药品附条件批准上市技术指导原则（试行）

二０二０年十一月

appendix

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1. Overview In order

to encourage clinical value-oriented drug innovation and accelerate the development of drugs with outstanding clinical value,

Clinically urgent drugs of clinical value are put on the market. According to the Drug Administration of the People's Republic of China,

"Vaccine Administration Law of the People's Republic of China", "Vaccine Administration Law of the People's Republic of China"

"Traditional Chinese Medicine Law" and "Measures for the Administration of Drug Registration", drawing on international experience and combining our

This guideline is formulated based on national drug review work practices.

The purpose of conditional approval for marketing is to shorten the development time of drug clinical trials.

time, so that it can be used as early as possible for critical diseases or public health measures that cannot wait any longer.

Meet urgently needed patients. Clinical trial data quality supporting conditional marketing approval should

Comply with the requirements and standards of ICH and relevant domestic technical guidelines. Conditional

Approval for marketing does not include defects in the design or execution of clinical trials.

Failure to meet marketing authorization requirements.

Generally, the pharmaceutical, pharmacological and toxicological requirements for conditionally approved marketing drugs are consistent with

The same as conventionally approved marketed drugs; for drugs urgently needed for public health or for emergencies

For major public health emergencies, drugs may be combined with drugs according to specific circumstances.

Evaluate the benefits-risks of the product.

After obtaining conditional approval for marketing, the drug marketing authorization holder must follow

Specific conditions attached to the drug registration certificate for new or continued ongoing

clinical trials, which are usually conducted to confirm expected clinical benefits.

The purpose is confirmatory clinical trials to provide sufficient evidence for routine marketing.

This guideline applies to traditional Chinese medicines and chemicals that are not marketed in China.

Drugs and Biological Products.

2. Conditional approval of listing

(1) During drug clinical trials, drugs that meet the following conditions can be

Application for conditional approval:

1. Treatment of serious life-threatening diseases for which there is no effective treatment, as well as public health

Drugs that are urgently needed for public health. Data from drug clinical trials have shown efficacy and

Can predict its clinical value;

2. Vaccines urgently needed to respond to major public health emergencies or national health

Other vaccines deemed urgently needed by the health committee and where the benefits have been assessed to outweigh the risks.

(2) Related definitions

Conditional approval for marketing refers to drugs that are seriously life-threatening and for which there is no effective treatment.

diseases, urgently needed drugs for public health, and existing clinical research resources.

The material has not yet met all the requirements for regular marketing registration, but clinical trial data are available

Demonstrate curative effect and be able to predict its clinical value. Applicants must fulfill specific requirements.

Based on surrogate endpoints, intermediate clinical endpoints, or early phase clinical trials

approved for marketing based on the data. Vaccines urgently needed to deal with major public health emergencies or

Other vaccines deemed urgently needed by the National Health Commission, based on Phase III clinical trials

After analyzing the data during the trial period, it can also be approved with conditions if the benefits are evaluated to outweigh the risks.

Listed.

A serious life-threatening illness is one that, if not treated early, can take months to

or a disease or a stage of a disease that results in the patient's death within a shorter period of time, e.g.

Advanced malignant tumors, etc.

Drugs that are urgently needed for public health refer to drugs that are urgently needed by the Ministry of Health and Human Services.

According to the needs of national public health, relevant departments such as the Ministry of Public Health and other relevant departments have proposed urgent listing.

of medicines.

Vaccines urgently needed for major public health emergencies refer to vaccines that are urgently needed in accordance with the "Public Emergencies"

"Health Incident Emergency Regulations", "National Public Health Emergency Emergency Plan", etc.

A recognized major public health emergency (Level II) or a particularly major public health emergency

Vaccines are urgently needed to prevent diseases related to public health emergencies (level I).

3. Technical requirements for conditional approval of listing

(1) Drugs approved for marketing with conditions should be able to provide effective treatments,

Specifically, one of the following conditions should be met:

1. Compared with existing treatment methods, it can significantly improve the prognosis of the disease;

2. For patients who are intolerant or ineffective of existing treatments, it can be obtained

Obvious curative effect;

3. Other key drugs or treatments that cannot be combined with existing treatments

The methods are effectively combined and achieve obvious curative effect;

4. The efficacy is equivalent to that of existing treatments, but it can be avoided by avoiding the complications of existing treatments.

Serious adverse reactions, or harmful drug interactions are significantly reduced and significantly improved

patient compliance;

5. Can be used to respond to emerging or anticipated public health needs.

Existing treatments refer to those that have been approved for the treatment of the same disease within the country.

medicines, or standard treatments, etc. Typically, these treatments should be current

standard treatment for the disease. Drugs that are conditionally approved for marketing have clinical benefits

It should not be used as an existing treatment method until proven.

(2) Key points to consider when evaluating effectiveness

The indicators usually used to evaluate drug effectiveness should be clinical endpoints. Clinical end

Point refers to the characteristics or variables that can directly reflect the efficacy of the drug, that is, the effect of the drug on the patient

Sensation (e.g. symptom relief), function (e.g. improvement in mobility, delay or obstruction)

functional decline, etc.) or direct evaluation of the impact on survival.

For drugs that qualify for conditional approval, they can be based on surrogate endpoints, intermediate

Conditional approval for marketing based on clinical endpoints or early clinical trial data. applicant

The selection of surrogate endpoints, intermediate clinical endpoints, or early selection should be fully evaluated and justified.

Correlation and rationality between phase 1 clinical trial data and expected clinical benefits,

and provide corresponding evidence.

1. Surrogate endpoints that are likely to predict clinical benefit

Surrogate endpoints refer to endpoint indicators that indirectly reflect clinical benefit.

For drugs that are in urgent clinical need, it is hoped that surrogate endpoints can be used to quickly evaluate their efficacy.

Surrogate endpoints may be laboratory tests, radiographic imaging, physical signs, or

Other measures, by themselves, do not measure clinical benefit but can predict clinical benefit.

For example, in some cancer types, imaging evidence of tumor shrinkage (response rate)

It is possible to predict improvements in overall survival. clinical benefit based on surrogate endpoints

Predictive ability, which can be an indicator known to reasonably predict clinical benefit

(can be used for routine approval), or are likely to predict clinical benefit (can

for conditional approval).

To assess whether surrogate endpoints can predict clinical benefit and its predictive power, it is necessary to

Based on the biological synthesis of the relationship between the disease, clinical endpoints, and the expected effects of the drug

Reason and evidence or experience to support the relationship. For example, replace the final

The relationship between points and disease etiology, the relationship between surrogate endpoints and clinical endpoints, and their predictions

value, the extent of the epidemiological relationship between surrogate endpoints and disease prognosis,

The extent of the drug's impact on surrogate endpoints versus the extent of the drug's impact on clinical endpoints

consistency, etc.

In pivotal registration clinical trials, it is likely that if prespecified

If the surrogate endpoint indicators of clinical benefit are used to evaluate the efficacy and obtain positive results, the

Apply for conditional approval for listing.

2. Intermediate clinical endpoints that allow early assessment of clinical benefit.

Intermediate clinical endpoints generally refer to outcomes in the treatment of chronic or progressive disease

In the evaluation of clinical benefit, it is generally considered that short-term clinical benefit is likely to predict long-term

clinical benefit. For example, drugs to treat multiple sclerosis are routinely approved

A 2-year clinical efficacy evaluation of the drug is required, while for conditional approval,

The intermediate clinical endpoint can be the 1-year evaluation of drug efficacy.

In pivotal registration clinical trials, if intermediate clinical endpoints are used

The study results can reasonably predict that the drug is likely to have efficacy and clinical benefit

Yes, you can apply for conditional approval for listing.

3. Early clinical trial data

Early clinical trial data usually refers to data before confirmatory clinical trials are carried out

Clinical data obtained. Based on early clinical trial data, it is reasonable to predict that

If the clinical benefit is judged, you can apply for an addendum before completing the confirmatory clinical trial.

Approved for listing.

For urgently needed new traditional Chinese medicines such as major public health emergencies, high-quality

Empirical data on human use of traditional Chinese medicine or summaries of well-designed clinical studies can be considered early stage

Clinical trial data.

In addition, innovative vaccines that are urgently needed for major public health emergencies and other emergencies can be

Consider using interim analysis data from phase III clinical trials to support conditional approval for marketing.

For example, in a phase III clinical trial of a vaccine, it can be carried out according to the protocol design.

1-2 interim analyses, conducted by the Independent Data Monitoring Committee (IDMC)

The data were reviewed, and the results of the interim analysis showed that the trial vaccine was more effective in terms of protection.

outperformed the placebo control group and met pre-set standards, and were able to improve

When it is shown that the benefits outweigh the risks, you can apply for conditional approval of the vaccine for marketing.

(3) Key points of communication regarding conditional approval of listing

Communication with regulatory authorities is very important in the development process of new drugs.

want. During the clinical trial process, the content of communication mainly involves clinical trials

Updates to the protocol, discussion of related issues in clinical trials, etc.

For drugs that meet conditional approval conditions, applicants can

Submit an application for conditional approval during the inspection period. Applicants should support conditional approval

Accurate clinical trial design and clinical trial results and national drug supervision and management

Communicate with the Drug Evaluation Center of the State Council (hereinafter referred to as the Drug Evaluation Center).

1. Before conducting clinical trials to support conditional approval for marketing

Applicants are encouraged to make decisions based on the actual situation of drug development when they are intended to support attached

Before conducting clinical trials for conditional approval for marketing, communicate with the Center for Drug Evaluation

flow to clarify the following issues:

(1) Surrogate endpoint indicators or intermediate clinical endpoints selected in clinical trials

The rationality of the indicators or early clinical trial data and their ability to reasonably predict clinical outcomes

benefit standards;

(2) Design and implementation plan for post-marketing clinical trials.

(3) Other prerequisites for conditional approval, including pharmacy, pharmacology and toxicology

Academic research, etc.

2. Before submitting a listing application

Before applying for conditional marketing approval, the applicant should obtain clinical trial

experimental data, pharmaceutical and pharmacological and toxicological data, and intention to apply for conditional marketing approval.

direction, as well as the design and implementation plan of post-marketing clinical trials and post-marketing risk management

Plan and communicate with the Center for Drug Evaluation. Before communicating, applicants should contact

The Center for Drug Evaluation submits all completed clinical trial results and applies for conditional approval

Reasons and basis for approval, post-marketing clinical trial plan and completion deadline, post-marketing

Risk management plans, etc., if it is deemed that they meet the requirements for conditional approval after communication,

A drug marketing authorization (NDA) application can be submitted; for conditions that do not meet the conditional approval

conditions and requirements, the clinical trial results should be considered to determine whether to continue product research and development.

development and the design of plans for continued clinical trials.

The minutes of the communication meeting will be used as a basis for the conditional approval of the listing application.

An important basis for file review and review. During the review period of the listing application, the applicant

You can still further communicate with the Center for Drug Evaluation on the above content and reach an agreement.

See.

4. Conditions attached to conditional approval of listing

(1) Clarify that the drug is “conditionally approved”

Drugs that are conditionally approved for marketing are listed in the instructions [Indications]/[Functions and Indications]

and [Clinical Trial], indicate that this product is based on surrogate endpoints (or intermediate clinical trials).

clinical endpoints or early clinical trial data) has been conditionally approved for marketing, but has not yet been

Clinical endpoint data have been obtained, and the effectiveness and safety need to be further confirmed after marketing.

The words “Approval for listing with conditions” should be noted under the [Approval Number]. drug labels

The relevant content should be consistent with the instructions.

(2) Post-marketing requirements

In view of the conditional approval of marketing drugs that have not yet met all the requirements for regular marketing registration,

Ministry of Industry and Commerce requirements, therefore the applicant should contact the Center for Drug Evaluation regarding the post-marketing commitments to be completed.

Research and other contents were discussed together and a consensus was reached. It should include at least the following content: Above

Post-market clinical study plan, study completion date, final clinical study report submission

date and post-listing risk management plan, etc. The applicant should commit to completing all the requirements on time.

Some clinical trials.

1. Post-marketing clinical research plan

The post-marketing clinical research plan should include the overall clinical trial plan, the applicant’s

Commit to various clinical trial plans that have been reviewed and approved by the Center for Drug Evaluation. For example, according to

Conditional approval for marketing based on surrogate endpoints and early clinical trial data should be designed

And complete a confirmatory clinical trial with clinical endpoints as the primary endpoints. according to

If the intermediate clinical endpoint is conditionally approved for marketing, confirmatory clinical trials should continue to be completed.

test.

2. Study completion date

Applicants should comprehensively consider the actual clinical research situation, clarify and commit to listing

The date after the study is completed.

3.Clinical study report submission date

Applicants should comprehensively consider the statistical analysis and writing of clinical studies after completion of the clinical study.

clinical research report and other actual conditions, clarify and commit to the expected clinical research report

Delivery date.

4. Post-IPO risk management plan

Drug marketing authorization holders should follow the established post-marketing risk management

Plan to take appropriate risk measures for existing or identified risks and potential risks

Risk management measures are implemented to ensure patient medication safety.

New or continued clinical trials after conditional approval for marketing are still

Need to comply with ICH E6 and "Good Clinical Practice for Drug Clinical Trials" related

Requirements and periodic submission of drug development safety update reports (DSUR),

Until the drug is routinely marketed.

The drug marketing authorization holder shall comply with the special requirements attached to the drug registration certificate.

Establish conditions to complete new or ongoing drug clinical trials within the specified period

After testing, the drug will be submitted to the Center for Drug Evaluation in the form of supplementary application to apply for routine approval for marketing.

7. References

[1] U.S.FOOD And DRUG ADMINISTRATIONÿFDAÿ. Guidance for Industry Expedited Programs for Serious Conditions – Drugs and Biologics.

[2] Beaver JA, Howie LJ, Pelosof L, et al. A 25-Year Experience of US Food and Drug Administration Accelerated Approval of Malignant Hematology and Oncology Drugs and Biologics: A Review. *JAMA Oncol,* 2018, 4(6):849-856.

[3] European Medicines AgencyÿEMAÿ. Guideline on the scientific application and the practical arrangements necessary to implement Commission Regulation (EC) No 507/2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004.