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Federal Ministry of Health

Announcement regarding the publication of the results of clinical trials in accordance with Section 42b of the Medicines Act (AMG)

of August 3, 2011

The Federal Ministry of Health in coordination with the Federal Institute for Drugs and Medical Devices (BfArM), the Paul Ehrlich Institute - Federal Institute for Vaccines and Biomedical Pharmaceuticals (PEI), and the German Institute for Medical Documentation and Information (DIMDI) hereby publishes explanations on the legal requirements for the publication of the results of clinical trials.

Introduction:

In the past, only the higher federal authority in charge received a summary of the clinical study report by the sponsor in question (Section 13 para. 9 of the [German] GCP ordinance) or the results of clinical trials as part of applications for marketing authorization by the future pharmaceutical entrepreneur (Section 22 para. 2 of the Medicines Act (AMG)).

With Article 7 of the Act for the Restructuring of the Pharmaceutical Market in Statutory Health Insurance (AMNOG[1]), the obligation to publish such results of clinical trials was introduced. The newly created Section 42b of the Medicines Act (AMG) became effective on January 1, 2011, and requires pharmaceutical entrepreneurs and sponsors to make reports on clinical trials available to the higher federal authorities in charge for the purpose of publication in a database. Section 42b of the Medicines Act serves the public interest, specifically the interest of physicians and patients to learn more details regarding the properties of medicinal products such as their benefit or risks. In addition, the obligation to publish is meant to promote the necessary scientific discourse on trial results. An improvement of public access to the results of clinical trials with medicinal products is also planned at the European level as part of the EudraPharm database.

The explanations below are meant to address frequently asked questions to government agencies and to provide explanations for better comprehension and uniform implementation of the new legal regulations. The explanations will be supplemented if and to what extent it seems necessary.

Content:

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1. Who is legally obligated to generate summaries of clinical study reports and make them available to the higher federal authority for publication in a database in accordance with Section 67a para. 2 of the Medicines Act (AMG)?

Section 42b para. 1 of the Medicines Act (AMG) is directed at pharmaceutical entrepreneurs based in Germany, in another member state of the European Union (EU) or in a state party to the Agreement on the European Economic Area, if they place on the market within the territorial scope of the Medicines Act (AMG) a medicinal product approved for human use that was authorized for marketing in a central procedure pursuant to Section 21 of the Medicines Act/Article 3 of Regulation (EC) No. 726/2004. This obligation applies regardless of whether one or several of the trial sites used were located in Germany, i.e. even when the clinical trial was entirely conducted abroad.

Section 42b para. 2 of the Medicines Act (AMG) is directed at the sponsor in terms of Section 4 para. 24 of the Medicines Act (or his representative), who is based in Germany, in another member state of the EU, or in a state party to the Agreement on the European Economic Area, if at least one of the trial sites used was located in Germany.

(Clinical trials that were exclusively conducted in another member state of the EU or in a state party to the Agreement on the European Economic Area, will not be made publicly accessible via the database pursuant to Section 67a of the Medicines Act (AMG) but via the EudraCT database; this also applies to clinical trials conducted on children according to Regulation (EC) 1901/2006[2] in countries that are not member states of the EU or party to the Agreement on the European Economic Area.)

2. When / by what date must the summaries of clinical study reports be submitted?

According to Section 42b para. 1 of the Medicines Act (AMG), the summaries of clinical study reports must be submitted by the pharmaceutical entrepreneur within six months after marketing authorization was granted (this must also be applied to subsequent changes of the marketing authorization). To accelerate the procedure, the summaries of clinical study reports should preferably be submitted to the higher federal authority in charge together with the application for marketing authorization pursuant to Section 21 of the Medicines Act (AMG). If a marketing authorization is to be changed, reports in accordance with Section 42b para. 1 of the Medicines Act (AMG) must be submitted, if the changes to which the application pertains are based on confirmatory clinical trials.

If a clinical trial is conducted with a medicinal product that has already been granted marketing authorization or centralized marketing authorization, the sponsor must submit the summary of the clinical study report pursuant to Section 42b para. 2 of the Medicines Act (AMG) within one year after the conclusion of the clinical trial.

If there are notification obligations for a clinical trial pursuant to Section 42b para. 1 and 2 of the Medicines Act (AMG), these reports must be submitted separately in observance of the respective deadlines, since the obligation is directed at different addressees. If a report required in accordance with Section 42b para. 1 or 2 of the Medicines Act (AMG) has already been published in the database pursuant to Section 67a of the Medicines Act, it should be referenced. More details on such references and the format to be used will be stipulated in a separate announcement.

For medicinal products that have already been granted marketing authorization/ centralized marketing authorization at the time the AMNOG became effective (January 1, 2011), the transitional regulation of Section 145 of the Medicines Act (AMG) shall apply.

According to this regulation, the summaries of clinical study reports must be published by the pharmaceutical entrepreneur pursuant to Section 42b para. 1 of the Medicines Act (AMG) or the sponsor pursuant to Section 42b para. 2 of the Medicines Act (AMG) for the first time within 18 months after the regulation pertaining to Section 42b of the Medicines Act (AMG) becomes effective (i.e. no later than July 1, 2012).

This regulation applies retroactively for all clinical trials that had to be in compliance with the requirements of Good Clinical Practice in the EU, that are included in Directive 2001/20/EC and that were implemented into national law in 2004 in Sections 40 to 42 of the Medicines Act[3] and the GCP ordinance.

3. What summaries of clinical study reports are subject to the publication requirement?

According to Section 42b para. 1 of the Medicines Act (AMG), these are summaries of clinical study reports on confirmatory clinical trials to prove the efficacy and safety of the medicinal product (comp. also the official justification [of the AMNOG1]). These are such clinical trials in which the key data for proving efficacy and safety were collected for the legal marketing authorization of medicinal products (typically phase III and – if marketing authorization is granted before phase III is concluded – phase II).

Pursuant to Section 42b para. 2 of the Medicines Act, these are summaries of clinical study reports on all clinical trials conducted with medicinal products that have already been granted marketing authorization or centralized marketing authorization, regardless of whether or not the sponsor simultaneously is a pharmaceutical entrepreneur (comp. also No. 6).

4. Does Section 42b para. 1 of the Medicines Act (AMG) also include bioequivalence studies in connection with the marketing authorization for generic pharmaceuticals?

While bioequivalence studies are “indirectly confirmatory” for the marketing authorization of a generic pharmaceutical, they do not have any special informative value for the public and for science, since their sole purpose is the confirmation of pharmacokinetic comparability.
Of interest for the public, however, are the confirmatory data of the originator product on which the marketing authorization of a generic drug is based. Therefore, in addition to the information that there are no confirmatory clinical trials for the affected generic drug in terms of Section 42b of the Medicines Act (AMG), a reference to the originator product and its reports pursuant to Section 42b of the Medicines Act is to be made. As reference, the holder of the marketing authorization of a generic product should indicate the name of the originator product and its marketing authorization number as well as the EudraCT numbers for its confirmatory clinical trials.
Reference is made to Nos. 1 and 3.

5. Is Section 42b of the Medicines Act (AMG) also applicable to medicinal products other than generic pharmaceuticals for which no confirmatory clinical trials are submitted (e.g. homeopathic drugs or parallel imports)?

Section 42b of the Medicines Act (AMG) does not apply in those cases where by law no results of clinical trials must be submitted as part of marketing authorization.
For bioequivalence studies regarding generic pharmaceuticals, see number 4.

6. Does the publication requirement depend on whether the clinical trials result in changes to the marketing authorization/centralized marketing authorization?

According to Section 42b para. 1 of the Medicines Act (AMG), the summaries of clinical study reports of all clinical trials that are confirmatory for an initial marketing authorization or an amendment of an existing marketing authorization must be published. This also includes such clinical trials that are submitted in connection with a notification of variation pursuant to Section 29 of the Medicines Act.

In contrast to paragraph 1, Section 42b para. 2 of the Medicines Act (AMG) contains no restriction to confirmatory clinical trials. Therefore, paragraph 2 includes all clinical trials, regardless of whether or not they are reflected in the marketing authorization. Frequently, these are phase IV or phase IIIb clinical trials (comp. also number 3).

7. What requirements apply to the submission of summaries of clinical study reports?

The summary of the clinical study report must be developed according to the ICH E 3 guideline[4], which includes an example of a synopsis (see enclosure [to ICH E 3]). Therefore, the summary of the clinical study report should be submitted in accordance with the format of the enclosed document.
The information provided must meet the requirements of Section 42b para. 3 of the Medicines Act (AMG) and may be presented in German or English. The summary of the clinical study report must be drafted in accordance with the requirements of Good Clinical Practice and must include all results of the clinical trial, regardless of whether they are favorable or unfavorable. Statements on substantial amendments made subsequently to the trial protocol as well as temporary halts or premature terminations shall also be made in the report. The summary of the clinical study report must include the name and address of the pharmaceutical entrepreneur (in the case of Section 42b para. 1 of the Medicines Act (AMG)) or the sponsor (in the case of Section 42b para. 2 of the Medicines Act (AMG)) and should also name the investigators. The author of the report must ensure that the report contains no other person-/patient-related information or any trade and business secrets.

The summary of the clinical study report must be submitted to the higher federal authority in charge in electronic format. Details on the format to be used will be fixed in a separate announcement.

A written assurance by the pharmaceutical entrepreneur/sponsor that the data in the summary of the clinical study report were collected properly and are correct must be attached to the summary. Any statements that might be construed as advertising are unacceptable and must not be made.

8. How will the summaries of clinical study reports be published?

The higher federal authority in charge examines the information in the synopsis (and the enclosed data/documents). If necessary, additional information will be requested and examined.

A note shall be added to the summaries of clinical study reports to the effect that these are the data of the pharmaceutical entrepreneur or the sponsor. They are published by the DIMDI, with cross-references on the websites of the BfArM or the PEI.

1) Act for the Restructuring of the Pharmaceutical Market in Statutory Health Insurance (AMNOG) of December 22, 2010 (Federal Law Gazette I p. 2262, 2273)

[2] Regulation (EC) No. 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No. 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No. 726/2004 (Official Journal of the European Union L 378 of December 27, 2008, p. 1)

[3] Article 1 of the 12th Amendment Act for the Medicines Act of July 30, 2004 (Federal Law Gazette I p. 2031)

[4] ICH E 3 “Structure and Content of Clinical Study Reports, Note for Guidance on Structure and Content of Clinical Study Reports,” CPMP/ICH/137/95

Bonn, August 3, 2011
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Federal Ministry of Health
By delegated authority
Dr. Dagmar Krüger

Annex:

Minimum data for the summaries of the clinical study reports according to the ICH E 3 guideline*)

1) Name of Sponsor/Company
2) Name of Finished Product
3) Name of Active Substance
4) Individual Study Table Referring to Part of the Dossier (Volume, Page)

Note: This information is only required in connection with filing of a dossier for marketing authorization.

5) Title of Study

Note: The latest protocol version must be clearly stated, this means including all amendments - the amendments are to be declared and identified.

6) Investigators
7) Study centre(s)
8) Publication (reference)
9) Studied period (years) date of first enrolment, date of last completed

Note: Here also study suspensions and premature terminations of a trial/ premature conclusions of a trial should be listed, including the reasons for that.

10) Phase of development
11) Objectives
12) Methodology
13) Number of patients (planned and analyzed)
14) Diagnosis and main criteria for inclusion
15) Test product, dose and mode of administration, batch number
16) Duration of treatment
17) Reference therapy, dose and mode of administration, batch number
18) Criteria for evaluation Efficacy, Safety
19) Statistical methods
20) Summary — Conclusions: Efficacy Results, Safety Results, Conclusion
21) Date of report

*) ICH E 3 Structure und Content of Clinical Study Reports, Note for Guidance on Structure and Content of Clinical Study Reports CPMP/ICH/137/

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