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CMDE Draft for Comment

Companion diagnostic reagents for marketed anti-tumor drugs.

Guidelines for clinical trials

English Translation

Notice on Public Solicitation of "Guidelines for Clinical Trials of Companion Diagnosis Reagents for Marketed Anti-tumor Drugs (Draft for Comment)"

2020-08-13 11:00

Relevant units: In accordance with the relevant requirements of the State Drug Administration's 2020 medical device registration technical guidelines formulation and revision plan, our center organized the drafting of the "Guidelines for Clinical Trials of Companion Diagnostic Reagents for Marketed Anti-tumor Drugs." A draft for soliciting opinions was formed through literature collection, enterprise research, special discussion and expert discussion.

In order to make the guiding principle more scientific, reasonable and practical, we will openly solicit opinions on the Internet today, and sincerely hope that experts, scholars, managers and practitioners in related fields will provide opinions or suggestions to promote the enrichment and improvement of the guiding principles.

Please send your comments or suggestions to our center by e-mail before September 10, 2020.

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Attachment:
1. Guiding Principles for Clinical Trials of Companion Diagnostic Reagents for Anti-tumor Drugs on the Market (Draft for Comments)
2. Feedback Form (Download)

State Drug Administration
Medical Device Evaluation Center
2020 August 13

Companion diagnostic reagents for marketed anti-tumor drugs Guidelines for clinical trials

(Draft for comments)

1 Introduction

Companion diagnostic reagents detect samples collected from cancer patients. The results can provide important information for the safety and effectiveness of anti-cancer drugs used by patients, including: identifying patients who are most likely to benefit from the drug; determining that the drug is related Patients with a greater risk of serious adverse reactions; identify subgroups of the population that have been fully studied for safety and effectiveness. etc. Products for the monitoring of therapeutic drugs and products for the detection of gene polymorphisms of drug metabolism enzymes are not managed as companion diagnostic reagents.

In recent years, with the development of precision medicine, tumor precision treatment drugs and companion diagnostic in vitro diagnostic reagents have been widely used in clinical practice, and related industries have flourished. At present, the registration and application of companion diagnostic reagents is increasing year by year and the situation is more complicated. In terms of product development, some products are jointly developed with related anti-tumor drugs, and some products are developed after the anti-tumor drugs are on the market. In my country, the current situation of developing multiple companion diagnostic reagents for the same anti-tumor drug is particularly prominent. This guideline aims to provide applicants with a clinical evaluation method of companion diagnostic reagents under the premise of fully considering my country's national conditions.

This guideline is a general requirement for the clinical evaluation of companion diagnostic reagents that have been on the market for anti-tumor drugs. Applicants should determine whether the contents are applicable based on the specific characteristics of the product. This document is a guiding document used by applicants and examiners. It does not involve administrative matters such as registration and approval, nor is it enforced as a law. If there are other methods that can meet the requirements of the law, it can also be used, but detailed research should be provided. data. The main points of this review are formulated under the current regulations, standard system and current level of awareness. With the continuous improvement of regulations and standards and the continuous development of science and technology, the relevant content of this document will also be adjusted in due course.

2 Scope of application

Based on the characteristics of companion diagnostic reagents and anti-tumor drugs, the relevant anti-tumor drugs must use companion diagnostic reagents or clinical trial analysis methods (CTA) for subject screening or marker stratification of the enrolled population when conducting drug-related clinical trials. analysis. The following companion diagnostic reagents or clinical trial analysis methods (CTA) used in the clinical trials of antitumor drugs are called "original companion diagnostic reagents". The original companion diagnostic reagents also include the clinical trial analysis method (CTA) used in the clinical trials of the drug during the joint development process of anti-tumor drugs and companion diagnostic reagents. After the drug clinical trial is completed, the bridge test is proved and the clinical trial analysis method (CTA) Equivalent reagent.

The accompanying diagnostic reagents for which anti-tumor drugs have been listed in this guideline refer to the accompanying diagnostic reagents declared by relevant in vitro diagnostic reagent manufacturers to cooperate with the listed anti-tumor drugs after the anti-tumor drugs have been marketed. For the declared product that is not the original companion diagnostic reagent, but a newly developed product (hereinafter referred to as the "newly developed companion diagnostic reagent") by the in vitro diagnostic reagent manufacturer, the following conditions should be met if applicable:

1. In vitro diagnostic reagent products in products The accompanying anti-tumor drug has been clarified in the design and development stage, and this anti-tumor drug should be one or several clear drugs already on the market, not a class of drugs. The name of the concomitant drug should be reflected in the product manual after clinical verification;
2. The biomarkers detected by the in vitro diagnostic reagents (such as the genes and mutation sites detected by the genetic testing product) and the status of the biomarkers to the applicable population The division should be consistent with the original companion diagnostic reagent;
3. The applicable population and applicable sample types of the in vitro diagnostic reagent should be consistent with the original companion diagnostic reagent;
4. The analytical performance of the in vitro diagnostic reagent, especially the analytical sensitivity, should be the same as the original companion diagnostic reagent Comparable.

The newly developed companion diagnostic reagents are different from the original companion diagnostic reagents, such as: detecting more markers, adapting to more sample types, and having higher analytical sensitivity. For the verification of the comparability between newly developed companion diagnostic reagents and original companion diagnostic reagents, refer to this guideline; for the differences between newly developed companion diagnostic reagents and original companion diagnostic reagents, sufficient clinical evidence should be provided to prove that the differences are useful for guiding related drugs For the impact of clinical application. if necessary. clinical trials jointly developed with anti-tumor drugs should be provided to prove the clinical significance of the accompanying diagnosis.

3 Clinical trial requirements

The clinical trials of companion diagnostic reagents consist of two parts, one is the clinical testing accuracy research. and the other is the clinical verification of companion diagnostics. According to whether the companion diagnostic reagent participates in the clinical trials of anti-tumor drugs and the characteristics of the companion diagnostic reagent itself, the verification of its companion diagnostic use can be divided into the following situations:

1. The application reagent is the original companion diagnostic reagent

   If it is the original companion diagnostic reagent, the clinical trial data of the drug can be submitted as the clinical trial data for verification of the companion diagnostic use. This part of the data should be consistent with the final clinical trial data submitted to the drug review department during the marketing of the anti-tumor drug. For details, please refer to the "Guiding Principles of Clinical Trial Technology for Simultaneous Development of Companion Diagnostic Reagents and Antitumor Drugs."

2. The application reagent is a newly developed companion diagnostic reagent

The verification of the companion diagnostic use of the declared reagents may take the methods of consistency comparison with the original companion diagnostic reagents, bridging tests. and observational studies of the efficacy of anti-tumor drugs on the market.

2.1 For the companion diagnostic reagents that have been on the market for anti-tumor drugs, have a wide range of clinical applications, have clear significance, and are easy to standardize in interpretation, if the performance of the declared reagent is comparable to the original companion diagnostic reagent, the clinical significance of the declared product can be verified The method of clinical comparison with the original companion diagnostic reagent is adopted. The list of such biomarkers is shown in Appendix 1. For the biomarkers that the applicant intends to develop that are not included in Appendix 1, the verification method of the clinical significance of the companion diagnosis should be determined after full communication with the regulatory authority.

2.2 for the presence of anti-tumor drugs companion diagnostic products to detect biomarkers in effect a negative selection of biomarkers. For example, the KRAS gene, the approved cetuximab instructions clearly state that the drug should not be used for colorectal cancer patients with mutations in the KRAS gene. For such biomarkers, the verification of the companion diagnostic use of newly developed companion diagnostic reagents can be carried out by clinical comparison with the original companion diagnostic reagents. Clinical trials focus on the consistency of the declared product and the original companion diagnostic reagent.

4 Clinical trial design

1. Verification of clinical testing accuracy

Companion diagnostic reagents shall verify the accuracy of the clinical sample detection of their products before carrying out the verification of the relevant accompanying clinical intended use. It is recommended that applicants carry out clinical trials to verify the accuracy of product clinical sample testing in accordance with the requirements of the Technical Guidelines for Clinical Trials of In Vitro Diagnostic Reagents.

1.1 Clinical trial institutions

Applicants are advised to choose a medical device by less than 3 clinical trials for the record of mechanical clinical institutions to carry out clinical trials. The clinical research unit should have the advantages of pathological diagnosis. molecular biology methods, etc. and the experimental operators should have enough time to be familiar with all aspects of the detection system (instruments, reagents, quality control and operating procedures, etc.), and familiar with the evaluation plan. Throughout the experiment, the assessment reagents and reference methods should be under effective quality control to maximize the accuracy and repeatability of the test data.

1.2 Enrolled population

The enrolled population should be able to represent the various characteristics of the target population of the product, rather than only some typical cases. In principle, prospective collection of samples can better represent the target population. If necessary, under the premise of reasonable control of bias. Can also collect cases retrospectively. For the past samples included in the group, the sample storage conditions should meet the requirements of the application reagents and reference

methods. In terms of tumor type, staging, pre-treatment plan, etc., the population enrolled in the clinical trial should be the population applicable to the companion diagnostic reagent, and the sample type for verification should be the sample type applicable to the companion diagnostic reagent. During clinical trials, the proportion of tumor cells in the sample should also be evaluated. Clinical test pin for each biomarker variant subgroup should be based on design features to determine the set of circumstances surrounding the case, such as PCR-based technique of gene mutation for detection of the product, should the respective mutant gene and the site should have enrolled in a number of cases. The clinical trial should fully explain the rationality of the case enrollment.

1.3 Choice of comparison method

For genetic testing products, it is recommended to use reference methods for comparison to evaluate the detection performance of the application reagents on clinical samples. The reference methods can be first-generation sequencing. mature second-generation sequencing, or clinically recognized genetic testing technologies. The test of the reference method can be completed in a clinical trial institution or entrusted to a qualified third-party institution. If a third-party institution is entrusted to conduct reference method testing, the entrustment agreement between the clinical trial institution and the third-party institution shall be provided. At the same time, the detailed information of the reference method should be provided, such as: the principle of the method, the required reagents and instruments, the performance verification of the reference method, the quality control of the reference method, the popularization data of the typical test chart, etc. The above information should be confirmed by the signature of the clinical trial institution.

For biomarkers for which there is no clinical reference method for testing, such as protein level biomarker testing, etc. clinical trials can also use laboratories used by clinical trial institutions for daily testing, provided that the test results are comparable. Test methods (such as immunohistochemistry). or use approved and marketed similar products as comparison products.

1.4 Clinical evaluation indicators

The clinical evaluation indicators of this type of clinical trial design mainly include the positive coincidence rate, negative coincidence rate, total coincidence rate, Kappa value, etc. of the application reagent compared with the comparison method, and the corresponding 95% confidence interval of each coincidence rate is calculated.

1.5 Estimation of clinical trial sample size

The sample size of clinical trials should meet statistical requirements, and appropriate statistical methods can be used for estimation. Clinical trials of this type of product focus on evaluating the compliance rate of the application reagent and the comparison reagent, so it is recommended to use the single-group target value method sample size formula to estimate the minimum sample size. In the sample size estimation process, the clinical acceptance criteria (P 0) of the evaluation index (negative/positive coincidence rate) should meet the clinical needs.

The sample size estimation process needs to consider the sample rejection rate in clinical trials. Generally speaking, the sample rejection rate should not be higher than 10%.

In addition to the minimum sample size requirements of the above statistical estimation, the clinical trial sample size should also ensure that the included cases cover various characteristics of the subjects; if there is a more reasonable sample size estimation method for the clinical trial research, it is reasonable Can also be used after sex.

1.6 Statistical analysis

Statistical analysis generally summarizes the detection results of the two analysis methods in the form of a four-frame table, and calculates the positive coincidence rate, negative coincidence rate, Kappa value and other indicators and their confidence intervals based on this. In addition, a hypothesis test should also be performed to evaluate the consistency of the two analysis methods.

Clinical trials should also conduct a baseline analysis of the demographic and clinical characteristics of the enrolled population, including age, gender, race, tumor type, stage, mutation status, cytogenetic risk status, disease recurrence type and number, and other disease-related information, etc. Focus on analyzing the proportion of tumor cells in the sample of the subject. covering all biomarker subgroups. and analyzing the collection of samples near the positive judgment value of the contrast reagent. The overall characteristics of the case should meet the requirements for evaluating the consistency of the application reagent and the comparison reagent.

2. Verification of companion diagnostic purposes

Declare the product be a companion diagnostic use verification before, to deal with the declaration of products associated with anticancer drugs and original research companion diagnostic reagents adequately studied, recommended that the product intended to accompany the anticancer drug instructions (Chinese territory listed version), original research companion diagnostic reagent instructions and The relevant clinical trial literature (if any) of anti-tumor drugs shall be attached as the product clinical trial report.

2.1 Comparative study with the original companion diagnostic reagent

For companion diagnostic reagents that are widely used, have clear clinical significance, and are easy to standardize in interpretation, clinical trials can use the method of comparing the test reagents with similar products on the market to evaluate the consistency of the test results of the two products/methods.

2.1.1 Comparison method

Because such products often have many similar products on the market, in order to avoid the phenomenon of sequential transmission in statistics, the original companion diagnostic reagent should be selected for the comparison reagent. The contrast reagent should be comparable to the declared reagent in terms of intended use, applicable population, sample type, and detection performance. For clinical trials, if the clinical trial analysis method (CTA) in the drug clinical trial process is selected as the comparison method, it should be noted that the test site, reagents used, related operations, and interpretation of results during the trial process should be consistent with the comparison method.

Based on the product's own design and the selection of contrast reagents, if this part of the clinical study can prove the accuracy of the application product for

the clinical sample detection of all biomarker variant subgroups, this part of the study can be combined with the clinical accuracy study.

2.1.2 Grouping

The clinical trial protocol should reasonably determine the selection requirements and sample collection methods of clinical trial subjects based on the intended use of the in-vitro diagnostic reagents, target populations, and testing requirements, including: subject entry/exclusion criteria, sample collection Forward-looking and retrospective design, etc. The enrolled population should be able to represent various characteristics of the target population of the product, and should not only enroll some typical cases. In addition to meeting the requirements of 1.2 in this chapter. the included cases should also be included in an appropriate amount of samples near the positive judgment value and evenly distributed on both sides of the positive judgment value.

In this comparative study, whether the enrolled population has used relevant anti-tumor drugs and whether the anti-tumor drugs used are consistent with the drugs intended to be accompanied by the declared product are not required. During clinical trials, the clinical efficacy of drugs will not be statistically analyzed. Therefore. the efficacy of anti-tumor drugs in the population selected for the application will not be evaluated. Correspondingly, the efficacy of the expected use of the declared reagents cannot be directly evaluated through the comparison study results. The clinical trials only verify whether the newly developed companion diagnostic reagents declared are consistent with the original companion diagnostic reagents in the common applicable population.

2.1.3 Evaluation Method

There are many methods in clinical trials to compare the newly developed companion diagnostic reagents with the original companion diagnostic reagents. Two methods are introduced below.

2.1.3.1 Consistency companion diagnostic reagents and original research

When using this method for clinical trials. the selection of clinical trial institutions. clinical evaluation indicators. sample size. and statistical analysis can refer to the related content of clinical accuracy research in Part 1 of this chapter.

Clinical trials should be able to fully assess the consistency of the newly developed companion diagnostic reagents and the original companion diagnostic reagents to screen the drug population. In the design of product clinical trials, more stringent clinical acceptance standards should be formulated.

2.1.3.2 External bioequivalence studies and original research companion diagnostic reagents

The applicant may also consider the performance difference between the application reagent and the original companion diagnostic reagent, and choose other reasonable clinical trial designs, such as "Statistical Methods for Clinical Validation of Follow-On Companion

Diagnostic Devices via an External Concordance Study" (Meijuan Li. Statistics in Biopharmaceutical Research). When applying this method, it should be noted that the determination of the non-inferiority threshold in the statistical analysis process should be able to meet the clinical needs and provide a basis for determining the non-inferiority threshold.

The sample size required by this method should be estimated using a reasonable statistical model, and the sample size should be able to meet the coincidence rate between the application reagent and the original companion diagnostic reagent. It is not inferior to the coincidence rate between the two original companion diagnostic reagents. Requirements.

2.2 Bridging test

During the development and clinical verification of companion diagnostic reagents, if the accompanying anti-tumor drugs have completed clinical verification, the design of a bridge test can be used to prove the safety and effectiveness of the companion diagnostic reagent to be verified. The bridging test is to detect the remaining samples of the enrolled patients in the completed drug clinical trial process through the application reagent, to evaluate the consistency of the application reagent and the companion diagnostic reagent or test method (CTA) used in the drug clinical trial, and then to evaluate the application reagent Determine the therapeutic effect of the subject.

2.2.1 Background information

The basis of bridging trials is the completed clinical trials of anticancer drugs. The principal investigators of clinical trials should fully understand the clinical trials of related drugs before designing bridging trials, and describe the clinical trials of the drugs in the clinical trial data, including but Not limited to the following: ①Name and number of drug clinical trials (if any); ②Clinical trial design type; ③Subject admission criteria and enrollment status; ④Number of clinical trial cases; ⑤Demography and baseline of included cases Analysis of clinical characteristics; ⑥ Biomarker status of the enrolled cases; ⑦ Main curative effect evaluation indicators and selection of clinical trial endpoints; ⑧ Summary of clinical trial statistical analysis; ⑨ Clinical trial conclusions.

2.2.2 Research purpose

The research purpose of bridging test is mainly to prove the clinical performance and clinical significance of companion diagnostic reagents to be evaluated. The study mainly includes two aspects: one is the consistency between the companion diagnostic reagents to be evaluated and the companion diagnostic reagents or CTA test results used in the drug clinical trials; the second is the population and the drug clinical trials of the companion diagnostic reagents to be evaluated The equivalence between the therapeutic effects or other evaluation indicators of the population selected by the accompanying diagnostic reagents or CTA after drug treatment.

2.2.3 Clinical trial institutions

The clinical trial institution of the bridging test is the institution that retains samples during the clinical trial of related drugs. and the clinical trial institution shall meet the requirements of the regulations. During the clinical trial process, the remaining samples of the drug clinical trial and the pharmacodynamic data of related cases should be obtained reasonably and legally.

2.2.4 Study population

The cases of the bridging test are from one or several clinical trials of the accompanying anti-tumor drugs. The investigator should clarify the selection criteria and exclusion criteria of the cases that can be subjected to the bridging test among the enrolled cases of the above clinical trials. The setting of entry and discharge criteria should focus on whether the subject retains sufficient and qualified samples for the testing of companion diagnostic reagents to be evaluated. If the amount of samples available for bridging tests in drug clinical trials is insufficient, especially for the insufficient negative cases in drug clinical trials, part of the case samples of non-pharmaceutical clinical trials can be included in the evaluation of the assessment reagents and the original companion diagnostic reagents or CTA Clinical performance. The entry and discharge standards for this part of supplementary cases should be strictly set, and should be the applicable population of the reagents.

2.2.5 Number of cases

The bridging test is based on a certain drug clinical trial, and all cases in the clinical trial that meet the bridging test entry and exclusion criteria should be included in the group. For patients to participate in clinical trials of drugs, for various reasons are not enrolled to test the bridge number should not be excessive. It is recommended to provide a flow chart of case screening to clarify the source of all the included cases. The number of cases should be able to meet the statistical requirements of the assessment reagents and the companion diagnostic reagents or CTA used in clinical trials of drugs and the statistical requirements for the efficacy of the selected population of the evaluation reagents.

2.2.6 Statistical analysis

The statistical analysis of the bridging test is mainly divided into three aspects: case demographics and baseline clinical characteristics analysis, analysis of the consistency of assessment reagents with approved reagents or CTA, and drug efficacy analysis.

2.2.6.1 case analysis of demographic and clinical characteristics

In the process of clinical trial statistical analysis, the basic characteristics of the population in clinical research should be analyzed, such as age, gender, race, disease status, mutation status, cytogenetic risk status, type and number of disease recurrences, and other disease-related information. The demographic and baseline clinical characteristics of the cases in the bridging trial should be basically the same as those in the drug clinical trial. If cases from

other clinical trials or non-pharmaceutical clinical trials are included in the bridging trial, attention should be paid to the analysis of the demographic and clinical characteristics of the additional cases, which should be consistent with the overall clinical trial.

2.2.6.2 Consistency

The coincidence rate analysis is a retrospective study of the consistency between the status of the markers detected by the reagents to be assessed and the status of the markers detected by the previous original companion diagnostic reagents or CTA. If the clinical trials are included in non-pharmaceutical clinical trials, this part of the cases will be targeted. The analysis is a synchronous consistency study between the reagent to be assessed and the original companion diagnostic reagent or CTA test. It is recommended to use a four-grid table analysis method to analyze the compliance rate to evaluate the positive agreement rate (PPA), negative agreement rate (NPA) and the corresponding 95% confidence interval of the test reagent and the approved reagent or CTA. If clinical trials involve different data sets, such as: full data sets, in line with protocol sets, etc., it is recommended to analyze each data set separately. The compliance rate of the reagents to be assessed and the approved reagents should be able to meet the clinical needs.

2.2 6.3 Antineoplastic efficacy analysis.

Bridging Efficacy analysis is proved to be important evidence of clinical performance evaluation of reagents, such as clinical trial conditions permit, the bridge can be tested course of the experiment subjects were divided into different groups of people, such as markers according to the state division of positive reporting agents & original research reagents positive The population, the reported reagent positive & original reagent negative population, the reported reagent negative & original reagent negative population, the reported reagent negative & original reagent positive population, and the population of main concern should be clarified among all populations. The comparison analysis of drug efficacy is mainly aimed at the drug users detected by the application reagent and the drug users detected by the original research reagent. The evaluation indexes of the bridging test should be determined according to the evaluation endpoints of the relevant drug clinical trials, and the main evaluation indexes and secondary evaluation indexes related to pharmacodynamics should be consistent with the indexes in the drug clinical trials. The method of statistical analysis for the clinical benefits of two different groups of people can be risk analysis methods, such as Cox proportional hazards model, drawing Kaplan-Meier curve, etc.

In some cases, all samples of drug clinical trials cannot be obtained due to objective reasons, such as unreserved samples of drug clinical trials. lack of informed consent, insufficient sample size of test

materials. low sample quality, and the inclusion of some non-pharmaceutical clinical trials in bridging trials Cases and other reasons. The bridging test should consider the impact of missing efficacy data in this part of the case on product evaluation. A reasonable statistical model should be used to analyze the missing data, such as whether the missing data is missing at random or non-random, and whether there is a tendency between the missing data and clinical outcomes Sexual relations, etc., while reasonable imputation of missing data. If the drug clinical trial adopts the enrichment method to enroll the cases, in the bridging test, there is no pharmacodynamic data for the cases with positive test results of the assessment reagents and negative test results of the original companion diagnostic reagents, and sensitivity analysis should be performed on these cases.

The results of drug efficacy analysis should show that there is no significant difference in drug efficacy between the population selected for the application reagent and the population selected for the original companion diagnostic reagent or CTA.

2.2.7 Bias control

Experimental bridge during the study bias should be strictly controlled, the type of the sample cases, the amount of sample, reagent storage conditions should meet the requirements of the assessment, evaluation of clinical trials should be strictly in accordance with the reagents and contrast agents (e.g., directed) described book operation. The testing of assessment reagents should meet the principle of blinding.

2.3. Observational study on the efficacy of anti-tumor drugs on the market

For related anti-tumor drugs and companion diagnostic reagents that have been on the market but have not yet been widely used, and the detection principles, operating procedures and results are more complex, it is recommended to follow the bridging test path. If the bridging test is not feasible, on the basis of completing the accuracy verification, observational studies on the efficacy of marketed anti-tumor drugs can be conducted in no less than 3 clinical trial institutions to prove their clinical significance. The test results of the assessment reagents during the clinical trial should not affect the subjects' normal diagnosis and treatment procedures.

2.3.1 Clinical trial design

The declared reagent and the original companion diagnostic reagent have the same clinical expected use. In clinical trials, the expected population of the original companion diagnostic reagent is the enrolled population. The application reagent and the original companion diagnostic reagent are used to simultaneously detect human samples from the enrolled population, and the original companion diagnostic reagent The test results of the diagnostic reagents provide guidance for patients to use anti-tumor drugs, and at the same time, follow-up and follow-up of patients who use the drugs to obtain drug efficacy. For example, the demographic characteristics of retrospective cases, basic disease characteristics, evaluation indexes and evaluation methods of drug efficacy all meet the requirements of clinical trial

programs, and a certain number of retrospective cases can also be included. After the efficacy data obtained, the original research should analyze the companion diagnostic reagents group population pharmacodynamic data. while reporting biomarker detection reagent Status Packet efficacy of different groups. Clinical trials should also examine the coincidence rate of the application reagents with the baseline test results of the original companion diagnostic reagents. This part of the clinical trial design is different from the parallel control design.

2.3.2 Enrolled population

The enrolled population of the clinical trial should be the applicable population of the original companion diagnostic reagent, and the selection and exclusion criteria of cases should be clarified. The enrolled population of the clinical trial should be as close as possible to the true clinical application of the declared product.

2.3.3 Sample size

Clinical trials should select a reasonable statistical model to calculate the sample size based on the purpose of clinical verification and clinical evaluation indicators. The sample size should meet the requirements of the evaluation of the evaluation reagent and the comparison reagent for the population drug efficacy evaluation. The purpose of clinical evaluation includes the equivalence or non-inferiority of the newly developed companion diagnostic reagent and the original companion diagnostic reagent to screen the population, and the choice of equivalence study or non-inferiority study model based on this. The calculation of sample size should be based on the main efficacy evaluation indicators such as objective response rate, progression-free survival and overall survival.

Based on the complexity of the biomarkers, the test results of the application reagent and the original companion diagnostic reagent will be different. An appropriate sample size should be included to meet the more scientific evaluation of the test reagent and the original companion diagnostic reagent. The requirements for efficacies.

2.3.4 Statistical analysis

The statistical analysis of clinical trials is mainly divided into three aspects: case demography and baseline clinical characteristics analysis, analysis of the coincidence rate of assessment reagents and approved reagents, and drug efficacy analysis.

2.3.4.1 Case analysis of demographic and clinical characteristics.4.1

In the process of clinical trial statistical analysis, the basic characteristics of the population in the baseline clinical study should be analyzed, such as age, gender, race, disease status, mutation status, cytogenetic risk status, type and number of disease recurrence, and other disease-related information. The demographic and baseline clinical characteristics of the clinical trial cases should be basically consistent with the actual clinical application of the product.

2.3.4.2 coincidence analysis

The conformance rate analysis is a study of the consistency between the status of the test markers of the reagents to be assessed and the status of the past approved products. It is recommended to use a four-grid table analysis method to analyze the compliance rate to evaluate the positive agreement rate (PPA), negative agreement rate (NPA) and the corresponding 95% confidence interval of the test reagent and the approved reagent. The conformity rate of the reagents to be assessed and the approved reagents should be able to meet the clinical needs.

2.3.4.3 Drug efficacy analysis

Drug efficacy analysis is an important evidence to prove the clinical efficacy of the reagents to be assessed. If the clinical trial conditions permit, the subjects in the trial process can be divided into different populations, such as dividing the reported reagent positive & original reagent positive population according to the status of the marker, and the application People with positive reagents & negative for original research reagents, people with negative application reagents & negative reagents from original research reagents, people negative for application reagents & positive reagents from original research reagents, etc., among all the populations, the population of main concern should be clarified. Analyze the relationship between the efficacy of anti-tumor drugs in the population selected by the original companion diagnostic reagent and the efficacy of the newly developed companion diagnostic reagent in the population selected for each group of population. Evaluation indicators should be determined based on the efficacy indicators of relevant anti-tumor drugs. Primary evaluation indicators and secondary evaluation indicators should be set, and acceptable clinical evaluation indicators should be used as the evaluation endpoints. such as ORR (objective response rate), PFS (progression-free survival)), CR (Complete Response Rate), PR (Partial Response Rate), DoR (Duration of Response), DCR (Disease Control Rate). OS (Overall Survival), etc. The method of statistical analysis for the clinical benefit of two different groups of people can be risk analysis, such as Cox proportional hazard model, drawing Kaplan-Meier curve, etc.

The results of drug efficacy analysis should show that there is no significant difference in drug efficacy between the population selected for the application reagent and the population selected for the original companion diagnostic reagent.

2.3.5 Bias control

In clinical trials, bias should be strictly controlled during the research process, and the sample type, sample size, and storage conditions of the case should meet the requirements of the assessment reagent. The clinical trial process should clarify the enrollment form of cases (such as continuous enrollment, etc.), and the enrollment of cases should be carried out in strict

accordance with the criteria for case enrollment, and any declared products caused by artificial selection of cases are consistent with the baseline test results of the original companion diagnostic reagents If the rate is too high or too low, it will cause bias in clinical trials. Clinical trials should be performed in strict accordance with the instructions of the assessment reagents and comparison reagents (if involved). The testing of assessment reagents should meet the principle of blinding.

5 Other

1. About the intended use and limitations of the product

   With the advancement of detection technology, more and more new detection technologies are applied to the detection of companion diagnostic-related biomarkers. In the product declaration process, more subgroups of biomarkers can be detected, and products with higher analytical sensitivity continue to appear. The intended use of such products should be determined based on the clinical research of the product.

   For people who can detect more subgroups of biomarkers, the instructions should specify the subgroups of markers and corresponding anti-tumor drugs that have been verified for use in companion diagnostics, and for other subgroups of other markers, if sufficient clinical testing has been carried out the accuracy of the study, and the relevant state marker in the relevant guidelines, such as expert consensus document has made it clear a diagnosis, in can be clearly in the description of the part of the part of the population through clinical detection accuracy, but not for guidance related to the use of anticancer drugs. If the declared product is a human EGFR gene detection kit, the declared gene mutation sites include the deletion of exon 19 (19del), the L858R mutation of exon 21. and the G719A, G719C, and G719D mutations of exon 18. On the basis of completing the verification of the accuracy of all detection sites, its clinical trials only conducted verification with gefitinib for the two sites of 19del and L858R. The instructions should make it clear that the 19del and L858R mutations can be used to guide the medication of gefitinib, and the G719A, G719C, and G719D mutations have only been verified for accuracy and are not used to guide the medication of gefitinib.

   The declaration of product analysis sensitivity was significantly higher than the original research companion diagnostic reagents, the declaration of the product should be based on. with reference to the accompanying diagnostic use originator companion diagnostic reagents positive determination value to determine a reasonable used in cases guidance medication positive determination value, while the companion diagnostic use In the verification process, the positive judgment value consistent with the original companion diagnostic reagent was used for research to prove the equivalence of the clinical application of the two. For reporting product more high sensitivity should provide relevant clinical evidence, such as the application asks failed to provide evidence, it should be made clear in the product specification, below the product positive value judgment to guide treatment for patients of test results are not used for medication guide.

2. Changes

   2.1 For changes to an already been approved companion diagnostic reagents such as increasing the already approved similar anticancer drugs (such as: are TKI drugs), clinical evidence may be submitted in accordance with appropriate clinical

evaluation methods to specific conditions above, the specific clinical trial requirements and applicable Participation The above section.

2.2 If the accompanying changes in the population in which anti-tumor drugs are applied, such as those involving parts of the accompanying diagnostic reagents, such as changes in the positive judgement, the registrant accompanying the diagnostic reagents shall apply for a change in licensing matters to maintain consistency with the accompanying anti-tumor drug specifications.

3. Multi-gene detection companion diagnostic reagents

The newly developed companion diagnostic reagent may have a product that can detect multiple gene mutations, thereby guiding the use of multiple anti-tumor drugs. Especially with the development of more and more companion diagnostic reagents based on high-throughput sequencing technology, the companion diagnostic products for multi-gene detection should include at least genes and variant sites with clear diagnostic significance, and such genes and sites are all The above appropriate evaluation path should be selected to provide accompanying evidence. For other sites, in addition to the accuracy study during the clinical evaluation process, the basis for including the site in the detection range should also be clarified. This basis includes approved overseas similar products, anti-tumor drugs and companion diagnostics that have been carried out at home and abroad Clinical trials of reagents jointly developed, relevant diagnosis and treatment guidelines, etc.

4. Regarding the accompanying anti-tumor drugs that have been listed in China

The domestically marketed anti-tumor drug mentioned in this guideline means that the drug has been approved in China for the indications declared for the companion diagnostic reagent.

Appendix 1

The biomarkers that can be compared with the original companion diagnostic reagents can be selected.

Based on the current understanding and the development and clinical application of related products in China, the list of accompanying diagnostic biomarkers with clinical applications has been listed, clinically widely used, meaningful, easy to standardize and clinically applied for many years is shown in Table 1.

This list will be updated as scientific awareness deepens and clinical applications of related products progress.

Table 1. List of relevant biomarkers

Cancer	Biomarker detection
Lung cancer	Epidermal growth factor receptor gene (EGFR gene) mutations, including deletion of exon 19 (19del), mutation of exon 21 (L858R), mutation of exon 20 (T790M); abnormal expression of EGFR protein (usually by immunohistochemistry) Method detection).
	Anaplastic lymphoma kinase gene (ALK gene) fusion mutation; ALK gene fusion protein expression (usually detected by immunohistochemistry).
	Fusion mutation of ROS1 gene.
Breast cancer	Human epidermal growth factor receptor-2 gene (Her2) amplification; Her2 gene protein expression detection (usually detected by immunohistochemistry).
Melanoma	BRAF gene mutations, including the V600E mutation in exon 15.
Blood system tumors	Platelet-derived growth factor receptor alpha polypeptide gene (PDGFR gene) mutations, including chromosome 5q31-33 rearrangements.
Nasopharyngeal carcinoma	Abnormal expression of epidermal growth factor receptor (EGFR) protein (usually detected by immunohistochemistry).