007).

https://www.ema.europa.eu/en/clinical-and-non-clinical-evaluation-during-consultation-procedure-medicinal-substances-contained-drug-eluting-medicinal-substance-eluting-coronary-stents-scientific-guideline

5. Instructions for use

Instructions for use intended for healthcare professionals must always be provided. This is to be submitted in English, as well as in Czech in case that those MDs are intended for the Czech market.
Indications and claims stated in the instructions for use must be based on and completely consistent with the submitted non-clinical and clinical data.
Instructions for use must contain sufficient information about the contraindications and warnings to ensure a safe use of the respective MD.

VI. Subsequent application for a scientific opinion (variation)

If changes are made to the active substance, particularly with regard to its manufacturing process, the NB must be informed of these changes and should ask the Institute for scientific opinion in order to confirm that quality and safety of the active substance is maintained. The Institute takes into account data on usefulness of incorporation of the active substance into the MD that were submitted by the NB to ensure that the changes have no negative impact on the assessed risk of incorporation of the active substance into the MD.
These changes include, for example, a change of the manufacturer of the active substance, a significant change in the manufacture of the active substance, a change in the specification of the active substance or a change of control methods, changes in MD production concerning the incorporation of the active substance into the MD, extension of the shelf-life of the MD, changes in the MD (design) that may affect availability or release of the active substance (e.g. change of the surface of the MD, change in size of MD with increase of amount of the active substance).

Subsequent application for a scientific opinion should be submitted on the Application Form REG-93. For issuing a subsequent opinion it is necessary to pay the reimbursement of costs referred to under code R-050 in accordance with the guideline *UST-29 Administrative fees, reimbursement of costs for professional tasks, compensation for activities associated with the provision of information and compensation for other tasks* in its valid version. Details of payment can be found at http://www.sukl.eu/sukl/uhrada-nahrad-vydaju-za-odborne-ukony-provadene-na-zadost?lang=2 .

The assessment process of issuing an opinion on the variation is similar to the original process and should be completed within 60 days from the date on which the application is found to be valid.
Changes in qualitative or quantitative composition of the active substance or substances including replacement of salts, esters, complexes or derivatives of the active substance require completing a new assessment on the basis of a new application for a scientific opinion.
Changes or addition of indication or indications and a change or addition of administration routes also require a completely new assessment on the basis of a new application for a scientific opinion.

VII. Contacts

Address for the receipt of applications for a scientific opinion:
State Institute for Drug Control
Pharmaceutical documentation assessment department (OPF)
Šrobárova 48
100 41 Prague 10
The Czech Republic

Questions: Pharmaceutical documentation assessment department (OPF)
e-mail: opf@sukl.cz