

INCardio project

Regulatory requirements for ATMPs in Italy and Austria

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1. Introduction

Medical University of Innsbruck is carrying out a project named “INCardio - Terapie Innovative per la cura delle malattie cardiovascolari”. The Client aims to prepare a document that compares the regulatory requirements to be addressed to bring an ATMP in the clinical phase, in Italy and in Austria.

2. Activity required

Medical University of Innsbruck requested the collaboration of Regulatory Pharma Net (RPN) to provide an overview of the applicable regulatory requirements to be considered to bring an ATMP into the clinical phase in Italy and in Austria, including the following aspects:

- Overview of the applicable regulatory requirements for hospital exemption
- Overview of the applicable regulatory requirements for early access (ie. “Early Access Programs”).

3. European regulation of ATMPs as Medicinal Products

In the European Union (EU) the regulatory framework for advanced therapy medicinal products (ATMPs) is primarily established in the Directive 2001/83/EC. All the regulations in force ensure that new medicinal products classified as ATMPs are subject to appropriate assessment by the European Medicines Agency (EMA). It should guarantee their appropriate quality, safety and efficacy in clinical trials in patient population, when finally granted a marketing authorization (MA). It is important to understanding the requirements that ATMPs must meet as well as familiarity with the relevant registration procedures are important factors to successfully lead the ATMP to MA (Figure 1).

According to Article 2(1)(a) of Regulation (EC) No. 1394/2007, “advanced therapy medicinal product” means any of the following medicinal products for human use:

- a gene therapy medicinal product,
- a somatic cell therapy medicinal product,
- a tissue engineered product

Any applicant developing a product based on genes, cells or tissues may request a CAT (Committee for Advanced Therapies) scientific recommendation of the Agency with a view to determining whether the referred product falls within the definition of an advanced therapy medicinal product. The ATMP classification procedure is voluntary, free of charge and, address questions of borderline cases where classification of a product based on genes, cells or tissues is not clear.

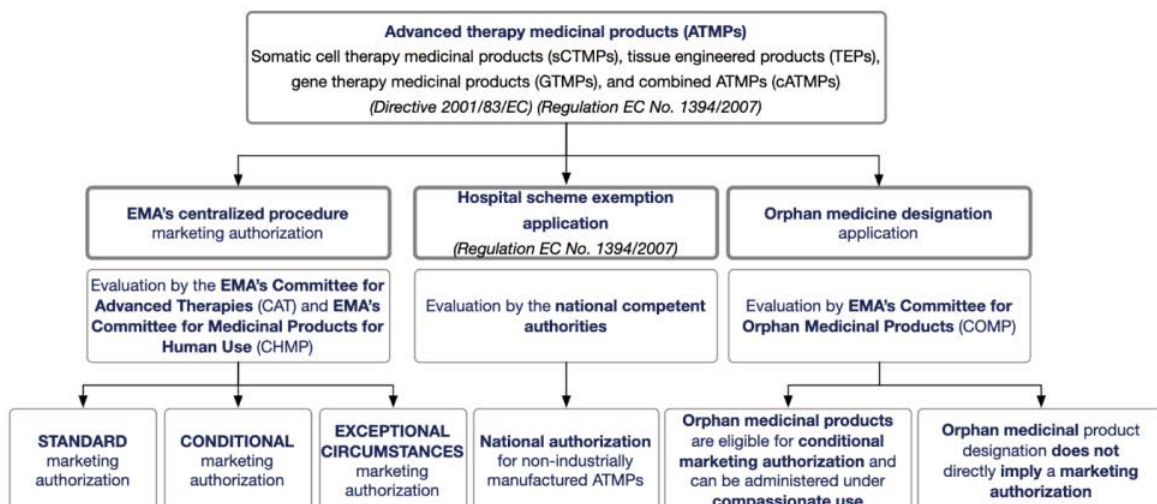
ATMPs are evaluated under the Centralised Procedure described in Regulation (EC) No. 726/2004, with the evaluation being performed primarily by the CAT according to the technical requirements of Directive 2009/120/EC. Therefore, it is not possible to obtain the MA for ATMP only in selected countries belonging to the Community or dealing only with National Agencies throughout registration. The Centralised Procedure itself is strictly formalized in terms of documentation (eCTD) as well as timeline of submission.

As defined in Regulation (EC) No 1394/2007, for ATMPs that are prepared on a non-routine basis according to specific quality standards, in order to comply with an individual medical prescription for a custom-made product for an individual patient, the hospital exemption scheme can be follow.

If a product is classified as an ATMP, it must undergo clinical trials to demonstrate safety and efficacy before a MA application (MAA). Clinical development must include pediatric studies if the medicine is intended to be used in children. If so, it is the obligation of the Applicant to establish the Pediatric Investigation Plan (PIP). PIP defines the clinical studies to be conducted in pediatric population to demonstrate that a new medicinal product is safe and effective in all subsets of the pediatric population. It should be noted that the PIP is not mandatory, if there is already sufficient information to demonstrate safety and efficacy in adults while further development in pediatric populations could delay the MAA submission. A waiver is also possible when the drug development for children is not appropriate, for example when a disease only affects the adults or the product is likely to be unsafe in the pediatric population.

Before submission of MAA it is necessary to fulfill Pre-Authorisation requirements such as submission of eligibility request and letter of intent. An MA may be granted in three ways: standard MA, conditional MA, or MA under exceptional circumstances. The type of MA applied for depends on the extent of clinical data obtained during development and/or whether the medicine addresses an unmet medical need.

Figure 1. Regulatory Pathways for ATMPs



4. Regulatory requirements to bring an ATMP in the clinical phase

Introduction

Clinical trials with ATMPs performed in the EU are governed by Regulation (EU) No 536/2014 and should comply with the requirements provided by Guideline on Good Clinical Practice (GCP) specific to ATMPs. These Guidelines develop the GCP requirements that are specific to clinical trials conducted with ATMPs. These Guidelines are to be read in conjunction with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines on good clinical practice, which are also applicable to ATMPs.

In general, for ATMPs the same principles as for other IMPs apply for the clinical development, especially current guidelines relating to specific therapeutic areas. The following documents should be consulted before starting ATMPs clinical trials:

- Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products
- Guideline on quality, non-clinical and clinical requirements for investigational advanced therapy medicinal products in clinical trials (EMA/CAT/852602/2018)
- Guideline on human cell-based medicinal products (EMEA/CHMP/410869/2006)
- Guideline on the quality, non-clinical and clinical aspects of gene therapy medicinal products (EMA/CAT/80183/2014)
- Guideline on the risk-based approach according to annex I, part IV of Directive 2001/83/EC applied to ATMPs (EMA/CAT/CPWP/686637/2011)
- Guideline on xenogeneic cell-based medicinal products (EMEA/CHMP/CPWP/83508/2009)
Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products (EMEA/410/01)
- Guideline on safety and efficacy follow-up and risk management of Advanced Therapy Medicinal Products (EMEA/149995/2008 rev.1)

Quality (including manufacturing) requirements

It is mandatory that ATMP manufacturing complies with good manufacturing practice (GMP) guidelines, which includes using GMP grade starting materials. The following essential documents apply to quality of ATMPs:

- Setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells: Directive 2004/23/EC, Directive 2006/17/EC, Commission Directive (EU) 2015/566
- For all starting and raw materials derived from blood, the European blood directive and its technical directives should be considered: Directive 2002/98/EC
- Traceability requirements, notification of serious adverse reactions and events and certain technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells: Directive 2006/86/EC, Commission Directive (EU) 2015/565

- Community code relating to medicinal products for human use regarding ATMPs: Directive 2009/120/EC
- Use of bovine serum in the manufacture of human biological medicinal products: Guideline CHMP/BWP/457920/2012 Rev. 1
- Good distribution practice (GDP) applies for medical products (Commission guideline 2013/C 343/01).

Non- clinical data before ATMPs first-in-human studies

In accordance with EMA Guideline (EMA/CAT/852602/2018), due to specific characteristics of ATMPs, the majority of non-clinical safety data may need to be available before first administration to humans. The extent of the non-clinical data package is determined on a case-by-case basis taking into consideration the risks, or the lack of risks, associated with the product and the intended clinical use, the availability of animal models and publicly available information from similar type of products. In exceptional cases, where appropriate in vitro, ex vivo or in vivo data with predictive value cannot be generated, a comprehensive risk assessment addressing risks related to the ATMP and its clinical use should be provided, and measures to mitigate the risks should be described. The following information should be available before human exposure:

- demonstration of proof of concept in a relevant model
- support for the use of administration route, application procedure and application devices
- support of the selection of safe and biologically effective starting dose with adequate safety margins for clinical use
- appropriate safety data

Conventional studies evaluating the ADME are not considered feasible or relevant for cell based medicinal product. Instead, based on the guideline on human cell based medicinal products (EMA/CHMP/410869/2006) studies should be carried out to demonstrate tissue distribution, distribution, migration and persistence of the cells in order to identify relevant risks related to unwanted biodistribution.

Based on Guideline on human cell-based medicinal products (EMA/CHMP/410869/2006) and Guideline on quality, non-clinical and clinical requirements for investigational advanced therapy medicinal products in clinical trials (EMA/CAT/852602/2018), non-clinical general safety or toxicity data are needed to support clinical testing. The need for additional toxicity studies e.g. genotoxicity, tumorigenicity, reproductive and developmental toxicity, and immunotoxicity studies should be determined on a case by case basis taking into consideration the risks related to the nature and characteristics of the particular class of ATMP and the intended clinical use.

Anticipated benefits and risks for trial subjects

According to Directive 2001/20/EC and Regulation 536/2014 and Guideline on the risk-based approach according to annex I, part IV of Directive 2001/83/EC applied to ATMPs (EMA/CAT/CPWP/686637/2011), the known and potential risks and benefits for the patient including an evaluation of the anticipated benefit and risk should be evaluated before starting a clinical trial with an ATMP. Potential benefits and risks include:

- the anticipated effect;
- the trial population (adult/paediatric);
- available treatment options and medical need;

- differences of trial-related interventions to normal clinical practice and existing therapies,
- additional trial interventions,
- risks of insertional mutagenesis in case of GTMPs;
- risks related to immune reactions

5. ATMP Hospital Exemption

Article 28 of Regulation 1394/2007/EC on ATMPs, referred to as the 'Hospital Exemption' (HE), foresees the exclusion of certain ATMPs from the scope of Directive 2001/83/EC on medicinal products for human use. These products are defined as: "ATMPs prepared on a non-routine basis according to specific quality standards and used within the same Member State in a hospital under the exclusive professional responsibility of a medical practitioner, in order to comply with an individual medical prescription for a custom-made product for an individual patient".

The HE allows Member States to permit the manufacture and use of ATMPs in their territories without fulfilling the requirement for submitting a MAA to be assessed by the CAT and Committee for Medicinal Products for Human Use (CHMP) within the EMA and an authorisation to be granted by the European Commission. Member States must ensure that the manufacture of ATMPs under the HE is authorised by the National Competent Authority and that manufacturing, traceability, pharmacovigilance and specific quality standards are equivalent to those provided for at EU level for ATMPs which are granted a centralized MA. The HE products must be produced in GMP-authorized sites.

The use of HE for ATMPs should allow the following aspects:

- HE usage should be limited to situations of high unmet medical need when patients are not eligible for treatment with a centrally authorized ATMP or as part of an ongoing clinical trial with an ATMP.
- Use of a HE product should be medically justified, and it should be demonstrated that an authorized ATMP or medicinal product or clinical trial with an ATMP for the same indication would not be suitable for the patient.
- Patients should be fully informed about the status of HE products including available data on safety and efficacy as compared to alternative treatment options before and as part of providing consent.
- When the use of a HE product is justified, long term safety (at least yearly for 10 years) and efficacy data must be collected.

The HE has been interpreted and implemented very differently across the EU (Table 1), which risks undermining the protections that are in place for patients. To ensure that patients always receive safe and effective treatments, it is necessary to restrictively apply the HE conditions stipulated in the ATMP Regulation to ensure that the HE is not used inappropriately.

In countries where the requirements for hospital exemptions have already been transposed into national law, the exact implementation varies across Member States, sometimes even resulting in divergent rules. These national differences mainly arise because key terms such as "industrial process", "custom made product" or "non-routine basis" have not been explicitly defined in the Directive/legislation.

Table 1. Comparison of HE requirements across EU countries

	Italy	Austria	Germany	France	Spain	Netherlands	Poland
NCA	AIFA	BASG	PEI	ANSM	AEMPS	IGJ	CPI
Main legal provision	Ministerial Decree 16 January 2015	Article 6a and 6b (AMG)	Section 4b AMG	Article L5121-1 (17)	Royal Decree 477/2014	Law of 8 February 2007 (Medicines Law), Article 40 3.d	Articles 2, 4, 38 and 43 of the Polish Act of 6 September 2001: The Pharmaceutical Law
Are clinical data required to obtain HE?	No	No	No	No	Yes	No	No
Can HE be granted if a similar or identical licensed ATMP is available?	No	Not explicitly restricted	Not explicitly restricted	Not explicitly restricted	Not explicitly restricted	Not explicitly restricted	Not explicitly restricted
Can HE be granted if an active clinical trial is running with a similar or identical ATMP?	Not explicitly restricted	Not explicitly restricted	Not explicitly restricted	Not explicitly restricted	No	Not explicitly restricted	Not explicitly restricted
Is safety reporting required?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Can the HE-ATMP be used outside of Member State?	No	No	No	Yes, in the scope of clinical trials	No	Yes	Unknown

5.1 ATMP hospital exception in Italy

Definition

Article 3(1) of Decree of the Italian Ministry of Health of 16 January 2015 provides that ATMPs prepared and intended for use under Hospital Exemption can be used (1) only on individual patient and (2) in the



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absence of therapeutic alternative and (3) in case of urgency and emergency which threatens the life of the patient or a serious harm to him/her health.

Manufacturer authorization

Is released following AIFA inspection and it is based on:

- Type of ATMP to be produced based on a “IMPD-like” dossier
- Previous production authorization, if any, and premises details
- Equipment
- QP and PhV responsible person identification and personnel
- Manufacturing process and IPC
- QC equipment
- QA, SOP and analytical methods

Authorization for use

The authorization for use of the ATMP is issued by AIFA, upon the assent of the Commission referred to in Article 7 of the Presidential Decree No. 439 of September 21, 2001. The Commission may be supplemented for this purpose by experts in the field of biological and clinical, from time to time chosen by the President of the Commission on the basis of technical profiles of prevailing relevance and may convene an expert indicated by the health facility applicant for authorization. The authorization is issued within a maximum period of thirty days from the submission of the application by the legal representative of the health facility where the authorization has already been issued to production referred to in Article 2, or within the time limit referred to in Article 2, paragraph 2, if the application for authorization for use is submitted at the same time as the application for the production authorization. In case of a request for supplementary documentation, the aforementioned deadline is suspended until the receipt of the supplementary documentation.

The application for authorization, to be sent to AIFA, must be accompanied by a copy of the dossier of advanced medical therapy (DMTA), the proposed treatment protocol, the favorable opinion of the ethics committee, exclusively for the profiles of competence, and suitable documentation to allow an congruous assessment of the relationship between the foreseeable risks and the conceivable benefits of the proposed treatment. In particular, all safety and efficacy data must be reported from any available clinical trials and the rationale for the proposed treatment, with specific reference to the biological characteristics of the populations cells used, the hypothesized mechanism of action, and the appropriateness of the route of administration in relation to the etiology, pathogenesis and natural history of the disease for which it is required to use the drug. In case of different indication, new authorization is required.

Producer / treating physician obligation

- The production must comply with authorization and current applicable requirements
- Traceability of product and patients
- Pharmacovigilance (including lack of efficacy)
- To communicate yearly the n. of produced lots
- According to cGCP principles

Data monitoring

- AIFA and NIH collect and evaluate safety clinical data

- Every 30 days from treatment, clinical data and records for efficacy evaluation should be transmitted to AIFA
- AIFA can suspend/retire the authorization

Reference

DECRETO 16 gennaio 2015_ Disposizioni in materia di medicinali per terapie avanzate preparati su base non ripetitiva. (15A01704) (GU Serie Generale n.56 del 09-03-2015)

5.2 ATMP hospital exception in Austria

Definition

Paragraph 7(6a) and (6b) of the AMG read as follows: "Medicinal products for advanced therapies which are not routinely manufactured in Austria for a specific patient on the basis of an individual doctor's prescription in order to be administered to that patient in an Austrian hospital under the exclusive professional responsibility of a doctor shall not be considered as medicinal products subject to marketing authorization.

Manufacturer authorization

According to Article 3(7) of Directive 2001/83/EC, the manufacture of these advanced therapy medicinal products must be authorized by the competent authority of the Member State. Article 3(7) of Directive 2001/83/EC states that "advanced therapy medicinal products as defined in Regulation (EC) No 1394/2007, which are not routinely manufactured to specific quality standards and are used in a hospital in the same Member State under the exclusive professional responsibility of a medical practitioner in response to an individual medical prescription for a medicinal product prepared specifically for an individual patient. The manufacture of these medicinal products must be authorized by the competent authority of the Member State. Member States shall ensure that the national traceability and pharmaco-vigilance requirements, as well as the specific quality standards referred to in this paragraph, are equivalent to those applicable at Community level to advanced therapy medicinal products for which a marketing authorization is required in accordance with Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency." The application has to contain the following information:

- proof of referral to the responsible ethics committee
- address data of the manufacturer
- justification for the existence of the requirements of the Hospital Exemption
- documentation and control of the manufacturing process including the packaging process according to Annex III of Regulation (EC) No. 1394/2007
- list of persons responsible for the manufacturing process and their qualifications; list of persons releasing the product for use with their qualifications, as well as other persons responsible for the manufacturing process
- requirements for the qualification of employees involved in the manufacturing process
- general description of the manufacturer's quality system
- description of the manufacturing site
- description of the equipment and devices used in the manufacturing process

- description of traceability with respect to human cells and tissues, blood or blood components used in the manufacturing process, and other starting materials, precursors, and materials that may affect the safety or quality of the product, as required
- description of the quality system for handling changes or any serious adverse events in the manufacturing process
- description of the pharmacovigilance system
- name of the responsible user

Authorization for use

In principle, the same regulatory requirements apply to ATMPs as to all other types of biotechnological medicinal products. Therefore, the following requirements apply as prerequisites for the use of ATMPs under the Hospital Exemption:

- Manufacture of the medicinal product in Austria by an approved facility under GMP Approval of the medicinal product by the qualified person
- Manufacture takes place non-routinely
- The ATMP is used in an Austrian hospital Application of the ATMP under the exclusive professional responsibility of a physician
- Obtaining any necessary approvals according to the GSG, BSG or GTG
- Consent of the ethics committee of the Austrian hospital for the application of the ATMP as a new medical method

The use of an ATMP within the framework of a hospital exemption may only be carried out after a positive assessment of the ethics committee regarding the safety and efficacy of the ATMP within the meaning of Section 8c of the Hospital and Spa Act and the approval of the manufacture of the ATMP in accordance with Section 63 of the AMG by the Federal Office for Safety in Health Care. Proof of the positive assessment by the Ethics Committee and of the authorization to manufacture the ATMP must be submitted to the Federal Office for Safety in Health Care as part of an informal notification to inspektionen@basg.gv.at prior to the start of use.

Producer / treating physician obligation

The user (responsible physician) of an ATMP (in the context of a hospital exemption) is obligated pursuant to Section 7 (6b) of the German Medicines Act (AMG) to take measures to ensure the follow-up of efficacy and side effects. An annual report on advanced therapy medicinal products within the scope of a hospital exemption must be submitted to the Federal Office for Safety in Health Care by March 31 of the following year at the latest.

Data monitoring

When using an ATMP, the traceability requirements according to article 5 para. 4 and 16 para. 5 of the Tissue Safety Act (GSG), as well as the reporting obligations according to article 17 and 32 of the Tissue Safety Act, apply in accordance with article 75p of the German Medicines Act (AMG). This also applies if the medicinal products contain cells or tissues of animal origin.



Leitfaden zur Anwendung von nicht zugelassenen ATMPs in Krankenanstalten (Hospital Exemption) in Österreich“

6. Early access options for Italy

6.1 Inclusion into the “648/96 list”

Definition

In Italy, law 648/96 allows NHS funding at national level for the use of unauthorized medicinal products or for off-label indications of authorized products included in a dedicated list (the so-called “648 list”) created and regularly updated by the Italian Medicines Agency AIFA.

Funding

NHS

Eligibility requirements

The medicinal products which can be included into the 648/96 list are the following:

When there is no valid, licensed therapeutic alternative for the concerned serious disease

- innovative medicinal products not authorized in Italy but registered in other countries;
- medicinal products under clinical investigation for which the results of phase II trials are available*;
- medicinal products for a therapeutic indication other than the one approved and for which the results of phase II trials are available.

When there is a valid, licensed therapeutic alternative for the concerned serious disease

- medicinal products to be used for a therapeutic indication other than the one approved, provided that the concerned therapeutic indication is known and compliant with researches performed by the national and international medical-scientific community, on the basis of criteria of inexpensiveness and appropriateness.

** Please note that apart from few exceptions, AIFA is not willing to approve reimbursed early access to drug BEFORE approval in EU/US. There also exist a formal importation issue (current rules do not allow importation of products not approved in any country in contexts other than clinical trial or compassionate use).*

Who can submit the request?

The request for inclusion into the 648/96 list can be submitted by Scientific Societies, physicians, Universities, hospitals, patients’ associations, Technical-Scientific Commission of AIFA (not by pharmaceutical companies).

How is the request formulated?

A formal request must be addressed to AIFA using a dedicated form (template made available by AIFA as of 22 March 2021) which must include:

- scientific report on the pathology, its seriousness and the lack of valid therapeutic alternatives;

- discussion on the availability of therapeutic alternatives for the same indication and on the place in therapy of the proposed treatment compared with other therapies;
- rationale and clinical data (at least phase II studies) in support of the proposed treatment;
- description of the proposed therapeutic plan (dosage, duration of therapy, inclusion and exclusion criteria);
- estimate of the number of eligible patients in Italy;
- cost estimate for the proposed treatment;
- Marketing Authorisation status of the medicinal product in Italy and abroad;
- Information relevant to ongoing clinical trials (for the proposed indication);
- Availability of the Company to provide the product for free under compassionate use.

The submission is made by email.

What is the procedure?

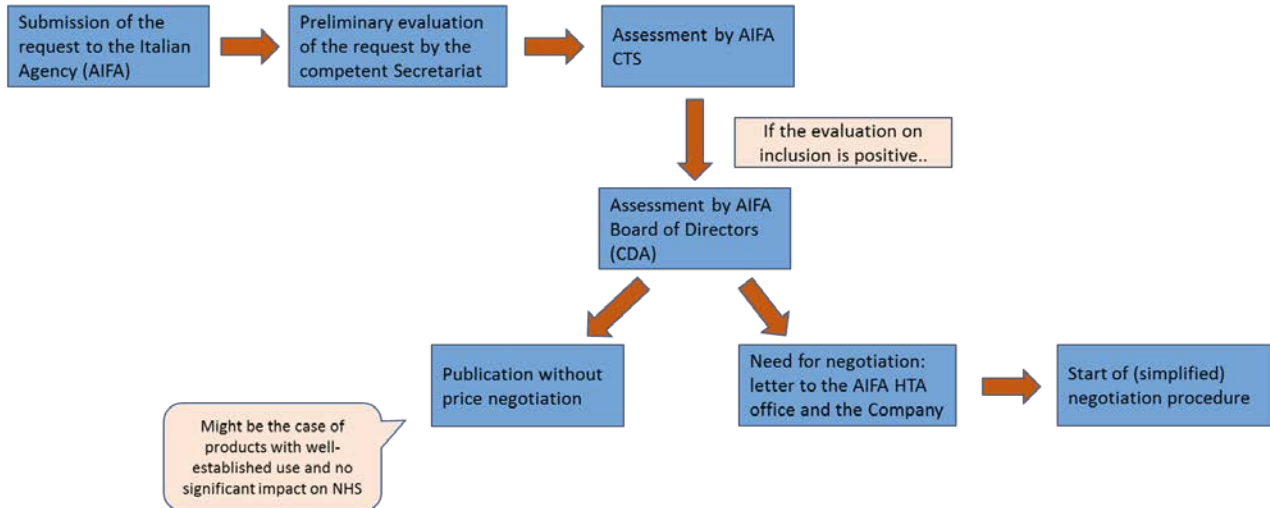
After the submission by physicians/Scientific Societies/Universities/hospitals/patients' associations, the request is evaluated by AIFA Technical-Scientific Commission (CTS).

If the CTS opinion on the inclusion is favourable, AIFA Board of Directors (BoD, CdA) will then decide whether there is also need for a price negotiation with the Company.

[Indeed, further to the publication of the Ministerial Decree 2 August 2019 ("*Criteria and procedures according to which the Italian Medicines Agency negotiates prices of medicines reimbursed by the National Health Service*", published in the Italian OJ no. 185 of 24 July 2020) and of AIFA Resolution no. 1372/2020 (adopting the "*Guidelines for the preparation of the dossier supporting the Pricing and Reimbursement application of medicinal products*"), in order to be included in the 648 list, medicinal products might have to be subject to a price negotiation with AIFA.]

If the negotiation is needed, the Pharmaceutical Company will be informed by AIFA and will be asked to provide a dedicated dossier (simplified dossier compared to the one needed for the P&R of medicinal products authorized through centralized, mutual recognition, decentralized and national procedures) and to actively participate in the price negotiation.

Figure 2. Inclusion in the 648 list – assessment procedure



At the end of the procedure, if positively concluded, the AIFA decision to include the product into the 648/96 list is published on the Italian Official Journal. From that moment, all patients meeting the eligibility criteria set in the AIFA approval decree will be able to receive reimbursed treatment with the drug.

References

- L.D. 648/96 <https://www.normattiva.it/uri-res/N2Ls?urn:nir:stato:legge:1996-12-23;648!vig=>
- L.D. 79/2014 <https://www.normattiva.it/uri-res/N2Ls?urn:nir:stato:legge:2014-05-16;79!vig=>
- CUF Act 20/07/2000 https://www.aifa.gov.it/documents/20142/0/tipo_file861e.pdf
- AIFA Website <https://www.aifa.gov.it/web/guest/legge-648-96>

6.2 Compassionate use (Decree 7 September 2017)

Definition

Compassionate use: supply, at the pharmaceutical company's expenses, of:

1. Medicinal products not yet authorized, under clinical investigation;
2. Medicinal products for a therapeutic indication other than the one approved;
3. Medicinal products with a marketing authorization but not yet available in Italy.

Funding

The product is provided by the Company free of charge and once a patient is “enrolled”, the Company needs to supply the product for free until the patient needs it or until the medicinal product becomes available on the Italian “regular” market.

Eligibility requirements

The compassionate use of the above-listed medicinal products is requested for the treatment of patients with severe diseases, rare diseases, rare tumors, patients with life-threatening conditions for whom no valid therapeutic alternatives are available or that cannot be included in a clinical trial or for patients that have



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already been treated in a clinical trial and have obtained clinical benefits, for the purpose of the therapeutic continuity.

The above-listed medicinal products must:

- At least be the object, in the same therapeutic indication for which the compassionate use is requested, of concluded/ongoing Phase III clinical trials or, in the case of life-threatening conditions, of completed Phase II clinical trials;
- Have available clinical data which are sufficient to support a favourable opinion on the efficacy and safety of the product;
- Have a GMP certification.

In case of rare diseases or rare tumors, the above-listed medicinal products must at least be the object of phase I trials already completed and which have proved the activity and safety of the medicinal product at a certain dose/therapeutic regimen, for indications even different from the one for which the compassionate use is requested. In this case, the possibility to obtain a clinical benefit from the medicinal product must be reasonably supported on the basis of the mechanism of action and on the pharmacodynamics of the product.

Who can submit the request?

The compassionate use request is submitted to the Ethics Committee by:

- A physician for the single patient not included in clinical trials, on a named basis or as part of an expanded access program;
- A group of physicians working in different centres;
- A physician or a group of physicians for patients who participated in a clinical trial with positive results in order to allow them to get immediately access to the treatment after the conclusion of the clinical trial
- (In case of rare disease or rare tumors) by the physician managing the regional clinical centre for the treatment of rare diseases or the clinical centre belonging to the rare tumors national network

How is the request formulated?

According to the decree, the request submitted to the EC must include:

- a) Clinical motivation of the request;
- b) Details on dosing scheme and administration procedures for which safety and activity have been demonstrated in the clinical trials;
- c) Details on the degree of comparability between patients included in clinical trials and patients for whom the compassionate use is being requested or, for rare diseases and tumors only, the existence of at least a common mechanism of action that makes a clinical benefit predictable on the basis of the available evidence on the product;
- d) Data on safety, tolerability and efficacy (IB or SPC);
- e) Patient information leaflet and informed consent form (in Italian)
- f) Company declaration about the availability to provide the drug free of charge;
- g) Procedures for data collection;
- h) Physician's declaration of responsibility for the treatment according to the protocol;
- i) Documentation proving Manufacture according to GMP

Note: additional documents may be requested by ECs (the concerned EC should therefore be contacted in advance to confirm the documents needed).

Requests for compassionate use are evaluated during routine EC meetings unless urgency is highlighted. Accelerated evaluations are based on extraordinary EC meetings or telematic procedure (opinion could be issued within 48-72 hours). Timelines need to be verified in advance with each EC. Once the EC has issued an opinion on the compassionate use, they must transmit it by email to AIFA within 3 days.

Nominal uses and Compassionate Use Programs

There are two options for a compassionate use:

- Named Compassionate Use: compassionate use of a medicinal product for a named patient, based on scientific evidence and not under a defined clinical protocol.

In this case, the physician submits a request to the competent EC with the documents listed above. The EC issues an opinion and then notifies the whole documentation along with their opinion to AIFA within 3 days.

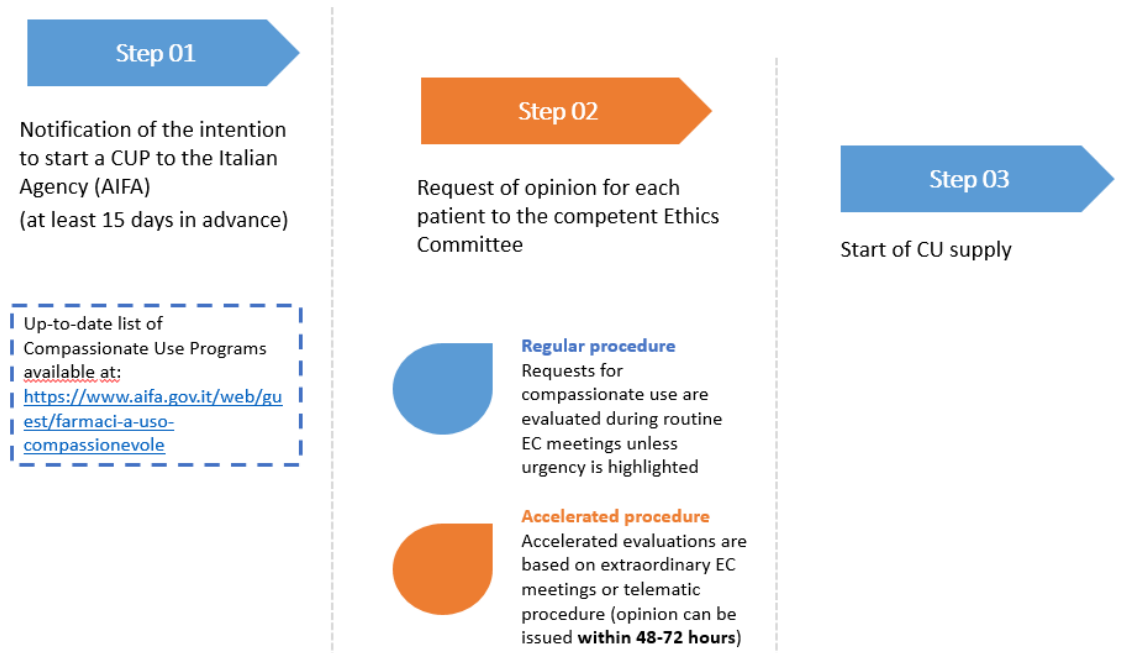
- Compassionate Use Program (CUP) (Expanded Access Program-EAP): use of a medicinal product for compassionate use in more than one patient, on the basis of a set clinical protocol identical for all patients.

In this case the steps are the following:

- At least 15 days before the activation of a compassionate use program, the Pharmaceutical company should inform AIFA with a letter (to be submitted by email) specifying the starting date, the closing date, the name of the concerned medicinal product and the estimated duration of the free of charge supply (If the closing date of the program is not known yet, this can be communicated at a later stage, but at least 30 days prior to the closing date). The Company should also provide the following:
 - CUP protocol
 - Documents supporting the manufacture according to GMPs or, if the product is manufactured in third countries, documentation proving that the manufacturing quality is at least equivalent to EU-GMPs
 - Details on dosing scheme and administration procedures for which safety and activity have been demonstrated in the clinical trials;
 - Data on safety, tolerability and efficacy;
 - Company declaration about the availability to provide the drug free of charge;
 - Procedures for data collection;
- The physician submits a request for compassionate use to the relevant competent EC including the documents listed above. A separate request should be submitted for each patient to be included in the Program. It is up to each EC to decide which documents should be submitted for each patient in the context of a CUP (i.e. if the full documentation is needed for each patient or if full documentation is needed only for the first submission and then only certain documents are requested for any other subsequent patient to be included in the CUP)
- The Ethics Committee issues an opinion and sends it to AIFA by email within 3 days along with documents a) and c) above (i.e. a) Clinical motivation of the request; c) Details on the degree of comparability between patients included in clinical trials and patients for whom the compassionate use is being requested or, for rare diseases and tumors only, the existence

of at least a common mechanism of action that makes a clinical benefit predictable on the basis of the available evidence on the product)

Figure 3. Compassionate Use Program - Process



Packaging

In the context of a compassionate use, the pack of the medicinal product must be in Italian language and follow the requirements set for investigational medicinal products (GMP Annex 13), with the exception of the information explicitly referring to a clinical trial (e.g. the wording “For Clinical Trial Use only” should be replaced with the wording “For compassionate use only”). A commercial, foreign pack could also be used provided that it is re-labelled (e.g. with a non-removable label) to include all the necessary information as set by GMP Annex 13, in Italian language.

Adverse Drug Reactions Reporting

According to the FAQ published by AIFA (April, 2018), physicians who become aware of any suspected adverse reaction to a medicinal product during a special use (e.g. compassionate use), are required to send the report according to the methods defined in the protocol, which must in any case comply with one of those provided for by current legislation (for more details see below).

There are 2 options for the reporting by the physicians:

1. The reporter transmits the ADR reports to the responsible person for pharmacovigilance of the health facility concerned or to the Web portal VigiFarmaco within 2 days (or 36 hours for biological medicinal products), specifying that the medicinal product is used according to a special use. The responsible person for pharmacovigilance will then enter (or validate, if through VigiFarmaco) them in the National

Pharmacovigilance Network (RNF), specifying "from study" and "for individual uses (compassionate use, NPPs)" as report type. Reports uploaded into RNF are automatically transmitted to Eudravigilance.

2. The reporter transmits the ADR reports directly to the MAH who shall enter them directly in EudraVigilance.

As explicitly indicated by AIFA in the FAQ, in order to avoid the creation of duplicates in the regulatory databases, it is important that physicians notify the report **either to the competent authority through the RNF or to the pharmaceutical company that supplied the medicine and not to both.**

In both options the reporter shall transmit the ADR reports also to the concerned Ethics Committee.

References

- M.D. 07/09/2017 <https://www.gazzettaufficiale.it/eli/id/2017/11/02/17A07305/sg>
- AIFA Website <https://www.aifa.gov.it/web/guest/farmaci-a-uso-compassionevole>
- CU AIFA FAQ https://www.aifa.gov.it/documents/20142/847411/FAQDR_uso_terapeutico_med_sper_clin_30.10.2019.pdf
- PV AIFA FAQ https://www.aifa.gov.it/documents/20142/1447627/FAQ_gestione_segna_lazioni_Marzo2021.pdf/
- GMP Annex 13 https://www.gmp-compliance.org/files/guidemgr/2009_06_annex13.pdf

6.3 Access to the AIFA 5% fund (Law 326/2003)

Definition

The so-called "AIFA 5% fund" is an "ad-hoc" fund to which pharmaceutical companies contribute (through the payment of 5% of their yearly expenditure for promotional activities) and is dedicated for the use, at AIFA's expenses, of orphan drugs for serious diseases and of drugs which represent the hope of treatment for particular and serious diseases, awaiting marketing in Italy.

Funding

AIFA

Eligibility criteria

INCLUSION CRITERIA FOR ACCESS TO THE AIFA NATIONAL FUND

- Medicinal products for rare and severe diseases required for individual cases on a nominal basis under conditions of urgency
- Absence of valid therapeutic alternative in a condition of maximum or important therapeutic need
- Medicinal products/indications for which published efficacy data from phase II clinical trials are available or, in the case of rare diseases, evidence of similar relevance, and which represent, in the applicant's view, a treatment opportunity for the individual patient for whom the request is made, assessed on the basis of clinical conditions, stage and rapid progression of the disease

- Denial and/or inability to place the patient in a compassionate use program or a clinical trial.

EXCLUSION CRITERIA FOR ACCESS TO THE AIFA NATIONAL FUND

- Medicinal products for rare and severe diseases, required for repeated uses for a specific indication.
- Medicinal products/indications available through other regulatory procedures:
 - Medicinal products/indications reimbursed by the Italian NHS (class A, H)
 - Medicinal products included in the list provided for by Law 648/96 for the requested indication
 - Medicinal products/indications in C(nn) or C class of reimbursement
 - Presence of compassionate use programs for the same clinical condition
 - Possibility of inclusion in an ongoing clinical trial with the drug for the same indication
- Medicinal products available in Italy for different indications from those objects of request and not under EMA evaluation
- Medicinal products which were rejected by EMA CHMP for the requested indication, or withdrawn by the Company following an ongoing negative evaluation by EMA CHMP
- Medicinal products/indications which were rejected by the AIFA CTS for the inclusion in the 648/96 List.

Who can submit the request?

The request for access to this fund is submitted by the clinical Centre and must be approved by AIFA.

How is the request formulated?

A formal **named patient request** should be addressed to AIFA through the dedicated section of the AIFA Front-End Portal “Gestionale Fondo 5%” (<https://servizionline.aifa.gov.it/jam/UI/Login?goto=https://servizionline.aifa.gov.it%2Fcinqueapp%2Fcinque-percento%2F>) including the following details:

- Applicant
- Patient
- Medicinal product
- Therapeutic indication for which the funding is requested, whether it is a rare disease and whether the concerned medicinal product has an orphan designation
- Rationale for the proposed treatment
- Eligibility of the patient for ongoing clinical trials in the specific indication (the physician should indicate whether there ongoing clinical trials, in particular at the applicant's facility, but also at other sites in Italy and the reasons for the patient's possible non-eligibility)
- Availability of the company to provide the product free of charge for compassionate use (the physician should preliminarily investigate the possibility of a compassionate use supply from the pharmaceutical company and state the company's response. The communication with the pharmaceutical company must also be attached to the AIFA form)

- Availability of hospital or regional funds for the proposed treatment
- Availability of authorized therapeutic alternatives (the physician should state the reasons for any non-eligibility for treatment with the available and authorized therapies)
- Clinical report relevant to the concerned patient (updated at the date of submission of the request)
- Proposed therapeutic plan (dosage regimen, treatment duration)

Moreover, a cost estimate shall be filled in by the hospital pharmacist of the treating center including the following:

- Proposed therapeutic plan (dosage regimen, treatment duration)
- Cost estimate for the proposed treatment

When the 5% Fund access has been granted, it is mandatory to communicate the start and the possible early termination of the treatment using the appropriate form (Communication start and stop treatment) to be sent to the email address 648.fondo5@aifa.gov.it

AIFA reimburses the cost of the medicinal products upon presentation of the relevant invoices (already paid) by the concerned hospital

Particular cases:

Should the requests for single uses become repetitive and systematic, considering the phase of clinical development or access to the market for the specific medicinal product/ indication, AIFA promptly assesses the possibility of:

- a) activating a compassionate use program by the company that owns the medicinal product;
- b) starting clinical trials also evaluating the opportunity of funding through dedicated tools, such as the 2% increase in the AIFA fund introduced by the recent law of 10 November 2021 n. 175 on the treatment of rare diseases;
- c) preparing the investigation for the evaluation by the CTS regarding the inclusion in the lists pursuant to Law 648/96.

In the case of a drug already on the market for which requests are submitted concerning the extension of the indications not yet negotiated and for which the C(nn) classification is not foreseen, AIFA - pending the conclusion of the negotiation process – takes action to verify the possibility of a compassionate use program.

In case of refusal:

- i. for individual cases, AIFA will evaluate the possible access, in line with the inclusion/exclusion criteria through the 5% fund;
- ii. in case of multiple uses, AIFA will prepare the preliminary investigation for the evaluation by the CTS of the temporary inclusion in the Law 648/96 list;

In case of inclusion in Law 648/96 List, this path may also become applicable for patients already being treated through the AIFA 5% Fund.

References

- Law 326/2003 <https://www.normattiva.it/uri-res/N2Ls?urn:nir:stato:legge:2003-11-24;326!vig=>
- AIFA Website <https://www.aifa.gov.it/web/guest/fondo-nazionale-aifa>

6.4 Importation from foreign countries (Decree 11/02/1997)

Definition

Medicinal products authorized and regularly marketed abroad but not authorized in Italy may be imported to Italy upon a physician's request if no valid therapeutic alternatives exist.

The product must be used according to the therapeutic indication(s) and conditions of use authorized in the foreign country from which it is imported.

Each importation request cannot exceed the number of boxes necessary to cover a treatment period of 90 days per patient.

Funding

The medicinal product is paid for by the importing hospital.

Procedure

The Competent Authority issuing the importation authorization ("Nulla Osta sanitario", i.e. provision stating that there is no impediment to the importation) is "USMAF" (territorial office of the Italian Ministry of Health).

The main practical steps (on the basis of our experience with FEDEX courier and the custom broker ANTELLI) are the following:

- 1) The physician has to prepare a request for importation as per the above-mentioned law, on the hospital's headed paper and then date, stamp and sign it. Each request cannot exceed the number of boxes necessary to cover a treatment period of 90 days per patient and it is mandatory to specify the patient's initials on the request.
- 2) The pharmaceutical company will prepare the shipment, which must be addressed to the hospital pharmacy (the precise address needs to be indicated) and must contain, on the outside, clear indication of the fact that it is a "Medicinal product imported according to DM 11.02.1997" ("Medicinale importato ai sensi del DM 11 febbraio 1997").

The pharmaceutical company will then hand the box to the appointed courier along with:

- the physician's request,
- the declaration on the correct storage of the product
- the invoice/waybill reporting the correct qualitative and quantitative description of the boxes shipped (and which will have to correspond with what reported on the physician's request).

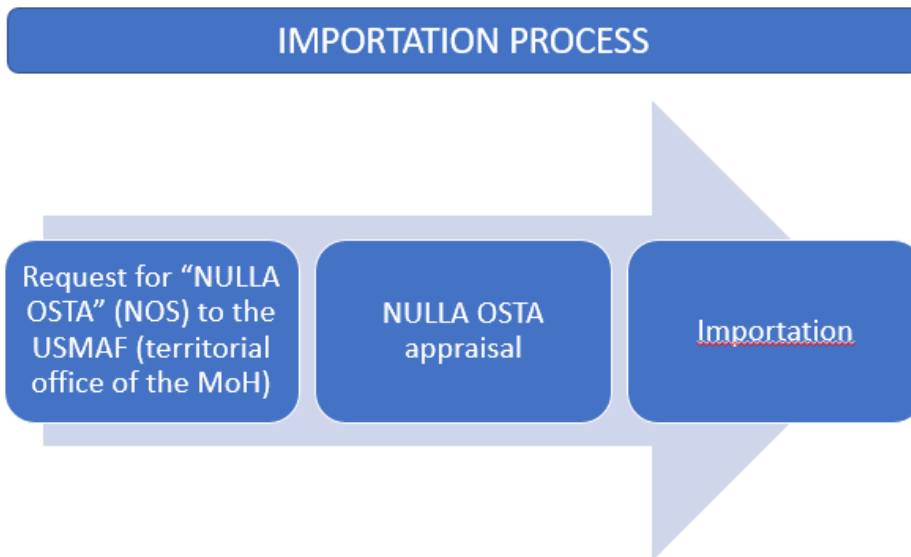
Moreover, when booking the shipment, the company will have to specifically ask the courier to make use of a customs broker who will take care of applying for the “Nulla Osta sanitario” to the “USMAF” (the competent territorial office of the Italian Ministry of Health) through the “Nuovo Sistema Informativo Sanitario” (NSIS, an online system of the Italian Ministry of Health).

As an alternative to the customs broker, we know that some hospital pharmacies are able to take care of the importation request autonomously, once they receive the shipment and before this is delivered to the hospital ward/physician who requested it (in this regard it is advisable to check with the hospital pharmacy).

Usually 2-3 working days are needed to obtain the “Nulla Osta sanitario”.

- 3) Once the “Nulla Osta sanitario” has been obtained, the medicinal product will be delivered to the hospital pharmacy.

Figure 4. Importation process



References

- M.D. 11/02/1997 <https://www.trovanorme.salute.gov.it/norme/dettaglioAtto?id=20747>
- SOP 10 https://www.salute.gov.it/imgs/C_17_pagineAree_3111_listaFile_itemName_17_file.pdf

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6.5 OFF-LABEL use according to the Di Bella law (Law 94/98)

Definition

OFF label use of an industrial medicinal product for a therapeutic indication or through an administration route different from the authorised ones under the prescribing physician's own responsibility

Conditions

- Absence of a valid therapeutic alternative
- Patient's informed consent
- Available scientific documentation (at least positive results of phase II studies)¹

Funding

The product is paid by the patient (unless hospitalized).

References

- L.D. 23/98 (Art. 3 comma 2) <https://www.normattiva.it/uri-res/N2Ls?urn:nir:stato:decreto.legge:1998-02-17:23>

6.6 Non-repetitive use of advanced therapies (M.D. 16/01/2015)

Definition

Access to advanced therapy medicines prepared on a non-repetitive basis, not yet authorized or not subject to a specific clinical trial in Italy, subject to AIFA's authorization to production and use, in the absence of a valid therapeutic alternative, in cases of urgency and emergency when the patient is in danger of life or of a major damage to health.

Conditions

- Absence of a valid therapeutic alternative
- Urgency and emergency when the patient is in danger of life or of a major damage to health
- Collection of the patient's informed consent
- Available scientific documentation

Procedure

The non-repetitive use of advanced therapies is dependent on the obtainment of the following authorisations from the Italian Agency AIFA:

Manufacturing authorization

The authorization for the manufacture of advanced therapy medicinal products prepared on a non-repetitive basis is mandatory and it is issued by AIFA to new pharmaceutical sites that intend to produce such

¹ art. 2, par 348 Law 244/2007 (Financial law 2008)



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medicinal products to be used exclusively in a public hospital, university clinic or Scientific Institute for Research, Hospitalization and Healthcare in the national territory (IRCCS, Istituto di Ricovero e Cura a Carattere Scientifico), under the exclusive professional responsibility of a physician, and in execution of an individual medical prescription for a specific medicinal product intended for a specific patient.

Who can submit the request?

The request must be submitted by the legal representative of the pharmaceutical site where the manufacture of an advanced therapy medicinal product prepared on a non-repetitive basis is intended to take place.

How is the request formulated?

The following documentation shall be presented:

- Authorisation application form with relevant attachments/supporting documents (https://www.aifa.gov.it/documents/20142/847574/Mod.396_01.pdf)
- Dossier of the Medicinal Product for Advanced Therapy (DMTA)
- Proof of payment of the due fee

Facilities that already have a GMP authorization to produce advanced therapy medicinal products are exempted from requesting an additional manufacturing authorization from AIFA, provided that the medicinal product is obtained through the same production process and with similar quality requirements. and upon presentation to AIFA of the Dossier of the Medicinal Product for Advanced Therapy (DMTA), to be able to start production for individual patients.

Timelines

The documentation is evaluated by AIFA within 60 days from the receipt of the request (a clock stop is foreseen in case of request for integration).

If the assessment of the documentation has a favourable outcome, within the following 60 days AIFA performs a verification, if necessary through an inspection, of the conformity of the facility, of the processes and of procedures to the European Good Manufacturing Practices.

Following the positive outcome of the abovementioned procedure, AIFA issue the authorization.

Other obligations

Manufacturers of advanced therapy medicines prepared on a non-repetitive basis are required to report to AIFA:

- any quality defect found on such medicinal products (Product Quality and Fighting Pharmaceutical Crime Office: qualita.prodotti@pec.aifa.gov.it)
- the number of batches of each advanced therapy medicinal product on a non-repetitive basis produced in the previous year and using a dedicated form, by January of each year, (GMP Medicinal Products Inspection and Authorization Office: ufficiogmpmed@pec.aifa.gov.it; Pre-Authorization Area: advancedtherapy@aifa.gov.it).

Authorization for the use

The authorization for the use of advanced therapy medicinal products prepared on a non-repetitive basis, which simultaneously satisfy the conditions of "lack of valid therapeutic alternative" and "urgency and emergency that place the patient in life-threatening conditions", is mandatory and is issued by AIFA with the



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assent of the Commission for the assessment of admissibility to the phase I trial, pursuant to Article 7 of the Presidential Decree n. 439 of 21/09/2001.

Who can submit the request?

The request is submitted by the legal representative of the health facility where the medicinal product will be administered.

How is the request formulated?

The following documentation shall be presented:

- Authorisation application form with relevant attachments/supporting documents (https://www.aifa.gov.it/documents/20142/847574/Modello_autorizzazione_impiego.pdf)
- Dossier of the Medicinal Product for Advanced Therapy (DMTA)
- Proposed treatment Protocol
- Favorable opinion of the Ethics Committee
- Any suitable documentation to allow an assessment of the expected risks and benefits of the proposed treatment, in particular, safety and efficacy data from clinical trials, the rationale for the proposed treatment, with specific reference to the biological characteristics of the cell populations used, the hypothesized mechanism of action and the appropriateness of the route of administration in relation to the etiology, pathogenesis and natural history of the pathology for which it is required to use the drug.

Timelines

The authorization is granted within 30 days from the submission of the application by the legal representative of the health facility where the manufacturing authorization has already been issued.

The use of advanced therapy medicinal products for non-repetitive use and the verification of compliance with the conditions set out in the Ministerial Decree 16/01/2015 is under the exclusive professional responsibility of the physician. Therefore, the prescribing physician will forward, together with the application for the use, a declaration (according to dedicated forms) in which he assumes full responsibility for the administration of the drug prepared on a non-repetitive basis.

References

- M.D. 16/01/2015 <https://www.gazzettaufficiale.it/eli/id/2015/03/09/15A01704/sg>
- AIFA Website <https://www.aifa.gov.it/web/guest/uso-non-ripetitivo-di-terapie-avanzate>

7. Early access options for Austria

7.1 Compassionate Use

Definition

Compassionate use is defined as an optional exceptional measure in Article 83 of Regulation 726/2004/EC. It was translated into National Law by amending the Austrian Medicinal Products Act in 2009 and incorporated as §8a.

According to article 6 of directive 2001/83/EC (§ 7 Austrian Medicinal Products Act, AMG) medicinal product may not be placed on the market of a Member State unless a marketing authorization has been issued by the competent authorities of that Member State or an authorization has been granted through a centralized procedure. Regulation (EC) No 726/2004 defines an exception to this requirement under defined circumstances within the framework of compassionate use pro-programmes. The compassionate use definition is laid down in article 83 of Regulation (EC) No 726/2004.

The choice of wording emphasizes the optional nature of compassionate use i.e. "Member States may make a medicinal product ... available for compassionate use. It is within the remit of member states to approve or accept these pro-programmes. A legal claim for applicants to conduct compassionate use programs cannot be deducted from the text of article 83.

Compassionate use facilitates the provision of unauthorized medicinal products to patients for whom no adequate treatment modalities exist and who cannot be included in clinical trials. Scientific data on Safety and Efficacy of the medicinal product have to be provided, and the applicant commits to the submission of a marketing authorization in due course. These requirements and the temporary limitation of the compassionate use program were instated to assure that only promising medicinal products qualify for compassionate use programs.

Other terms such as "Early Access Program" are also used internationally, but do not appear in Austrian law.

Funding

Usually the costs for the medicinal products of the compassionate use are covered by the applicant (MAH), however, negotiations with the health insurance/sick fund can be undertaken. We are not aware about any case where the costs have been reimbursed by the sick fund.

Eligibility requirements

Compassionate use is granted as a temporary exemption for a group of (unnamed) patients.

Taking into consideration the "Guideline on Compassionate Use of Medicinal Products, Pursuant to Article 83 of Regulation (EC) No 726/2004 (Doc. Ref: EMEA/27170/2006)" the requirements can be summarized as follows:

1. Art 3 para 1 and 2 of Regulation (EC) No 726/2004 have to apply to the medicinal product in question (see 3.1.). Therefore, CUPs are only possible for medicinal products for which an application for centralized approval can be submitted to the European Medicines Agency (EMA). A CUP cannot be applied to a medicinal product, which has already been authorized via the centralized procedure, even if the proposed conditions of use and target population are different from those of the marketing authorization.
However, the existence of a Community authorization for a medicinal product is without prejudice to the national legislations on CU.
2. Proof that the patients to be treated (Patient group) suffers from a chronically or seriously debilitating disease, or a life-threatening disease;
3. Proof that the patient group cannot be treated satisfactorily by an authorized medicinal product in Europe;

4. Documentation that the medicinal product is either the subject of an application for a centralized marketing authorization in accordance with Article 6 of Regulation (EC) No 726/2004 or is undergoing clinical trials in the Euro-pean Union and/or elsewhere;
5. Generally, the results of a „mature randomized phase III trial” should be available. If patient safety is guaranteed, this requirement can be handled on a case-by-case approach (appropriate data from Phase II studies);
6. Confirmation that the applicant will make the medicinal product available to patients in the interim time between approval of the marketing authorization application and introduction to the market;
7. Assurance of compliance with pharmacovigilance requirements according to article 24 para 1 and article of Regulation (EC) No 726/2004 in the context of the CUP.

Distinction from other programs:

In Austria, Compassionate Use, as a program approved by the authorities for a defined group of patients, can be clearly distinguished from other terminologies.

In contrast to the Compassionate Use, the Named Patient Use always only refers to a specific patient. In Austria, the Named Patient Use is not subject to authorization by or notification to the authorities, but is the so responsibility of the treating physician.

Who can submit the request?

According to § 8a paragraph 2 AMG the applicant for a CUP can either be a manufacturer, if also the sponsor of approved clinical trials for the respective medicinal product, or the applicant for a marketing authorization according to article 6 Regulation (EC) 726/2004 for the respective medicinal product.

How is the request formulated?

It is the applicant’s task to write the treatment protocol for the CUP. The purpose of this document is to provide relevant information on the medicinal product and its indication to the authorities and to treating physicians. Further, the protocol includes the provisions for patient treatment and data collection within the CUP.

The treatment protocol should contain the following information:

1. Contact details for the person responsible and, if applicable, the legal representative located within the European Union or a member state of the European Economic Area;
Further, contact details need to be provided for the person to be named on the BASG Website as National contact for the public
2. Name of the medicinal product, declaration of active substance and composition, mode of application, dosing and therapeutic application,
3. Description of the disease and justification that the patients for whom the medicinal product is intended suffer from a chronically or seriously debilitating disease, or a life-threatening disease;
4. Criteria for patient selection and estimate of patient number;
5. Justification that no adequate treatment with a medicinal product legally on the market is available in Austria;
6. Justification, why the intended patient group cannot be included in a currently active clinical trial;

7. Justification and data illustrating the safety and efficacy of the medicinal product in the proposed indication, generally through the provision of results of pivotal clinical trials,
8. Details on
 - a) the approved pivotal clinical trial with the medicinal product in the proposed indication referenced by its EudraCT number, or
 - b) the approved pivotal clinical trial of the medicinal product in the proposed indication in a third country and proof that this trial has been conducted according to the internationally harmonized requirements of Good Clinical Practice (GCP), or
 - c) the marketing authorization application submitted to EMA, BASG or the competent authority of another member state for the medicinal product in the proposed indication;
9. The demands on the medical facilities and the qualifications of participating physicians;
10. Criteria leading to the interruption or early termination of the CUP;
11. The justification for the therapeutic use of a medicinal product in a CUP which has received a negative opinion in a MAA, has been withdrawn from the market or whose marketing has temporarily been suspended; or for which the conduct of a clinical trial has been refused, withdrawn after approval, suspended or the approved under the condition of specific commitments. In each case, the grounds for the decision should be outlined.
12. Description of the data collection plan
13. The commitment that pharmacovigilance requirements will be fulfilled according to articles 24 and 25 of Regulation (EC) 726/2004 and that safety related information collected in the CUP will be integrated in the DSUR/annual safety report and submitted to the BASG.

Further documents:

1. The Information and documentation provided to patients, in German, and a description of the procedure followed to obtain patient consent after information of the patients by the treating physicians;
2. A list of currently approved CUPs in other member states of the European Union or the EEA and, when available, the opinion of the Committee for Human Medicinal Products (CHMP) according to article 83 of Regulation (EC) No 726/2004;
3. The current Investigator's Brochure supplied to investigators in the clinical trials or the proposed draft summary of product characteristics (SmPC) for the medicinal product submitted as part of the application for marketing authorization;
4. Manufacturing documentation (IMPD), including a statement by a qualified person according to § 7 Arzneimittelbetriebsordnung (AMBO) that the medicinal product has been manufactured according to the principles and requirements of Good Manufacturing Practice. In cases where the medicinal product previously has been assessed as part of a BASG procedure, reference to the documentation of that procedure is sufficient, taking potential updates into consideration.

Exceptional case of compassionate use with a medicinal product fulfilling the definition of a gene therapy:

In case of CUP with a medicinal product that fulfils the definition of a gene therapy or with a medicinal product that constitutes a genetically modified organism according to § 4 (3) of the Austrian Gene Technology Act (Gentechnikgesetz, GTG), BGBl. No 510/1994, the requirements of both the AMG and the GTG apply. Separate approvals by the BASG and the Federal Ministry of Health apply.

The definition of a gene therapy medicinal product differs between the AMG and Directive 2001/83/EC and the Austrian GTG and is presented in the following:

Directive 2001/83/EC: Gene therapy medicinal product means a biological medicinal product which has the following characteristics:

- (a) it contains an active substance which contains or consists of a recombinant nucleic acid used in or administered to human beings with a view to regulating, repairing, replacing, adding or deleting a genetic sequence;*
- (b) its therapeutic, prophylactic or diagnostic effect relates directly to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence.*

Gene therapy medicinal products shall not include vaccines against infectious diseases.

What is the procedure?

The application for a CUP can either be submitted at the same time as a Marketing Authorization Application (MAA), or earlier, provided that the applicant commits to the submission of an MAA according to article 6 of Regulation (EC) No 726/2004 in the foreseeable future in writing. The provisional timeframe should be noted.

The conduct of a CUP has to be preceded by a written approval by the Austrian Federal Office for Safety in Health Care (Bundesamt für Sicherheit im Gesundheitswesen, BASG).

BASG evaluation is based on the requirements of art. 83 of Regulation (EC) No 726/2004, and the framework outlined in the relevant Guidance and Questions & Answers of the European Medicines Agency (EMA):

- Guideline on compassionate use of medicinal products, pursuant to article 83 of regulation (EC) no 726/2004
- Question and Answer document on Compassionate use for centralized medicinal products

These documents are publicly available on the website of the EMA www.ema.europa.eu

The placing on the market of a medicinal product within a CUP is approved by the BASG until regular availability on the national market after granting of the marketing authorization. The approval of an application is contingent on the provision of a protocol of the intended treatment. In the interest of public health CUP approval can be modified or withdrawn, if the approval conditions are no longer met.

The application for a CUP is to be submitted electronically to the BASG via the following e-mail:

compassionate-use@ages.at.

Receipt of the submission documents will be confirmed electronically.

Should the information be too extensive for transfer per e-mail, a submission on electronic data-carrier with cover letter is also possible, with the following address:

Austrian Federal Office for Safety in Health Care (BASG)
Austrian Agency for Health and Food Safety (AGES)
Institute Surveillance (INS), Department for Clinical Trials (CLTR)
Traisengasse 5
A-1200 Vienna; Austria

Duration of validity of CUP approval:

1. A CUP approval is valid until availability of the medicinal product on the market unless terminated early or stopped by the agency.



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2. CUP approval is contingent on the obligation to submit DSURs. Information of national interest concerning the ongoing CUP (e.g. number of Austrian patients treated) should be included in the cover letter of the DSUR submission. Annual submission of DSURs is expected, but not fixed to the date of CUP approval, given that other processes (DSUR compilation and submission) may dictate another periodicity. It should be noted, that non-compliance in regard to DSUR submission might result in interdiction of the CUP.
3. In case of a negative change in the benefit/risk a CUP can be interdicted by the agency anytime DSUR assessment is currently included in the fee for CUP.

Switching from Compassionate Use to Marketing:

Once marketing approval is granted for a medicinal product with an existing CUP in Austria, the authorization holder is required to inform the BASG on the actual availability of the product on the Austrian market. This date will be considered as the termination date for the CUP.

Import of medicinal products in the context of a CUP

Medicinal products that are shipped to or imported into Austria in the context of an approved CUP are exempted from the requirements of the Medicinal Products Importation Act (Arzneiwareneinfuhrgesetz 2010, BGBl. I No 79/2010), according to article 11 para 1.3. Therefore, no shipment notification or import application to the BASG is required.

Pharmacovigilance requirements

According to article 83 § 6 of Regulation (EC) 726/2004 pharmacovigilance requirements according to article 24 paragraph 1 and article 25 apply to medicinal products in the context of compassionate use programs.

Fees

The applicable fees can be found in the Schedule of Fees of the BASG according to the Act on Safety in Health and Food. They are indexed and cited in the Regulation issued by the Federal Office for Safety in Health Care and may be found at this internet site: www.basg.gv.at/en/about-us/fees/

References

- Austrian Medicinal Products Act (Arzneimittelgesetz, AMG), BGBl Nr. 185/1983, current version
- Medicinal Product Site Regulations (Verordnung des Bundesministers für Gesundheit über Betriebe, die Arzneimittel oder Wirkstoffe herstellen, kontrollieren oder in Verkehr bringen und über die Vermittlung von Arzneimitteln, Arzneimittelbetriebsordnung 2009 – AMBO 2009), [BGBl. II Nr. 324/2008](#), current version
- Ordinance of the Federal Minister for Health on the labeling of medicinal products (Verordnung der Bundesministerin für Gesundheit, Familie und Jugend über die Kennzeichnung von Arzneispezialitäten 2008, Kennzeichnungsverordnung 2008), [BGBl. II Nr. 174/2008](#), current version
- Federal Law on the Importation and Transfer of Medicinal Products, Blood Products and Products of Natural Cure (Bundesgesetz über die Einfuhr und das Verbringen von Arzneiwaren, Blutprodukten und Produkten natürlicher Heilvorkommen, Arzneiwareneinfuhrgesetz 2010 – AWEG 2010), [BGBl. I Nr. 79/2010](#), current version



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- Fee Regulation (Verordnung des Bundesamtes für Sicherheit im Gesundheitswesen über den Gebührentarif gemäß GESG), current version
- Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, current version

7.2 Named Patient Use

Definition

The definition for named patient use is found in article 5 of directive 2001/83/EC.

A Member State may, in accordance with legislation in force and to fulfil special needs, exclude from the provisions of this Directive (2001/83/EC) medicinal products supplied in response to a bona fide unsolicited order, formulated in accordance with the specifications of an authorized health care professional and for use by his individual patients on his direct personal responsibility.

This text has been translated into National Law in § 8 article 1 (2) AMG:

§ 8. (1) *Arzneispezialitäten bedürfen keiner Zulassung, wenn ...*

2. ein zur selbständigen Berufsausübung im Inland berechtigter Arzt, Zahnarzt oder Tierarzt bescheinigt, dass die Arzneispezialität zur Abwehr einer Lebensbedrohung oder schweren gesundheitlichen Schädigung dringend benötigt wird und dieser Erfolg mit einer zugelassenen und verfügbaren Arzneispezialität nach dem Stand der Wissenschaft voraussichtlich nicht erzielt werden kann

English translation:

§ 8. (1) *Proprietary medicinal products do not require a marketing authorisation, if:*

2. a physician, dentist or veterinarian licensed for independent practice in Austria certifies that the proprietary medicinal product is urgently needed to ward off a life-threatening condition or one that is severely damaging to the patient's health, and that this is unlikely to be possible with a proprietary medicinal product that is authorised and available in Austria in the light of current medical knowledge

In contrast to compassionate use programs that apply to a group/cohort of patients, named patient use, as the name implies, refers to a single individual. Named patient use in Austria does not require agency notification or approval and lies in the sole responsibility of the treating physician.

As outlined in § 8 para. 1 Z 2 AMG, named patient use is intended to facilitate the urgently needed treatment of a specific patient to avert a life-threatening or chronically debilitating situation. A systematic collection of data on safety and efficacy of the medicinal product used is not legally acceptable in this framework. Systematic collection of these data is only possible in the framework of an authorized clinical trial.

Funding

Medicinal products for Named Patient Use may be paid either by the patient, the hospital holder, or the health insurance. This has to be checked case by case.

Eligibility requirements

See above section Definition B.1.

Who can submit the request?

The treating physician has to complete a clinic requirement form (so called “Klinikanforderung”) based on the medical justification provided which is needed for the release by customs.

How is the request formulated?

The treating physician has to complete a clinic requirement form (so called “Klinikanforderung”) based on the medical justification provided which is needed for the release by customs.

What is the procedure

Hospital doctors need the co-operation of the hospital pharmacy or the public pharmacy, which supplies the hospital. The applicable procedure may vary depending on the hospital and needs to be clarified in consultation with this pharmacy.

Resident practicing physicians need cooperation with a public pharmacy.

Import of medicinal products in the context of Named Patient Use

For the importation/shipment of a medicinal product that is not licensed in Austria, the Austrian Medicinal Products Importation Act 2010 (AWEG, BGBl I Nr. 79/2010, as amended) needs to be applied. If the criteria of § 8 para. 1 Z 2 AMG apply, the exemption of § 11 para. 1 Z 2 Medicinal Products Importation Act 2010 applies for importation/shipment.

The exemption of § 11 para. 1 Z 2 Medicinal Products Importation Act 2010 requires the following: A medical doctor, dentist or veterinarian licensed for independent exercise of profession confirms that the respective medicinal product is **urgently** needed for the treatment of specific patient to avert a life-threatening or chronically debilitating situation and that successful treatment with licensed or available medicinal products cannot be achieved based on the scientific state of the art.

Urgency as referred to § 8 para. 1 lit 2 AMG applies, if the need for the medicinal product to avert a life-threatening or chronically debilitating situation which is not foreseeable, respectively plannable, and if it is required without delay. Only if these criteria apply importation can proceed without the involvement of the Austrian Federal Office for Safety in Health Care.

Import or shipment of the medicinal product lies in the responsibility of the treating physician. Release by customs needs to be based on the medical justification provided.

In absence of urgency according to § 8 para. 1 lit 2 AMG, import of a medicinal product which is not authorized in Austria but is required for medical, dental or veterinary treatment for a specific patient must follow the requirements of the Medicinal Products Importation Act 2010. As a consequence, an application for importation authorization or a shipment notification is necessary as applicable, whenever the need for the medicinal product is foreseeable or plannable.



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Pharmacovigilance requirements

All suspected adverse reactions of a medicinal product applied in Austria need to be documented and notified to the Austrian Federal Office for Safety in Health Care. The pharmacovigilance reporting obligations also concern medicinal products which are not licensed in Austria, including those which are applied in the framework of named patient use.

According to § 75 g AMG , members of the health care professions are obliged to notify all suspected adverse drug reactions that come to their notice as part of their occupation. These notifications must be made without delay.

Marketing authorization holders are obliged to electronically report suspected adverse drug reactions according to § 75 j AMG. The reporting obligation is within 15 days of the event becoming known for suspected serious adverse reactions and 90 days for suspected not serious adverse reactions.

Fees

No fees arise.

References

- Austrian Medicinal Products Act (Arzneimittelgesetz, AMG), BGBl Nr. 185/1983, current version
- Federal Law on the Importation and Transfer of Medicinal Products, Blood Products and Products of Natural Cure (Bundesgesetz über die Einfuhr und das Verbringen von Arzneiwaren, Blutprodukten und Produkten natürlicher Heilvorkommen, Arzneiwareneinfuhrgesetz 2010 – AWEG 2010), [BGBl. I Nr. 79/2010](#), current version