Federal Institute
for Drugs
and Medical Devices

Guideline for Notification of a Compassionate Use Programme in Accordance with the Ordinance on Medicinal Products for Compassionate Use ("*Arzneimittel-Härtefall-Verordnung*", AMHV)

Version 1.3 of 20 April 2017

Contents

Revisions

Version 1.0, 1 August 2013: First issue

Version 1.1, 5 August 2013: Clarification under 3.3.1 regarding the number of copies

Version 1.2, 25 March 2014: Correction of the algorithm under 2.2. regarding Question 4

Version 1.3, 20 April 2017: First English translation, minor linguistic adjustments

1 Glossary

AMHV	Ordinance on the placing on the market of unauthorised medicinal products for compassionate use (Ordinance on Medicinal Products for Compassionate Use - AMHV) [*Verordnung über das Inverkehrbringen von Arzneimitteln ohne Genehmigung oder ohne Zulassung in Härtefällen* (*Arzneimittel-Härtefall-Verordnung* – AMHV)]
BOB	In accordance with the provisions laid down in Section 77 Medicinal Products Act (AMG), the competent higher federal authority "*Bundesoberbehörde*" (BOB) responsible for compassionate use programmes is either the Paul-Ehrlich-Institut (PEI) or the Federal Institute for Drugs and Medical Devices (*Bundesinstitut für Arzneimittel und Medizinprodukte*, BfArM)
Compassionate Use	Making a medicinal product not authorised nationally or centrally that is subject to the obligation to obtain a national or central marketing authorisation available to a group of patients for humanitarian reasons who have a disease that is seriously debilitating or life-threatening and who cannot be treated satisfactorily with a medicinal product authorised nationally or centrally
Compassionate Use Programme	Compassionate use programme as defined in Section 2 sub-section 1 of the Ordinance on Medicinal Products for Compassionate Use (AMHV)
Data lock point	Time when the safety database is closed for the safety report. Adverse reactions reported after this date are not covered in the current safety report but will be included in the following safety report.
Responsible person	A person who assumes responsibility for the commissioning, organisation and financing of a compassionate use programme (Section 3 sub-section 1 AMHV) and is responsible for the notification and the proper conduct of a compassionate use programme (Section 7 AMHV)

2 Introduction

On 22 July 2010, the Ordinance on the Placing on the Market of Unauthorised Medicinal Products for Compassionate Use ("*Verordnung über das Inverkehrbringen von Arzneimitteln ohne Genehmigung oder ohne Zulassung in Härtefällen*" or short: "*Arzneimittel-Härtefall-Verordnung*" – AMHV) came into force. This ordinance by the German Federal Ministry of Health pursuant to Section 80 sentence 1 number 3a in conjunction with sentences 3 and 4 and in conjunction with Section 83 of the German Medicinal Products Act ("*Arzneimittelgesetz*" – AMG) regulates the procedures in connection with compassionate use programmes as defined in Section 21 sub-section 2 number 6 AMG.

Section 21 sub-section 2 number 6 AMG stipulates that medicinal products do not require a marketing authorisation if they "[...] are made available **free of charge** under the conditions specified to in Article 83 of Regulation (EC) No. 726/2004 for administration to patients **with a seriously debilitating disease** or **whose disease is life-threatening and** who cannot be treated satisfactorily with an authorised medicinal product; this applies equally to medicinal products which do not fall under the categories stipulated in Article 3 first or second paragraph of Council Regulation (EC) No. 726/2004; rules of procedure shall be specified in an ordinance pursuant to Section 80 [...]"

Article 83 of Regulation (EC) No. 726/2004 states:

"1. By way of exemption from Article 6 of Directive 2001/83/EC Member States may make a medicinal product for human use belonging to the categories referred to in Article 3(1) and (2) of this Regulation available for compassionate use.

2. For the purposes of this Article, 'compassionate use' shall mean making a medicinal product belonging to the categories referred to in Article 3(1) and (2) available for compassionate reasons to a group of patients with a chronically or seriously debilitating disease or whose disease is considered to be life-threatening and who cannot be treated satisfactorily by an authorised medicinal product. The medicinal product concerned must either be the subject of an application for a marketing authorisation in accordance with Article 6 of this Regulation or must be undergoing clinical trials.

3. When a Member State makes use of the possibility provided for in paragraph 1 it shall notify the Agency.

4. When compassionate use is envisaged, the Committee for Medicinal Products for Human Use, after consulting the manufacturer or the applicant, may adopt opinions on the conditions for use, the conditions for distribution and the patients targeted. The opinions shall be updated on a regular basis.

5. Member States shall take account of any available opinions.

6. The Agency shall keep an up-to-date list of the opinions adopted in accordance with paragraph 4, which shall be published on its website. Article 24(1) and Article 25 shall apply *mutatis mutandis*.

7. The opinions referred to in paragraph 4 shall not affect the civil or criminal liability of the manufacturer or of the applicant for marketing authorisation."

Since coming into force of the Ordinance on Medicinal Products for Compassionate Use, the so-called responsible person is thus obligated to notify the competent higher federal authority in accordance with Section 3 AMHV prior to commencing a compassionate use programme. The compassionate use programme cannot be commenced until the competent higher federal authority has confirmed the notification ("confirmed notification") and has not raised any objections against the compassionate use programme.

2.1 Demarcation between compassionate use programmes and individual cases

In its regulations regarding exemption from the obligation to obtain a marketing authorisation in Section 21 sub-section 2 number 6 AMG, the Medicinal Products Act explicitly refers to the prerequisites stated in Article 83 of Regulation (EC) No. 726/2004. The definition of "compassionate use" in Article 83 (2) of Regulation (EC) No. 726/2004 refers specifically to a **group of patients** with a seriously debilitating or life-threatening disease who cannot be treated satisfactorily by an authorised medicinal product. Thus, in conjunction with Section 2 AMHV it is clear that the regulations of AMG and AMHV regarding compassionate use refer exclusively to compassionate use programmes, i.e. to programmes in which **groups** of patients are treated. Isolated cases where only one patient is treated individually with a medicinal product that is not authorised nationally or centrally in one physician's direct responsibility are not covered by the Medicinal Products Act and thus also not by the AMHV. Therefore, the BfArM is not responsible for such issues outside of compassionate use programmes.

Due to the non-applicability of both Section 21 sub-section 2 number 6 AMG and the AMHV, neither restrictions regarding the import of medicinal products not authorised nationally or centrally that are subject to the obligation to obtain such marketing authorisations, nor the prohibition of the marketing of medicinal products not authorised nationally or centrally, that are subject to the obligation to obtain such marketing authorisations, are abrogated for isolated cases where only one patient is treated individually. Thus, in individual cases, making a medicinal product not authorised nationally or centrally which is subject to the obligation of obtaining a national or central marketing authorisation available, could constitute a punishable act. In such cases, the extent to which the requirements e.g. for a justified necessity as defined e.g. in the criminal code are fulfilled in the specific individual case, has to be reviewed on a case-by-case basis. In this connection, the BfArM is not in the position to give advice on such individual cases.

If a medicinal product not authorised nationally or centrally that is subject to the obligation to obtain such a marketing authorisation, was already made available in the past and if further dispensing to a different patient in the same indication is now planned, a compassionate use

notification as defined in Section 2 sub-section 1 AMHV is required. As a rule, planned dispensing of the same medicinal product to more than one patient within the same medical indication (even if it occurs at different times) is to be considered a compassionate use programme as defined by the AMHV. Therefore, prior to commencing such a compassionate use programme, the competent higher federal authority is to be notified of this intention in accordance with Section 3 AMHV.

2.2 Prerequisites for compassionate use programmes

AMG and AMHV define specific basic prerequisites for compassionate use programmes. The following decision algorithm shown in Figures 1 and 2 is suggested in order to evaluate whether these conditions are met.

1. Shall the medicinal product be made available in an individual case?

If the answer is "yes": The legal prerequisites of Section 21 sub-section 2 number 6 AMG and of the AMHV for commencing a CU programme have not been met. Dispensing of medicinal products in individual cases is not regulated by AMG or AMHV.

If the answer is "no" continue with question 2

2. Does the medicinal product which is intended for the CU require a national or centralised marketing authorisation and is neither authorised in Germany nor in any other Member State of the EU/EEA?

If the answer is "yes", continue with question 3

If the answer is "no": The prerequisites for a compassionate use programme have only been met if there is no possibility of prescribing a medicinal product for a recognised off-label use and importing it for this purpose from a Member State of the EU or the EEA. Note: As a rule, the use of a licensed medicinal product outside its licensed indication is no therapeutic alternative. However, this does not apply if the off-label use conforms with generally accepted scientific standards.

3. Do the patients suffer from a seriously debilitating disease or from a disease which is life-threatening?

If the answer is "yes", continue with question 4

If the answer is "no": The legal prerequisites of Section 21 sub-section 2 number 6 AMG in conjunction with Article 83 (2) of Regulation (EC) No. 726/2004 have not been met. Therefore, the conditions for a CU programme are not fulfilled.

4. Can these patients be treated satisfactorily with another medicinal product that is authorised in Germany?

If the answer is "no", continue with question 5

If the answer is "yes": The legal prerequisites of Section 21 sub-section 2 number 6 AMG in conjunction with Article 83 (2) of Regulation (EC) No. 726/2004 have not been met. Therefore, the conditions for a CU programme are not fulfilled.

5. Was an application for marketing authorisation submitted to EMA or any other NCA in the EU/EEA?

If the answer is "yes", continue with question 10

If the answer is "no", continue with question 6

6. Is an authorised clinical trial in the same indication currently being conducted in the EU/EEA?

If the answer is "yes", continue with question 8

If the answer is "no", continue with question 7

7. Is an ICH-GCP compliant clinical trial in the indication currently being conducted in a third state outside the EU/EEA?

If the answer is "yes", continue with question 10

If the answer is "no": The prerequisites of the AMHV have not been met. Therefore, the conditions for a CU programme are not fulfilled.

8. Is this clinical trial also conducted in Germany in this indication?

If the answer is "yes", continue with question 9

If the answer is "no", continue with question 10

9. Can the patients intended for the compassionate use programme also be included in this clinical trial?

If the answer is "yes": The prerequisites of the AMHV have not been met. Therefore, the conditions for a CU programme are not fulfilled.

If the answer is "no", continue with item 10

10. Basically, the prerequisites for a CU programme have been met. Prior to commencing the programme, the competent higher federal authority has to be notified and has to give its confirmation.

Figure 1: Decision algorithm (text version)

A diagram of this decision algorithm is displayed in

Figure 2.

If the requirements for a compassionate use programme have basically been fulfilled, the competent higher federal authority has to be notified prior to beginning the programme. After receipt of the confirmation from the competent higher federal authority that the notification has been submitted correctly, the compassionate use programme can be commenced, provided the competent higher federal authority has not raised objections (Section 4 sub-section 3 AMHV).

2.3 Competent higher federal authority

The competence of the competent higher federal authority is specified in Section 77 AMG. In accordance with Section 77 AMG, the competent higher federal authority shall be the Federal Institute for Drugs and Medical Devices ("*Bundesinstitut für Arzneimittel und Medizinprodukte*", BfArM) unless the Paul-Ehrlich-Institut (PEI) is responsible. In general, the competent higher federal authority that was or would be responsible for authorisation of a clinical trial with the medicinal product concerned is also responsible for the compassionate use programme.

Figure 2: Decision tree for compassionate use programmes

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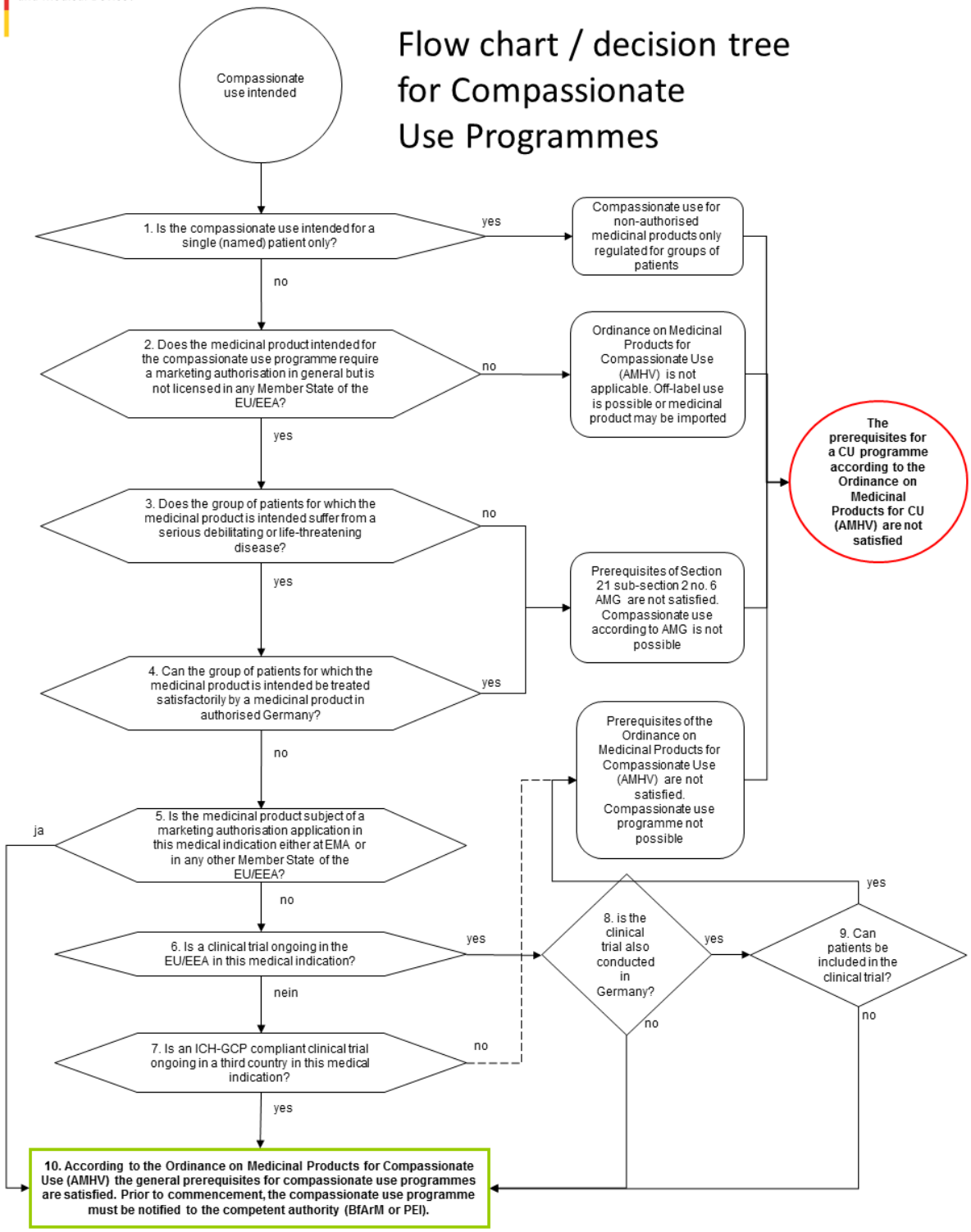
Flow chart / decision tree for Compassionate Use Programmes



AMHV: Ordinance on Medicinal Products for Compassionate Use; AMG: German Medicines Act; EMA: European Medicines Agency; EU: European Union; EEA: European Economic Area; ICH-GCP: Good Clinical Practice (GCP) harmonised by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)

3 Notification

3.1 Responsible person

If the prerequisites for a compassionate use programme have been fulfilled (cf. Chapter 2.2), a notification is to be submitted to the competent higher federal authority pursuant to Section 3 sub-section 1 AMHV prior to commencing the compassionate use programme. This notification is to be made by the so-called "responsible person" pursuant to Section 3 sub-section 1 AMHV. The wording of the AMHV does not lay down specific requirements regarding the legal personality of the responsible person. Thus, a responsible person can be both a natural or a legal person but can also be a civil law partnership ("*Gesellschaft bürgerlichen Rechts*", GbR). The responsible person can be the applicant for a central or national marketing authorisation or the sponsor of the authorised clinical trial. Section 3 sub-section 1 AMHV specifies that the responsible person must have a representative registered in a Member State of the European Union or in another State Party to the Agreement on the European Economic Area if the responsible person himself/herself does not have his/her registered place of business there. This regulation ensures that there will always be a responsible person within the scope of European law. If a representative has been named, this person has the same obligations as the responsible person. The responsible person bears the overall responsibility for the compassionate use programme. This includes initiation, organisation and financing of the compassionate use programme. The organisation of the programme also covers necessary measures during conduct of the compassionate use programme.

3.2 Necessary information and documents

3.2.1 Cover letter

Any notification of a compassionate use programme is to be accompanied by a cover letter indicating that this letter is the introduction to a notification of a compassionate use programme by a responsible person. The cover letter should contain the following information:

a) Name of the medicinal product,

b) planned medical indication,

c) information whether a clinical trial with the medicinal product has already been authorised by the competent higher federal authority and whether this clinical trial concerned the same medical indication,

d) information whether an application for marketing authorisation has been submitted in Europe,

e) confirmation that the medicinal product has not been granted a marketing authorisation in Germany nor in another Member State of the EU/EEA to date,

f) confirmation that the submitted electronic documentation is identical with the submitted paper version,

g) Information whether a medicinal product with genetically modified organisms is supposed to be used in the compassionate use programme,

h) if the cover letter is not signed by the responsible person himself/herself, a confirmation by the responsible person stating that the signatory of the cover letter is authorised to submit the compassionate use programme in the name of the responsible person and to exchange the relevant correspondence with the BfArM,

i) contact data for publication on the BfArM website of the institution/establishment that is supposed to serve as contact for the compassionate use programme concerned (name, telephone and/or telefax number, e-mail or postal address).

3.2.2 Documents pursuant to Section 3 sub-section 2 AMHV

Pursuant to Section 3 sub-section 2 AMHV, the following information and documents in German *or* English are necessary for the notification (for exceptions regarding the language please refer to No. 14):

No. 1 Name or firm and address of the responsible person and, where available, that of the representative registered in the European Union or in another State Party to the Agreement on the European Economic Area,

Note: The responsible person can be both a natural or a legal person but can also e.g. be a civil law partnership. Typical responsible persons can be e.g. the applicant for marketing authorisation or the sponsor of an authorised still ongoing clinical trial in the notified indication. The responsible person bears the overall responsibility for the compassionate use programme. This includes initiation, organisation and financing of the compassionate use programme. If a representative has been named, this person has the same obligations as the responsible person.

No. 2 the name or code of the medicinal product, the name of the active substances by type and quantity, other constituents by nature, pharmaceutical form, route of administration, dosage and treatment plan,

Note: The name of the medicinal product and statement of the active substances serve to identify the medicinal product used in the compassionate use programme. The name can e.g. be the trade name applied for in the course of the licensing procedure or the code that is used for an investigational medicinal product within a clinical trial. If the active substance has an INN[1] it is also absolutely necessary that this be stated.

No. 3 description of the disease that leads to a serious disability, or is life-threatening, from which the patient is suffering and for the treatment of which the medicinal product is intended,

Note: Here, it should be stated from which seriously debilitating disease the group of patients for which the compassionate use programme is notified suffers. In order to comply with the prerequisites of a compassionate use programme in accordance with AMHV and AMG, the disease must lead to a serious disability or has to be life-threatening. Since the definition of the term "disability" covers a duration of at least 6 months, it also encompasses the requirement "chronic" provided for in European law. It

[1] INN: International Nonproprietary Name

*should be observed that the medicinal product has to be directly treatment-related with this disease, i.e. it must be administered **directly** for treatment of the condition.*

No. 4 criteria for the selection of patients and notification of the anticipated number of patients,

Note: Here, the criteria for selection are to be described (e.g. inclusion and exclusion criteria for patients). These depend on the one hand on the disease and type of pretreatment already given without lasting success and on the other on the profile of the medicinal product which might exhibit e.g. certain limitations with regard to its administration. For example, if the compassionate use programme is used in a so-called second-line therapy of a disease, it should be stated which first-line therapy/therapies already have to have been employed as prerequisites for participation in the compassionate use programme and/or are contra-indicated. Furthermore, information on the anticipated number of patients is required. This statement is an estimate and is merely intended to yield information on the number of patients anticipated for the programme. However, significant deviations (upward by more than 20 %) from the estimate are to be notified in accordance with Section 5 AMHV.

No. 5 grounds explaining why these patients cannot be satisfactorily treated with a medicinal product authorised nationally or centrally for placing on the market within the territorial scope of the Medicinal Products Act,

Note: Here, the responsible person is supposed to justify why no satisfactory treatment with a medicinal product authorised nationally or centrally within the scope of the Medicinal Products Act is possible for the patient group of the compassionate use programme. The absence of therapeutic alternatives for the group of patients concerned must be established objectively. In this connection "not satisfactory" means that no nationally or centrally authorised medicinal product for treatment of the disease concerned is available in Germany. This applies regardless of whether the therapeutic alternative has been licensed in centralised, decentralised or national procedures. As a rule, the use of a licenced medicinal product outside its licensed indications is no therapeutic alternative. That may be a different matter if the off-label use conforms with generally accepted standards. On the other hand, there are those cases where there is a medicinal product but it has failed in the patients intended for the compassionate use programme, is contraindicated in the patients intended for the compassionate use programme in accordance with the information contained in the authorisation, or has more frequent or severe side effects as compared to the medicinal product used in the compassionate use programme. The statement that the new medicinal product dispensed in the compassionate use programme is "better" than the licensed therapeutic standard and shall therefore be administered directly even without previous treatment with the licensed therapeutic standard, can generally not be accepted, as superiority is mostly not sufficiently proven at the time of application or is confirmed by way of a marketing authorisation granted for "first-line" therapy in the course of extensive testing of the licensing documentation.

No. 6 grounds explaining why the patients cannot be included in an ongoing trial,

Note: Compassionate use programmes are no systematic substitute for clinical trials. Patient monitoring is better in clinical trials than in compassionate use programmes and only clinical trials can generate quality-assured data for the purpose of gaining a marketing authorisation. Therefore, both from a scientific point of view as well as due to safety aspects for the patients, inclusion in a clinical trial is the treatment option of choice. If patients fulfil the criteria for enrolment in a clinical trial and treatment within an ongoing

clinical trial is possible, they should be enrolled in that trial and should not be treated within a compassionate use programme. In cases where an extension of the clinical trial is feasible, this should be tested prior to performing a compassionate use programme.

No. 7 evidence to support the fact that the medicinal product is of the appropriate quality in keeping with recognised pharmaceutical regulations, as well as confirmation by the qualified person pursuant to Section 14 of the Medicinal Products Act that the medicinal product has been manufactured according to the principles and guidelines of good manufacturing practice for medicinal products,

Note: The appropriate pharmaceutical quality must be proven by way of suitable documentation. This can be e.g. the investigational medicinal product dossier submitted for the medicinal product in the course of a clinical trial or - if an application for marketing authorisation has already been submitted - the documents to be submitted for the licensing procedure presented as summaries. Additionally, the explicit submission of a certification by the qualified person (QP) regarding the GMP-compliant manufacture of the medicinal product is required.

No. 8 evidence and grounds for the assumption that the medicinal product is safe and effective for the envisaged use, as a rule through submission of the results of confirmatory clinical trials,

Note: For the protection of patients in compassionate use programmes, sufficiently evidenced findings are to be provided for the assumption of efficacy and safety of the medicinal product that is supposed to be used in the compassionate use programme for the disease in question. This is generally done by way of a phase III clinical trial or by (confirmatory) results that have justified an ongoing not yet concluded phase III clinical trial. In certain exceptional cases such evidence can also be gained in phase II clinical trials. When presenting completed studies, it is mainly a synopsis of the final study report that should be submitted.

No. 9 criteria for the suspension or premature discontinuation of the compassionate use programme,

Note: In order to ensure patient safety, the responsible person has to present criteria for suspension or premature termination of a compassionate use programme.

No. 10 further details regarding

a) the authorised clinical trial of the medicinal product in the intended indication, giving the EudraCT number, or

b) the clinical trial of the medicinal product in the intended indication in a third state and evidence that this is being conducted according to the internationally harmonised Standards of Good Clinical Practice, or

c) the application for national or central marketing authorisation, which has been submitted for the medicinal product in the intended indication, to the European Medicines Agency, the competent higher federal authority or to an authority responsible for marketing authorisation in a Member State,

Note: Exemption from the obligation to obtain a national or central marketing authorisation in connection with a compassionate use programme is only justified if parallel to this programme a clinical trial with the medicinal product and in the same

indication has been authorised or an application for national or central marketing authorisation has been submitted. Compassionate use programmes are not a legitimation to permanently place medicinal products on the market without a national or central marketing authorisation. In cases where a successful treatment outcome can reasonably be expected, a group of patients suffering from a serious disease who can be treated with a medicinal product not licensed nationally or centrally in the European Union or in a country party to the Agreement on the European Economic Area, is given a treatment option as early as during the trial phase and the national or central licensing procedure. However, compassionate use programmes can never replace a national or central licensing procedure and can thus also not compensate for hardships that result if – for whichever reasons – a pharmaceutical entrepreneur refrains from submitting an application for national or central marketing authorisation within the scope of the Medicinal Products Act or in a Member State of the European Union or a country party to the Agreement on the European Economic Area.

re a) In the case of an ongoing clinical trial in the intended indication performed in Germany or another Member State of the EU/EEA the EudraCT number of the authorised clinical trial is to be stated when submitting the notification.

re b) A compassionate use programme can also be considered if a clinical trial is only being conducted in a third state. In such cases the responsible person must supply proof that the clinical trial is performed in accordance with the internationally harmonised standards of good clinical practice (ICH-GCP). Suitable proof for this can be e.g. a vote from the competent Ethics Committee that operates independently as laid down in Section 3.2 of the ICH-GCP Guidelines. The independent Ethics Committee's vote must show which study was evaluated, on which documents the evaluation was based, which decision was reached with regard to the trial and the reasoning for this decision. The vote or an accompanying document by the independent Ethics Committee should show that the independent Ethics Committee adheres to the ICH-GCP Guidelines. If the vote or potential accompanying documents are not available in German or English, certified translations are to be submitted.

re c) The application for national or central marketing authorisation must have been submitted for the same indication as that of the notified compassionate use programme either to the EMA, to the competent higher federal authority or to the competent authority of the EU/EEA Member State. An application for national or central marketing authorisation submitted exclusively to a licensing authority of a third state (e.g. the USA's Food and Drug Administration) does not fulfil the requirements listed under c).

No. 11 in the case of medicinal products which consist of or contain a genetically modified organism or a combination of genetically modified organisms, documents pursuant to Annexes II and III of Directive 2001/18/EC of the European Parliament and the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC (OJ L 106 of 17 April 2001, p. 1),

Note: Special documents have to be submitted for medicinal products which consist of or contain a genetically modified organism or a combination of genetically modified organisms. In accordance with Annex II of Directive 2001/18/EC these include: an explanation and assessment of the risks to the health of non-trial subjects as well as an explanation of the intended precautions and, pursuant to Annex III of that Directive, information on the genetically modified organism, information on the conditions of the compassionate use programme and the clinical trial and on the environment into which the genetically modified organism is possibly released, information on the interaction between the genetically modified organism and the environment, an observation plan to

determine the effects on the health of non-trial subjects and the environment, a description of the intended surveillance measures and information on the resulting residues and their handling as well as emergency plans.

No. 12 justification for treatment with a medicinal product the application for national or central marketing authorisation of which has been rejected, withdrawn, revoked or suspended or the authorisation of a clinical trial with which has been refused, withdrawn, revoked or suspended, together with the reasons for this decision,

Note: These documents are only to be submitted if application for national or central marketing authorisation of the medicinal product has been rejected, withdrawn, revoked or suspended or if the authorisation of the clinical trial has been refused, withdrawn, revoked or suspended or was granted conditional approval. Refusal of an application for national or central marketing authorisation or an application for authorisation of a clinical trial does not generally oppose conducting a compassionate use programme. However, the reasons for this refusal should be presented to the BfArM, so that it can decide whether this could result in an objection (e.g. an unfavourable risk/benefit ratio). This specification of the reasons for suspension refers both to the suspension ruled by the authority as well as to the withdrawal initiated by the sponsor. Furthermore, it is important whether the clinical trial was approved under specific conditions.

No. 13 the current investigator's brochure provided to the investigator in the clinical trial or the draft summary of the medicinal product's product characteristics contained in the application for national or central marketing authorisation,

Note: If an application for national or central marketing authorisation was submitted pursuant to the documents stated in No. 10 c), a draft Summary of Product Characteristics (SmPC) in German or English is to be submitted which is identical with the expert information ("Fachinformation") pursuant to Section 11a AMG. If no application for national or central marketing authorisation has been submitted yet, the notification is to be accompanied by the investigator's brochure pursuant to Section 3 sub-section 4 of the Ordinance on the Implementation of Good Clinical Practice in the Conduct of Clinical Trials on Medicinal Products for Use in Humans ("Verordnung über die Anwendung der Guten Klinischen Praxis bei der Durchführung von klinischen Prüfungen mit Arzneimitteln zur Anwendung am Menschen", GCP-V) for the study authorised and conducted in this indication. In the case of clinical trials conducted exclusively in third states, a documentation comparable in nature, content and scope to that pursuant to Section 3 sub-section 4 GCP-V is to be submitted.

No. 14 information and documents which are given to patients, in **German**, as well as a description of the procedure for informed consent after instruction by a participating physician,

Note: The responsible person must guarantee that the patient is properly informed about the compassionate use programme by the participating physician, i.e. extensively, accurately from the content point of view and in a manner understood by the patient. For the protection of the patients it is therefore necessary that the BfArM has the possibility of reviewing the patient information. The patient information must be submitted to the authority in German. With regard to the characterisation of the medicinal product, the patient information should be based on the patient information of the ongoing clinical trial and/or the model of the package leaflet. In addition, reference should be made to the specific characteristics of the compassionate use programme and especially to the fact that the medicinal product is not yet authorised. In the text, the patients should be

requested to inform the treating physician of all adverse effects they consider to be treatment-related. In general, the text should not be of a promotional nature and should especially not create the impression that the participation in the programme is attached to special conditions aside from the legal provisions. The informed consent should contain a confirmation by the patients that they have been given information on the basic conditions of compassionate use programmes in general and on the characteristics of this specific compassionate use programme in particular, that they wish to participate in the compassionate use programme and that they are aware of the fact that they can terminate their participation at any time without this resulting in any disadvantages for them. The patient should additionally submit a separate declaration of consent with regard to data-protection issues. This should include a statement that the patients agree with the pseudonymised disclosure of suspected cases of adverse effects by the treating physician and are aware of the fact that once having declared this consent for pseudonymised disclosure of their data for reasons of drug safety, it cannot be retracted.

No. 15 requirements to be met by the medical facilities and qualifications of the participating physicians,

In order to ensure the highest possible safety when using the medicinal product for which the trials have not yet been completed, choice of the facilities and the participating medical staff is particularly important. Therefore, the responsible person must define which quality requirements should be met by the facility (e.g. equipment) and by the physicians (e.g. special expertise) in order to assure the safest possible use.

No. 16 description of the measures to be taken to guarantee the safe storage, use and fate of the medicinal products made available,

In order to ensure the highest possible safety in the handling of the medicinal product that has not been licensed yet, the responsible person must indicate the particular safety precautions to be taken by the participating physicians and facilities when administering the medicinal product. This must also include information on what is to be done with the stock of medicinal products not used up at the end of the compassionate use programme (e.g. a return to the responsible person).

No. 17 information, where appropriate, on ongoing compassionate use programmes in Member States of the European Union or other States Party to the Agreement on the European Economic Area and, where available, expert opinions of the Committee for Medicinal Products for Human Use pursuant to Article 83 (4) of Regulation (EC) No. 726/2004,

Knowledge gained from previously conducted or ongoing compassionate use programmes can yield information with regard to efficacy and safety. Information on whether compassionate use programmes have been performed and e.g. whether they have been terminated prematurely is important for the overall assessment of a compassionate use programme. This applies all the more to the availability of an opinion from the competent committee of the European Medicines Agency (the EMA's CHMP).

No. 18 declaration of consent regarding the publication of information on the main features of the notified compassionate use programme.

In agreement with the competent higher federal authority's information obligation towards the European Medicines Agency, it is specified that the responsible person must agree with the publication of the essential content of the compassionate use programme on the BfArM's website. The essential content to be published about the programme includes

the name of the responsible person (and the company, if applicable), the name of the medicinal product, information on active substance, pharmaceutical form and dosage, route of administration as well as on the group of patients, the contact details (of the responsible person unless the latter is a natural person) and the duration of the programme. This publication serves transparency and especially for information of patients and healthcare professionals.

3.3 Submission of the notification

The notification and the necessary documents pursuant to Section 3 sub-section 2 AMHV must be submitted in writing and electronically. For this purpose the BfArM provides a form on its website that should be used for such notifications. The documents submitted electronically should be sent as PDF files that are protected in such a manner as that copying contents is not possible. In order to allow a simple and speedy processing in this administrative procedure, it is possible to submit the documents accompanying the notification in German or English. However, this does not apply to the patient information which must be submitted in German (cf. Section 3 sub-section 2 number 14 AMHV). Every submission must contain a cover letter stating the purpose of the submission (cf. Chapter 3.2.1)

3.3.1 Notification in written form

Applicants are requested to submit the written documents in the original version in single copy. Provided the format for the electronic media described in Annex 9.2 is adhered to, no further copies are necessary. Together with the cover letter, the written documents should be submitted in accordance with the structure given for documents to be submitted pursuant to Section 3 sub-section 2 AMHV. Alignment with the directory structure of the electronic documents is helpful (cf. Chapter 3.3.2).

3.3.2 Notification in electronic form

The electronic submission is made on CD-ROM or DVD in the usual file format for such electronic media. The directory structure shown in Figure 3 should be used for submission and naming convention.

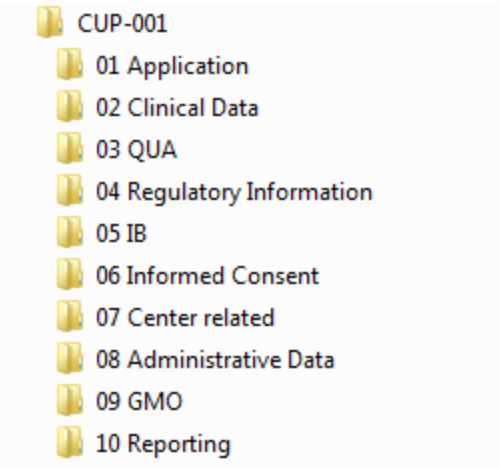


Figure 3: Directory structure for electronic submission

All documents should be submitted in a shared folder bearing the code name of the compassionate use programme. Other than that, the root directory of the electronic medium for notification should not contain any further data or folders. All other folders should be created in the folder of the compassionate use programme. If no documents are available for a specific subfolder, this folder remains empty. In the case of supplements, only those folders should be created on the electronic medium that contain documents. A detailed description of the directory structure and contents of the folders is described in Chapter 9.2.

4 Confirmation of the notification by the BfArM

4.1 Notification procedure

In accordance with Section 4 sub-section 1 AMHV, the competent higher federal authority shall confirm the applicant's notification at least 2 weeks after receipt thereof by the competent higher federal authority stating the date of receipt, provided that the notification is complete and in accordance with the regulations (for exceptions cf. Chapter 4.2). If documents are missing or the notification is not in accordance with the regulations for other reasons, the applicant will receive an information stating the reasons and the fact that the confirmation of the notification is refused for the time being, since the notification was incomplete and/or not in accordance with the regulations for other reasons. Additionally, the responsible person is requested to complete the documentation or to remedy those deficiencies that led to refusal of the confirmation. After the responsible person has supplemented the missing or revised documents, the evaluation process begins again, i.e. the competent higher federal authority confirms the applicant's notification at least 2 weeks after it has received the supplement (stating the date of its receipt), provided the notification is now complete and in accordance with the regulations. Otherwise, the applicant is again informed that the confirmation of the notification is refused, since the notification remains incomplete and/or not in accordance with the regulations for other reasons despite the supplement. In this case, the responsible person is also requested to complete the documentation or to remedy the deficiencies that led to the refusal of the confirmation.

If the notification is confirmed by the competent higher federal authority, the compassionate use programme can be commenced, unless an authorisation as described in Chapter 4.2.1 is required for specific medicinal products containing genetically modified organisms. The compassionate use programme must not be commenced until the competent higher federal authority has confirmed the notification, even if the deadlines stated in this chapter and in Chapter 4.2 are exceeded.

4.2 Deadlines

Notwithstanding the deadlines stated in Chapter 4.1. there are special deadlines applicable under certain circumstances in accordance with Section 4 sub-sections 4 and 5 AMHV. If the notification concerns an advanced therapy medicinal product **or** a medicinal product, which has not yet been evaluated by the competent higher federal authority in an authorisation procedure for any clinical trial in the same indication, an appropriate deadline shall apply, by way of derogation from Section 3 sub-section 1 AMHV which shall not exceed 60 days. All deadlines given refer to calendar days. If the period would end on a Sunday or a national public holiday the deadline shall be extended to the following working day.

4.2.1 Medicinal products with genetically modified organisms

In the case of medicinal products which consist of or contain genetically modified organisms or a combination of genetically modified organisms, the authorisation of the clinical trial by the

competent higher federal authority shall also include the release of these genetically modified organisms within the framework of the compassionate use programme. This shall apply only in so far as no changes are made to the authorised clinical trial which would modify the assessment of the risk it poses to the health of third parties and the environment. In the case of changes capable of modifying the assessment of the risk to the health of third parties and the environment, the competent higher federal authority shall take a decision within an appropriate period of time, in consultation with the Federal Agency for Consumer Protection and Food Safety ("*Bundesamt für Verbraucherschutz und Lebensmittelsicherheit*", BVL). By way of derogation from Section 4 sub-sections 2 and 4 AMHV, a compassionate use programme with medicinal products for which such a new risk assessment is necessary, may only be commenced upon receipt of the authorisation required for this purpose.

5 Objection

5.1 Objection raised by the higher federal authority prior to commencement of the compassionate use programme

In accordance with Section 4 sub-section 3 AMHV, the competent higher federal authority may raise objections against the implementation of a compassionate use programme, even if the documents submitted for notification were complete, if it is of the opinion that

- the prerequisites for implementation of the compassionate use programme are not fulfilled or
- there are indications that the submitted information is incorrect or,
- that the safe use of the medicinal product is not guaranteed.

The prerequisites for a compassionate use programme are specified in Section 21 sub-section 2 number 6 AMG in conjunction with Article 83 of Regulation (EC) No. 726/2004. Section 3 sub-section 2 AMHV contains more specific regulations regarding the prerequisites of a compassionate use programme. Exercising the right to raise objections is within the dutiful discretion of the competent higher federal authority. In such cases, patient interests are to be given priority. The compassionate use programme must not be commenced if the higher federal authority has raised an objection.

5.2 *A posteriori* objection against an ongoing compassionate use programme by the higher federal authority

In accordance with Section 4 sub-section 3 AMHV, the competent higher federal authority can raise objections *a posteriori* even if a compassionate use programme has already been commenced if prerequisites for conducting a compassionate use programme subsequently cease to apply, or there are indications that the submitted information was incorrect, or if it later unfolds that the safe use of the medicinal product is no longer guaranteed (cf. Chapter 5.1). If the competent higher federal authority has raised objections, the compassionate use programme can no longer be continued and must be stopped. In this case, all physicians treating patients within this compassionate use programme are to be advised immediately as to the discontinuation of the compassionate use programme and are instructed not to include any further patients in the compassionate use programme and to stop treating patients already receiving the medicinal product within the compassionate use programme. Medicinal products already dispensed must be handled in accordance with the statements under Section 3 sub-section 2 number 16 AMHV or the responsible person must ensure that the medicinal product is returned. If the higher federal authority has raised an objection the medicinal product must not be placed on the market without a marketing authorisation. In cases of objections raised by the competent higher federal authority, the exemption from the obligation to obtain a marketing authorisation is not or no longer applicable. In the case of an *a posteriori* objection, the competent higher federal authority will particularly consider patients' interests when exercising its dutiful discretion.

5.3 Legal remedy against the BfArM's notice of objection

The responsible person can lodge an appeal against a notice issued by the BfArM. Information regarding form, time limits and recipient is stated in the legal remedy of the respective notice. Pursuant to Section 4 sub-section 3 AMHV, a compassionate use programme must not be commenced or continued if the BfArM has raised an objection. This prohibition remains unaffected by the appeal.

6 Duration and renotification of a compassionate use programme

6.1 Duration of a compassionate use programme

A compassionate use programme ends

- if the responsible person terminates it prematurely,
- if the competent higher federal authority raises objections against its continuation or
- if the medicinal product has been licensed and is in fact available on the market.

Notwithstanding the circumstances listed above, the compassionate use programme ends at the latest after one year. Compassionate use programmes provide treatment for patients in narrowly defined exceptional cases, they are not intended as a long-term treatment option. They are supposed to offer an alternative prior to national or central marketing authorisation of the corresponding medicinal product but do not replace national or central licensing procedures. Pursuant to Section 5 sub-section 1 AMHV, a notified compassionate use programme ends notwithstanding the provisions laid down in Section 4 sub-section 3 AMHV with its discontinuation by the responsible person or with the actual availability of the medicinal product on the market, but at the latest **one year after receipt** of the confirmed notification or the authorisation required in accordance with Section 4 sub-section 5 AMHV. The date of receipt is considered the date the confirmation of the notification or of the authorisation required in accordance with Section 4 sub-section 5 AMHV was dispatched by the competent higher federal authority.

In accordance with Section 6 sub-section 3 AMHV, the competent higher federal authority is to be informed immediately if the compassionate use programme is discontinued prior to expiry of the one year period. After completion of the compassionate use programme and regardless of a possible renotification, a safety report containing and evaluating, in particular, all serious adverse effects and all non-serious, unexpected adverse effects is to be submitted to the competent higher federal authority (cf. Chapter 7.4).

6.2 Renotification of an already confirmed/authorised compassionate use programme

In accordance with Section 5 sub-section 2 AMHV, renotifications are permissible. In this renotification process, reference may be made to documents already submitted, in so far as they have not been altered. In each case, it is to be justified why the compassionate use programme shall be continued. Possible reasons given generally include a still ongoing licensing procedure or if no application for marketing authorisation has been submitted yet, a still ongoing clinical trial in the intended indication. If reference is made to an ongoing compassionate use programme, the cover letter must include a confirmation that no changes have been made regarding the documents or information therein. In order to avoid interrupting treatment of patients already included in the ongoing compassionate use programme, the renotification should be submitted in due time so that the confirmation of the notification or the authorisation required in accordance with Section 4 sub-section 5 AMHV can be sent prior to expiry of the one-year deadline. In the case of simple notifications in accordance with Section 3 sub-section 1 AMHV, the renotification should generally be sent approximately 4½ weeks prior to the end of the compassionate use programme. In the case of a repeated renotification, in other words, more than one renotification, a sufficiently large time frame should be calculated for possible further questions from the BfArM.

6.2.1 Safety report in case of renotification

As the compassionate use programme ends formally at the latest after one year, a safety report containing and evaluating, in particular, all serious adverse effects and all non-serious unexpected adverse effects, is also to be submitted to the competent higher federal authority in the case of renotifications pursuant to Section 6 sub-section 1 number 4 AMHV. In the case of a renotification, this report is also to be included with the reference notification. The data lock point for the safety report should not be earlier than 8 weeks prior to the expiry of the one-year deadline. In the case of a repeated renotification, the follow-up report should then cover the period between the previous data lock point and the current data lock point (then generally exactly one year).

7 Obligation of the responsible person to disclose information

In accordance with Section 6 AMHV, the responsible person has various obligations to disclose information during the course of a compassionate use programme.

7.1 Suspected cases of serious adverse effects

Pursuant to Section 6 sub-section 1 number 1 AMHV, responsible persons are obliged to document every suspected case of a serious adverse effect reported to them by participating physicians or otherwise brought to their attention and to inform the competent higher federal authority electronically and immediately, but at the latest within a period of 15 days. The notification should be made to the EudraVigilance database of the EMA using the usual standards. With the notification to the EudraVigilance database, the obligation to notify the BfArM according to Section 6 (1) AMHV is deemed to be fulfilled.

7.2 Changes in the information pursuant to Section 3 AMHV

Pursuant to Section 6 sub-section 1 number 2 AMHV, the responsible person is obliged to inform the competent higher federal authority immediately of every change in the information pursuant to Section 3 AMHV and to include the corresponding documents. These documents are then kept in the competent higher federal authorities' files. The competent higher federal authorities do not automatically send confirmations of receipt. If such a confirmation is required, a sufficiently stamped and addressed return envelope should be enclosed with the notification.

7.3 Early termination of the compassionate use programme

Pursuant to Section 6 sub-section 1 number 3 AMHV, the responsible person is obliged to inform the competent higher federal authority immediately of the early termination of a compassionate use programme together with a reasoned justification. If such an early termination of a compassionate use programme was notified, that same compassionate use programme can only be resumed after a confirmed renotification. If a compassionate use programme has been terminated early it is also necessary to submit a safety report. Termination of a compassionate use programme is only possible for medical reasons.

7.4 Safety report

In accordance with Section 6 sub-section 1 number AMHV, the responsible person is obliged to submit a safety report after completion of the compassionate use programme containing and evaluating, in particular, all serious adverse effects and all non-serious unexpected adverse effects. The format for compiling the safety report can be found in Annex 9.1.

Information from the safety report should be included as additional information in the annual safety report for clinical trials. In contrast, however, it is not necessary to include information

from annual safety reports of clinical trials in the safety report of a compassionate use programme.

7.5 Expert opinion

Pursuant to Section 6 sub-section 1 number 5 AMHV, the responsible person is obliged to submit to or inform the competent higher federal authority of new expert opinions pursuant to Article 83 (4) of Regulation (EC) No. 726/2004 and findings from other compassionate use programmes which are being conducted in another Member State of the European Union or in another State Party to the Agreement on the European Economic Area.

7.6 Significant changes

The compassionate use programme can generally only be conducted for the medicinal product and the indication stated in the notification. If the responsible person intends changes that relate to

- the therapeutic indication of the medicinal product,
- the strength of the medicinal product, or
- the pharmaceutical form of the medicinal product,
- or that could have an effect on the safety of the patients,

Section 6 sub-section 2 AMHV requires a **new confirmed notification** in accordance with Section 3 AMHV. In connection with this new notification reference can be made to the already confirmed notification provided the information remains unchanged. Corresponding changes must not be implemented prior to receipt of the confirmed notification.

8 Area of responsibility of the responsible person

8.1 Recording and prevention of risks

Pursuant to Section 6 sub-section 3 AMHV, the responsible person has to ensure that the competent higher federal authority is immediately informed of risks of the medicinal product. The responsible person has to take the necessary measures for the prevention of risks immediately; this includes especially the withdrawal of medicinal products that pose a risk.

8.2 Conduct of the compassionate use programme

The responsible person bears the entire responsibility for the proper conduct of the notified compassionate use programme. This also includes that the responsible person ensures (as far as necessary in view of the specific medicinal product) that the participating physicians are sufficiently trained. These measures are to be described among others in the information in accordance with Section 3 sub-section 2 numbers 13, 15 and 16 AMHV.

Pursuant to Section 7 number 2 AMHV, the responsible person has to ensure that all conditions and restrictions with respect to the safe and effective use of the medicinal product are observed and that the persons involved receive the information necessary to this end. As a matter of principle, the responsible person is to compile a protocol for the compassionate use programme in order to ensure a controlled administration of the medicinal product, the monitoring thereof, as well as the completeness of the information. This protocol shall specify prospectively both that and how the participating physicians as well as the patients will receive the necessary information. The protocol should also state the obligations of the physicians with regard to documentation and especially the reporting of adverse effects.

8.3 Labelling

The responsible person must make certain that only medicinal products are placed on the market within the compassionate use programme that bear information ensuring patient protection and traceability and allowing identification of the medicinal product and the trial, as well as assuring proper use of the medicinal product.

In accordance with Section 7 number 3 AMHV, the responsible person must therefore assure that the medicinal product only enters the market if the containers and, if used, the outer packaging, bear at least the following information:

- name or code of the medicinal product,
- name and address of the responsible person,
- batch identification,
- route of administration,

- name of the active substance,
- expiry date,
- retention and storage instructions (where necessary),
- indication that the medicinal product is made available within the framework of a compassionate use programme without national or central marketing authorisation.

8.4 Manufacture and import (GMP)

The regulations of the Ordinance on the Application of Good Manufacturing Practice in the Manufacture of Medicinal Products and Active Substances and on the Application of the Codes of Good Practice in the Manufacture of Medicinal Products of Human Origin ("*Verordnung über die Anwendung der Guten Herstellungspraxis bei der Herstellung von Arzneimitteln und Wirkstoffen und über die Anwendung der Guten fachlichen Praxis bei der Herstellung von Produkten menschlicher Herkunft*" or short: Ordinance on the Manufacture of Medicinal Products and Active Substances, AMWHV) with regard to investigational medicinal products are applicable to the manufacture, the import, as well as the release of medicinal products, that are placed on the market in connection with a compassionate use programme. The requirements specified there for investigational medicinal products with regard to manufacture, import and release are also appropriate for medicinal products used within compassionate use programmes due to the comparable constellations (unlicensed medicinal products). Thus, pursuant to Section 7 number 4 AMHV, the responsible person shall ensure that the manufacture, import and release is in accordance with the regulations specified for investigational medicinal products in the AMHWV.

8.5 Archiving

The archiving periods for the documents of compassionate use programmes conducted and terminated are adapted to the periods applicable to clinical trials (Section 13 sub-section 10 GCP-V). Pursuant to Section 7 number 5 AMHV, the responsible person has to ensure that the essential documents of the compassionate use programme are kept for at least ten years after its completion or early termination; other regulations concerning the keeping of medical documents remain unaffected.

9 Annexes

9.1 Format of the yearly safety report

The safety report is supposed to allow the BfArM a speedy overview regarding the safety of the patients included in the compassionate use programme. The format is based on the format for Development Safety Update Reports (DSURs) according to the ICH E2F Guideline; however, only data from the compassionate use programme in Germany are to be included. It should be observed that the safety report should contain and evaluate all serious adverse effects and all non-serious unexpected adverse effects (Section 6 sub-section 1 sentence 1 number 4 AMHV). It is requested that the safety report be submitted according to the following structure which is adapted to that of DSURs:

1. Introduction and Summary
Short description of the compassionate use programme giving information on the product and the medical indications concerned as well as a summarising assessment of the safety of the patients included.

2. Worldwide marketing authorisation status
Information on the worldwide marketing authorisation status of the medicinal product. If the medicinal product has already been granted a license in other countries, these are to be listed. If this concerns Member States of the EU, a statement concerning the market availability in the EU and in Germany is also to be given.

3. Safety measures taken within the reporting period
If measures to improve the safety of the medicinal product have been taken within the current reporting period in the compassionate use programme, these are to be listed here.

4. Changes to reference safety information
If the reference safety information, e.g. the SmPC or the relevant parts of the investigator's brochure (IB), have been altered within the reporting period, these changes are to be listed here.

5. Overview of clinical trials in this indication
Statement of ongoing or completed clinical trials within the reporting period with the medicinal product in the indication used in the compassionate use programme.

6. Patient exposure
Number of patients treated in the respective compassionate use programme within the reporting period.

7 List of adverse effects

7.1 List of serious adverse effects
Table listing all serious adverse effects within the reporting period including a short assessment thereof.

7.2 List of all non-serious unexpected adverse effects
*Table listing all non-serious **unexpected** adverse effects including a short assessment thereof.*

8. Significant new findings from clinical trials
Brief description of significant new findings from clinical trials.

9.2 Description of the directory structure for electronic submissions

No.	*Name of the folder*	*Documents contained*	*Comment*
🗀 01	Application	• Cover letter	Cover letter for notification of the compassionate use programme
		• Notification form	BfArM form for notification of compassionate use programmes (http://www.bfarm.de/SharedDocs/1_Downloads/DE/Arzneimittel/1_vorDerZul/compUse/AMHV-Anzeigeformular.rtf)
		• Information about the responsible person*	Section 3 sub-section 2 number 1 AMHV: Name or company as well as address of the responsible person and, where available, that of the representative registered in the European Union or in another State Party to the Agreement on the European Economic Area,
		• Information about the medicinal products*	Section 3 sub-section 2 number 2 AMHV: The name or code of the medicinal product, the name of the active substances by type and quantity, other constituents by nature, pharmaceutical form, route of administration, dosage and treatment plan
🗀 02	Clinical Data	• Description of the disease*	Section 3 sub-section 2 number 3 AMHV: Description of the disease that leads to a serious disability, or is life-threatening, from which the patient is suffering and for the treatment of which the medicinal product is intended
		• Information on patients*	Section 3 sub-section 2 number 4 AMHV: Criteria for the selection of patients and notification of the anticipated number of patients
		• Grounds explaining why treatment with authorised medicinal products is not possible*	Section 3 sub-section 2 number 5 AMHV: Grounds explaining why these patients cannot be treated satisfactorily with a medicinal product authorised for placing on the market within the territorial scope of the Medicinal Products Act.
		• Grounds explaining why inclusion in ongoing clinical trials is not possible*	Section 3 sub-section 2 number 6 AMHV: Grounds why the patients cannot be included in an ongoing clinical trial.

		• Reasoning for safety and efficacy	Section 3 sub-section 2 number 8 AMHV: Proof and reasoning for the assumption that the medicinal product is safe and effective in the intended indication, generally by submitting the results of confirmatory clinical trials
		• Criteria for termination*	Section 3 sub-section 2 number 9 AMHV: Criteria for the suspension or premature termination of the compassionate use programme
🗀 03	QUA	• Proof of pharmaceutical quality	Section 3 sub-section 2 number 7 AMHV: Evidence to support the fact that the medicinal product is of the appropriate quality in keeping with recognised pharmaceutical regulations, as well as confirmation by the qualified person pursuant to Section 14 of the Medicinal Products Act that the medicinal product has been manufactured according to the principles and guidelines of good manufacturing practice for medicinal products
🗀 04	Regulatory Information	• Authorised clinical trials in the EU	Section 3 sub-section 2 number 10 a) AMHV: Further details on the authorised clinical trial with the medicinal product in the intended indication together with the EudraCT number
		• Clinical trials in third states	Section 3 sub-section 2 number 10 b) AMHV: Further details on the clinical trial with the medicinal product in the intended indication in a third state and evidence that it is conducted according to the internationally harmonised standards of Good Clinical Practice
		• Applications for marketing authorisation	Section 3 sub-section 2 number 10 c) AMHV: Further details on the application for national or central marketing authorisation which has been submitted for the medicinal product in the intended indication to the European Medicines Agency, the competent higher federal authority or to the responsible national licensing authority of a Member State
		• Refusals	Section 3 sub-section 2 number 12 AMHV: Reasoning and rationale for the decision to administer a medicinal product for which the application for national or central marketing authorisation has been refused, withdrawn, revoked or suspended or for which the authorisation of a clinical trial has been refused, withdrawn, revoked, suspended or granted under certain conditions

		• Information on ongoing compassionate use programmes • CHMP's expert opinion	Section 3 sub-section 2 number 17 AMHV: Information, if applicable, on ongoing compassionate use programmes in Member States of the European Union or other States Party to the Agreement on the European Economic Area and, where available, expert opinions of the Committee for Medicinal Products for Human Use pursuant to Article 83 (4) of Regulation (EC) No. 726/2004,
🗀 05	IB	• Product information	Section 3 sub-section 2 number 13 AMHV: The current investigator's brochure placed at the disposal of the investigator in the clinical trial or the envisaged draft of the Summary of Product Characteristics of the medicinal product included in the application for authorisation of marketing authorisation
🗀 06	Informed Consent	• Patient information	Section 3 sub-section 2 number 14 AMHV: Information and documents which are given to the patients, in German, as well as a description of the procedure for informed consent after instruction by a participating physician
🗀 07	Centre-related	• Requirements to be met by physicians and facilities	Section 3 sub-section 2 number 15 AMHV: Requirements to be met by the medical facilities and the qualifications of the participating physicians
		• Storage of the medicinal products	Section 3 sub-section 2 number 16 AMHV: Description of the intended measures to guarantee the safe storage, use and fate of the medicinal products made available
🗀 08	Administrative Data	• Declaration of consent regarding publication	Section 3 sub-section 2 number 18 AMHV: Declaration of consent regarding the publication of information on the main features of the notified compassionate use programme
		• Power of attorney	Power of attorney for submission of the notification by third parties
🗀 09	GMO	• Documentation on genetically modified organisms (GMO)	Section 3 sub-section 2 number 11 AMHV: In the case of medicinal products which consist of or contain a genetically modified organism or a combination of genetically modified organisms, documents pursuant to Annexes II and III of Directive 2001/18/EC of the European Parliament and the Council of 12 March 2001 on the deliberate release of genetically modified organisms into the environment and repealing Council Directive 90/220/EEC (OJL L 106 of 17/4/2001, p. 1),

🗀 10	Reporting	• Reports on serious adverse effects • Reports on premature discontinuation of the compassionate use programme • Safety report after conclusion of the compassionate use programme • Findings from other compassionate use programmes	Reports based on the obligations in accordance with Section 6 AMHV

* Only if this information is not exclusively given in the notification but is submitted in a separate document