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Overview of the Regulatory Regime for Advanced Therapy Medicinal Products in the EU

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Abstract: Through the introduction and analysis of the development of advanced therapy medicinal products and the regulatory framework, pre-market approval and post-market supervision of ATMP in Europe in recent years, it is found that the classification and definition of ATMP by EMA is relatively scientific, and the regulatory framework and laws and regulations are relatively complete. It not only has strict approval procedures for listing licenses, but also has certain flexibility in the approval path, giving active industrial support to ATMPs. At the same time, the MAH has strict requirements on the post-market supervision system of ATMP, which is worth learning and learning from China.

1. Introduction

For a specific condition, the traditional treatment method is usually standardized treatment, which is one-size-fits-all for all patients. Advanced therapy drugs are medical therapies based on genes, cells or tissues, which can be customized according to different patients and may be used to treat various human health problems, especially those that are insufficiently treated by traditional methods, severe Incurable and chronic diseases, including cancer, neurodegenerative, genetic and autoimmune diseases, have the potential to reshape the treatment of a wide range of diseases. It opens up new possibilities for the prevention and treatment of a large number of diseases that have hitherto not been effectively treated[1]. These therapies are at the forefront of innovation and, while always controversial, have grown in number and prominence every year over the past decade. Technologies based on advanced treatments are the present and future of medicine, bringing precision medicine one step closer.

As one of the pioneers of drug regulation, the European Medicines Agency has implemented scientific regulation of ATMPs since 1999, covering the entire life cycle of ATMPs, including ATMPs classification procedures and scientific advice, preclinical research and clinical trial guidance, marketing authorization and Post-market regulation[2]. More than 700 companies in Europe are currently researching new gene, cell and tissue engineering therapies. This paper studies the regulatory mechanism of advanced therapy drugs in Europe, in order to provide reference for the supervision and development of similar industries in China.

2. Overview of Advanced Therapy Medicinal Products

2.1 Definition

The European Union Regulation 1394/2007/EC defines advanced therapy medicinal products (ATMPs) as drugs for human use based on gene, cell or tissue engineering, including gene therapy drugs, cell therapy drugs and tissue engineering drugs. Among them, gene therapy drugs are products of biological origin containing recombinant nucleic acids, and play therapeutic, preventive or diagnostic effects by inserting recombinant genes into the body. Cell therapy drugs are drugs that contain cells or tissues that have undergone extensive manipulation in order to alter their biological properties, or to serve different basic functions in the body. The recipient and donor of the drug may be the same person[3]. Tissue engineering drugs refer to drugs containing modified cells or tissues to repair, regenerate or replace human tissues. In addition, some ATMPs may contain one or more medical devices as a component of a drug, known as combination ATMPs, and are regulated by both the Drugs Guide and the Medical Device Guide.

2.2 Characteristic

Compared with traditional medicines, ATMPs have some unique characteristics. First, the healing potential is great. ATMPs are designed to focus more on the biological mechanisms of the disease and are selectively produced according to the individual patient's therapeutic needs, which means that these innovative therapies may provide curative solutions for patients with refractory diseases, effectively improving the lives of patients quality and extended life. Second, the production process is complicated[4]. It usually requires highly specialized production equipment, production process and technical requirements, and production requires a sterile environment to ensure the consistency and stability of starting materials, production processes, production equipment, etc. At the same time, the raw materials have variability, and the production process must be highly flexible. Third, one-time treatment. ATMP is typically used once and provides lifetime benefits, thereby increasing patient adherence to treatment, while reducing the need for routine treatments and routine care, saving health systems long-term costs. Fourth, it is expensive. Due to the difficult research and development of ATMPs, high production costs, and small target population, their drug prices are high. At the same time, this treatment usually requires a one-time upfront fee, so it is challenged in terms of payment and reimbursement. Finally, transportation is difficult. Some ATMPs are living cells, and the product has a short shelf life. Measures to ensure product stability and quality control are required, so there are certain obstacles in transportation.

2.3 Classification Procedure

To ensure that medicines are classified correctly, the European Medicines Agency's (EMA) Advanced Therapeutic Committee (CAT) is responsible for providing scientific advice to applicants as to whether an application drug can be classified as a ATMP, for clarification or confirmation before further development. The classification procedure is mainly divided into the following steps:

1) The ATMP classification application is submitted by the producer;

2) The appointment of the EMA and CAT coordinators;

3) The draft scientific advice is drafted by the CAT members and discussed. If the applicant needs to provide additional information, the time suspension mechanism will be activated, and the timing will be restarted after receiving the answers to the applicant's relevant questions;

4) CAT will draw the final scientific advice in combination with the European Commission's advice;

5) Inform the applicant of the classification results and publish the scientific advice.

6) The whole process will take about 60 days, not including time suspension. In addition, in the early stages of development, the EU hosts Innovation Task Force (ITF) briefings, where informal information exchanges with agencies on developments in scientific, regulatory and legal issues, and advice and recommendations are obtained. For complex products, such meetings may also be useful for obtaining legal and scientific feedback on product classification. The ATMP classification procedure is of great value in addressing common boundary classification issues when incorporating ATMPs, defining drug product frameworks, and identifying product ATMP types, thereby developing products according to specific dossier requirements and quality guidelines.

2.4 The Development Status of ATMPs

Although ATMP has great potential in the prevention and treatment of many diseases, due to its complex production process, rare indications and tailored production, high R&D and manufacturing costs, strict regulatory requirements, and difficulty in reimbursement, ATMP is often used. It is regarded as a product with low commercial value and high commercial risk. In 2009, the European Union approved the first ATMP product, ChondroCelect, a tissue engineered product for the treatment of cartilage defects. To date, the EMA has approved 15 advanced therapy drugs, and 10 have obtained marketing authorization, including 7 gene therapy drugs, 1 cell therapy product and 2 tissue engineering products. The other 5 were withdrawn or discontinued by the manufacturer and withdrawn from the market for various reasons. Although ATMPs have been slow to develop, they are continuing to evolve or will become one of the most popular and fastest-growing treatments in the world, and the number of newly approved ATMPs is expected to increase substantially in the coming decades.

3. Regulation of ATMPs

While ATMPs may become solutions to currently incurable diseases, bringing us closer to personalized medicine, they are specific, complex, and novel, and must be tightly regulated. Before entering the market, it is necessary to ensure that it is safe, effective, and quality controllable. Specifically tailored and harmonized rules are needed to ensure high levels of health protection, and to coordinate and facilitate market access, foster competitiveness and provide legal certainty.

3.1 Legal framework

Table 1: Legal Guidance Documents

Regulatory Framework	File Name
Programmatic Regulations	Regulation (EC) No. 1394/2007
	Medical Devices Act 93 /42 /EEC Directive 2001/83/EC
	Good Clinical Practice Guidelines on GMP Manufacturing Practice specific to Advanced Therapy Medicinal Products
Other regulations	Regulation(EC)No. 1235/2010、Directive2010/84/EU
	Good Pharmacovigilance Practices Guidelines on safety and efficacy follow-up-risk management of Advanced Therapy Medicinal Products

The EU introduced cell- and gene-based therapy into European medicines legislation through Directive 2003/63/EC, and in June 2003 amended Directive 2001/83/EC as a new class of biological medicines, called ATMP. Subsequently, the European Commission revised the original regulations in 2007 and promulgated Regulation1394/2007/EC,Which is a special advanced therapy drug regulation. The regulation establishes the general idea, regulatory framework and technical framework for how such cutting-edge therapeutic products should be regulated in EU countries. EU regulations and guidance documents ensure that ATMPs provide detailed and adequate guidance throughout the entire life cycle of ATMPs, from research and development to marketing to post-marketing surveillance, from multiple perspectives, and are constantly updated.Table 1 lists some important legal guidance documents

3.2 Regulatory Bodies and Functions

Following the promulgation of the relevant laws, the European Union established the Advanced Therapies Commission (CAT) in 2007. EMA has high requirements for CAT members, and their expertise covers a wide range of fields, including tissue engineering, gene therapy, cell therapy, bioengineering, medical devices, pharmacovigilance, risk management and other disciplines. CAT membership includes 1 representative member and 1 alternate member from all member states, 5 advisory committee members and representatives of clinicians and patient organizations. CAT is primarily responsible for providing scientific advice on the classification of ATMPs and conducting preliminary assessments of ATMP applications for marketing authorization to ensure its quality, safety and efficacy[5]. They are also responsible for supporting the scientific advisory process, advising on pharmacovigilance or risk management systems, evaluating post-approval change submissions, and writing scientific guidelines.

In addition, there is the Committee for Medicinal Products for Human Use (CHMP) established within the EMA responsible for participating in scientific advisory meetings with its working groups, preparing scientific guidelines and providing support to drug developers on development plan requirements prior to marketing authorisation[6]. Also responsible for the scientific evaluation of pharmaceuticals for human use (except for herbal products), discussing the draft preliminary evaluation submitted by CAT, and arriving at the final opinion. The Pharmacovigilance Risk Assessment Committee (PRAC) is responsible for evaluating and monitoring the safety of medicines for human use, evaluating risk management plans (RMPs), and post-authorization safety studies.

Regulators in EU member states are called National Competent Authorities (NCAs), and they are primarily responsible for approving applications for marketing authorization and clinical trial authorization (CTA) for drugs that are not subject to centralized procedures in their member states, and Provide scientific advice for the design of clinical trials during the ATMP development process.

4. Pre-Market Supervision

The regulation of advanced therapy drugs mainly includes pre-marketing licensing and post-marketing regulation. In order to sell an ATMP in the market, a Marketing Authorization (MA) is first required. The marketing authorization process requires regulatory review of quality, safety and efficacy data generated during clinical development prior to marketing to ensure the quality, safety and efficacy of all medicinal products for use.

4.1 Marketing Authorization Process

Due to advanced therapeutics often involve areas beyond traditional pharmaceuticals such as

biotechnology and medical devices, their evaluation often requires very specialized knowledge. In the EU, applications for clinical trials of advanced therapy medicines are submitted separately to national competent authorities. But for marketing approval, all ATMPs are assessed through a centralized process to ensure they apply to a single assessment and authorisation across the EU.

Before submitting an application for marketing authorization, the applicant is obliged to submit an application for review eligibility according to the centralized procedure and to submit a notification of intent to apply 7 months prior to submission. Upon acceptance of the submission, EMA will appoint a rapporteur and a co-rapporteur to conduct a scientific assessment of the dossier and a PRAC rapporteur to assess the RMP. Following appointment, the Rapporteur holds a pre-submission meeting with the applicant to discuss the regulatory aspects of the upcoming application and clarify any application-specific issues before submitting the marketing authorization application.The main process is shown in Figure 1.

Evaluation of the Marketing Authorization Application is the responsibility of the Advanced Therapies Committee and the Medicinal Products Committee for Human Use. The Advanced Therapy Committee is responsible for the classification of ATMPs and the preliminary assessment of the quality, safety and efficacy of ATMPs, and submits a draft evaluation opinion to the Committee for Medicinal Products for Human Use, which then issues comments, and the European Commission makes the final decision. If the ATMP is used in an unconventional manner in the hospital setting of an individual Member State, the Hospital Exemption Scheme may be followed. If the drug is intended for use in children, clinical development must include pediatric studies.

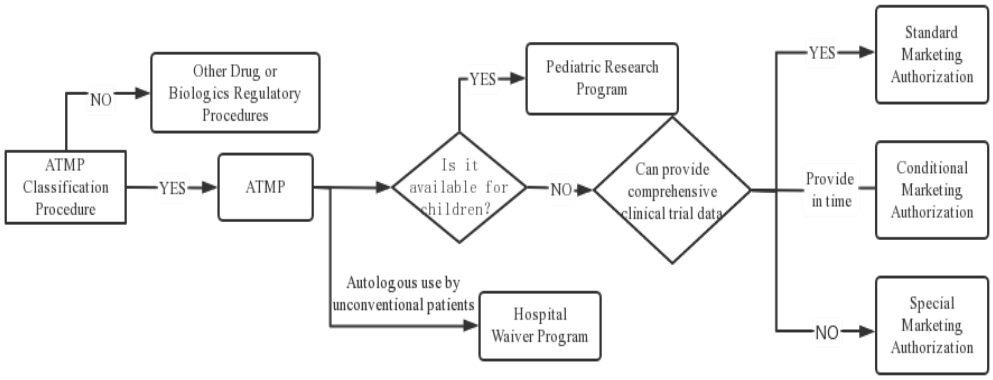

Figure 1: Marketing Authorization Process

4.2 Marketing Authorization Application Category

Depending on the extent of clinical data obtained during development and whether the drug meets a medical need, marketing authorization obtained through a centralized procedure may be granted in three ways: standard marketing authorization, conditional marketing authorization, and special marketing authorization.

4.2.1 Standard Marketing Authorization Procedure

The standard marketing authorization pathway is generally applicable when clinical data is not limited and does not require further demonstration of the quality, safety and efficacy or benefit-risk balance of the drug product being evaluated, other than the data required to support the grant of the marketing authorization application. That is, it is awarded on the basis of a positive benefit-risk balance supported by comprehensive clinical data.

4.2.2 Conditional Marketing Authorization Procedure

Conditional marketing authorization needs to be considered when comprehensive clinical data may not be readily available, such as for a drug being developed for a rare disease with a small target patient population. Drugs eligible for conditional marketing authorization typically include those that treat, prevent, or diagnose a severely debilitating or life-threatening disease, and a conditional marketing authorization application may be submitted after the completion of a phase II study to expedite the availability of the drug. For urgent or unmet medical needs, the Conditional Marketing Authorization pathway may be granted when initial efficacy with a positive benefit-risk balance is demonstrated by surrogate clinical endpoints. The benefit-risk balance of a product for a conditional marketing authorization application must be positive, pending confirmation of the availability of comprehensive clinical data, and the applicant needs to provide comprehensive clinical trial data within a certain period of time after approval. After the applicant has fulfilled its post-authorization obligations, it may eventually transition to the standard marketing authorization process.

4.2.3 Special Marketing Authorization Procedure

The special marketing authorization route is only available in extreme cases where the disease is very rare or the clinical endpoint is difficult to measure, and the comprehensive safety and efficacy data required for standard marketing authorization will never be available for scientific or ethical reasons. Applicants need to agree to specific obligations to monitor the continued safety of the product and to notify the competent authorities of any incidents and actions taken related to use. Accumulated clinical data will be reviewed in an annual reassessment process to continuously assess the benefit-risk balance and monitor the achievement and continued relevance of specific obligations required by MAH. Unlike a conditional marketing authorization, a special marketing authorization is unlikely to be converted to a standard marketing authorization pathway.

4.3 Optimization measures

4.3.1 PRIME Plan

In order to enable new medicines to enter the market as soon as possible and facilitate their development and commercialization, the European Union launched the PRIority Medicines (PRIME) designation scheme in 2016, which is the latest regulatory pathway used by the EMA to accelerate the development and approval of new medicines. Drugs are eligible for inclusion in the PRIME program if they have the potential to provide a greater therapeutic advantage over existing treatments, or to benefit patients who have no treatment options.The plan promises early mutual dialogue on development plans and evidence requirements to obtain EMA and producer approval. By participating in the EMA's scientific advice programme, the PRIME programme allows manufacturers to obtain extensive regulatory advice from regulators and other stakeholders (such as the Agency for Health Technology Assessment, the National Institute for Health and Care Excellence, etc.) on trial design, shortening regulatory Review time. In addition, the Innovation Working Group provides a forum for informal dialogue between EMA and ATMP developers early in the drug development process, facilitating enhanced communication.

4.3.2 Joint Proposal Pilot

To facilitate more efficient data collection, understanding data needs, and how best to collect data when data needs differ, since 2010 the European Medicines Agency EMA has established a

partnership with the European Health Technology Assessment Network (HTA) A pilot program for parallel scientific advice, allowing developers to receive advice on new drug development plans from both regulatory agencies and HTAs, helping drug developers understand the different data requirements of different agencies in the drug development process, and get timely feedback to support marketing Authorization and new drug reimbursement decisions. Parallel consultation between regulators, HTA agencies and other relevant stakeholders provides a key platform for discussing important new drug development to pre-plan and maximize efficient, high-quality and needs of stakeholders to facilitate timely access to these medicines. Parallel scientific advice is one of the EU's support tools to promote drug development for the benefit of patients. It helps to promote safe, continuous and timely access to innovative and effective technologies for patients, reduce the duplication of clinical research, data generation and analysis faced by developers, and provide technical support for technology. Provides a seamless transition from development to regulatory and implementation phases.

5. Post-Market Regulation

After the approval of ATMPs, all MAHs are required to continuously monitor the safety and efficacy (benefit-risk balance) of their products. Continue to submit a Periodic Security Update Report (PSUR) that includes the results of the Post-Delegation Obligation study. Post-authorization safety studies (PASS) and post-authorization efficacy studies (PAES) may be required if a benefit-risk balance assessment is performed. PASS is designed to identify, characterize or quantify safety hazards, confirm the safety of pharmaceutical products, or measure the effectiveness of risk management measures. PAES, on the other hand, is a study that is important to supplement existing efficacy data and aims to further evaluate the efficacy of an approved product to obtain more evidence on the long-term efficacy of the product is shown in Figure 2.

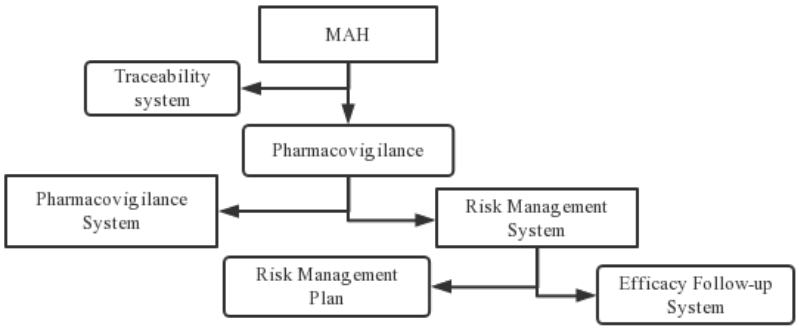

Figure 2: MAH's ATMP Post-Approval Monitoring System

5.1 Pharmacovigilance System

For ATMP, post-approval pharmacovigilance activities for human medicinal products apply to all advanced therapy medicines, and additional pharmacovigilance activities can be introduced to identify, characterize or quantify safety hazards, measure the effectiveness of risk management measures or investigate missing information. Implementation of pharmacovigilance activities requires consideration of: any specific aspects of routine pharmacovigilance, such as specific methodological requirements regarding spontaneous reporting, follow-up reporting, signal detection; active surveillance, especially when ATMP is expected to be When used as a sentinel

"center of excellence"; Use traceability data for surveillance; Describe the follow-up of patients exposed to the product in all ongoing compassionate use and clinical trials, and as a long-term monitoring/post-approval Fundamentals of Safety Research.

5.2 Risk Management System

The EU encourages applicants to seek scientific advice from the European Commission on risk management plans. The risk management system includes risk identification, risk minimization measures and risk minimization effectiveness. Risk identification refers to the comprehensive scientific consideration of identified or potentially important risks and missing important information when developing a risk management plan for a specific ATMP. Risks to consider are generally living donors, patient-specific reactions, drug storage and distribution processes, drug delivery procedures, drug-patient interactions, scaffold-based biomaterials, close contacts, etc. Once risks are identified, steps should be taken to minimize or even eliminate them. Risk minimization measures include routine risk minimization and additional risk minimization. Conventional risk minimization mainly manages risks from product packaging, labeling, specifications and prescriptions. Additional risk minimization is mainly in the following aspects:

The use of the product is limited to fully trained and experienced clinicians, and may also include a controlled distribution system, only for professional (certified) centers.

Specific risk communication. Risk communication is an integral part of the education program, ensuring that patients receive risk communication through patient alert cards, patient ID cards, informed consent forms, etc.; risk guidance to close contacts or potential.

Introduce barriers to prevent errors. Active monitoring of errors such as cross-checks, double patient identification, second opinions, dedicated teams, etc.

Education plan. Train healthcare professionals on procurement, storage, handling, management, clinical follow-up, and environmental risk assessment protection, and educate families and carers, such as signs of significant or potential adverse reactions identified, clinical follow-up procedures etc., and regularly test and assess the knowledge and skills of the target audience.

Finally, the effectiveness of risk minimization is measured through objective indicators (measurement and evaluation systems), such as the introduction of barriers to prevent errors (e.g. product design), active monitoring of errors can be used as indicators of barrier effectiveness; if controlled Distribution, traceability data can be used to assess the true path of a product to a patient.

5.3 Efficacy Follow-Up System

Considering the special nature of ATMP and the characteristics of the disease it is intended to treat, at the end of the pre-approval clinical trial, only limited efficacy data may be available, further research is required in the post-approval phase, and a full efficacy assessment may require years of follow-up. At the same time, the efficacy of many ATMPs is obviously highly dependent on the quality of drug delivery procedures, including patient conditioning, surgery and clinical follow-up, pre-marketing clinical trials and post-marketing medical services, and there may be significant differences in efficacy between different medical institutions. It is only possible to detect and address these issues with a good post-marketing efficacy follow-up system. Therefore, the EU requires ATMP developers to ensure that patients enrolled in clinical trials (starting from Phase I) or compassionate use receive appropriate follow-up to generate long-term safety and efficacy follow-up data, and to consider the use of disease registries or other data sources to collect data for planning purposes. In this regard, there should be appropriate agreements between different parties (e.g. hospitals, registry owners, patients and developers of ATMPs) allowing the legitimate use of patient data collected in clinical trials, for compassionate use or regulation, and signed by the

patient Informed consent. In addition, for efficacy follow-up, established or to-be-established safety follow-up systems should be used wherever possible to conserve resources and increase the motivation of medical professionals.

6. Conclusion

Advanced therapy drugs offer new possibilities for restoring, correcting or modifying physiological functions or making diagnoses. At the same time, due to their novelty, complexity, and technological specificity, they may pose new, unexplored risks to public health and individual patients, and thus require strict regulation. The construction of the regulatory system for ATMPs in China is lagging behind, and the legal framework for this new type of drugs has not yet been established, and a hierarchical and classified management and technical evaluation system has not yet been established. The supervision of EU ATMPs is based on the law. Special committees are set up to perform inspection functions, and they accept the supervision and guidance of the European Commission. It has truly realized the law to abide by, and established a supervision system with special drug management and top-level supervision and guidance. It is worthwhile for China Reference and reference when establishing innovative drug regulatory models.

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