Key Points of Review for New Drug Registration

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Introduction

To respond to the development of Taiwan's pharmaceutical and biotechnology industry, to enhance the transparency of the Administration's review, and to serve as a reference and basis for pharmaceutical companies' preparation of technical information, key points of review for various kinds of new drugs have been formulated. These key points of review are formulated in consideration of the current review regime, and may be updated in the future to follow the progress of regulations and science. For purposes of compatibility with international laws and regulations, the key points of review are formulated primarily based on international and domestic laws and regulations. The key points of review do not cover the content of submissions for registration. Submissions shall still follow the Regulations for Registration of Medicinal Products and the announcements of the competent central health authority.

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A. Key points of review for new drugs/biological drugs with new ingredients

I. CMC

(i) Chemical drugs

1. Active Pharmaceutical Ingredient (API)

Are the source and control of materials, process, controls, process validation, characteristics and structural identification, specifications, batch analysis, Validation of Analytical Procedures, rationale for specification, container closure system and stability of the API sufficient to support the quality and consistency of the API?

2. Are the source and controls for the excipient in the preparation portion, process of the finished product, control, process validation, specification, batch analysis, Validation of Analytical Procedures, rationale for specification, container closure system, and stability sufficient to support the quality and consistency of the drug? Are the design, data and/or statistical analysis data of the drug stability testing sufficient to support the shelf life?

(ii) Bio-pharmaceuticals:

1. API

(1) Source of origin (genetic engineering: cell bank system; vaccines: batch (and cell bank) system(s); plasma preparations: plasma raw materials) and control, source and control of raw materials, process and control, process validation (including validation of virus removal/inactivation), characteristic analysis, release specification, rationale for specification, Analytical Procedures and validation of method, batch analysis, container closure system, and stability testing.

(2) Safety control of materials from biological sources

(3) If there are significant changes during the manufacturing process development phase, corresponding comparative tests must be performed, including batch analysis, characteristic analysis and acceleration/pressure tests.

2. Preparation

(1) Source and control of excipients, drug composition, process and control, process validation, specification of finished product, rationale for specification, Analytical Procedures and validation of method, batch analysis, container closure systems, and stability testing.

(2) Safety control of materials from biological sources

(3) If there are significant changes during the manufacturing process development phase, corresponding comparative tests must be performed, including batch analysis, characteristic analysis and acceleration/pressure tests.

II. Drug toxicology

(i) Chemical drugs

1. Are the non-clinical pharmacological test items and results sufficient to support the efficacy validation?
2. Have non-clinical safety tests (safety pharmacological testing, pharmacokinetic testing, and toxicological testing) been performed on suitable animal species? Is the pivotal safety test compliant with the GLP? Are the non-clinical safety test items and results sufficient to explain safety concerns for the drug?
3. Are the non-clinical efficacy and overall safety assessment sufficient to support the efficacy validation of the drugs for its indications, and to

provide clinically appropriate safety assessment information?

(ii) Bio-pharmaceuticals:

1. Are the non-clinical pharmacological test items and results sufficient to support the efficacy validation?

2. Have non-clinical safety tests (safety pharmacological testing, pharmacokinetic testing, and toxicological testing) been performed on suitable animal species? Is the pivotal safety test compliant with the GLP? Are the non-clinical safety test items and results sufficient to illustrate the safety concerns of the drug?

   (1) Safety pharmacological testing can be combined with general toxicological testing and evaluated together.

   (2) Assessment on immunogenicity is required.

   (3) It is generally acceptable to not perform a genotoxicity test unless there are special considerations.

   (4) A standard carcinogenicity test is usually not appropriate. However, methods to assess the carcinogenic risks of this type of drugs shall be designed based on the drugs' characteristics.

3. Are the non-clinical efficacy and overall safety assessment sufficient to support the efficacy validation of the drugs for its indications, and to provide clinically appropriate safety assessment information?

III. Pharmacokinetics/pharmacodynamics

(i) Is there sufficient data to clarify its absorption, distribution, metabolism and excretion characteristics?

(ii) Is there corresponding linkage data when the product-to-be-marketed in Taiwan and the clinical trial drug are different and when they involve primary or secondary changes?

(iii) Are pharmacodynamic information and the relationship between pharmacokinetics and pharmacodynamics provided?

(iv) Are special populations evaluated and are appropriate recommendations given?

(v) Are drug interactions fully evaluated and are appropriate recommendations given?

(vi) Has the bridging study evaluation (BSE) been waived, and are there racial disparities in the pharmacokinetics and pharmacodynamics of the claimed indications, usage and dosage?

IV. Clinical and statistical aspects

(i) Clinical:

1. Is the clinical data submitted sufficient to support the efficacy of the stated indications, usage and dosage?
2. Is the clinical data submitted sufficient to support the safety of the stated indications, usage and dosage?
3. If the drug is a long-term drug, is there sufficient information to support the efficacy and safety of long-term use?
4. The rationale for the usage and dosage recommended by the manufacturer.
5. Is there a post-marketing periodic safety update report?
6. Has the bridging study evaluation been waived, and are there racial disparities in the safety and efficacy of the stated indications, usage and dosage?
7. If there are other approved therapies for the indications, are there any comparisons with such other therapies?
8. Is a post-marketing study required?

9. Is a risk management plan required?

10. Benefit-risk assessment

(ii) Statistical

1. Is there an appropriate pivotal test for the stated indications, usage and dosage?

2. Are the design and statistical method of the pivotal test appropriate?

3. Do the results of the pivotal test support the efficacy of the stated indications, usage and dosage?

4. Does the overall evidence of efficacy support the efficacy of the stated indications, usage and dosage?

V. General considerations

Is the manufacturer's provided draft Chinese package insert appropriate?

B. Key points of review for new drugs with new efficacy

I. CMC

Are there discrepancies with the CMC technical data of already-marketed drugs? If there are discrepancies, the key points of review for the API and preparation are the same as those of the new drugs with new ingredients.

II. Drug toxicology

(i) Based on the new indications applied for, evaluate whether the pharmacological test data provided is sufficient to support the evidence of the new efficacy. Where there are insufficiencies, new pharmacological test or other supporting data must be submitted to support the stated new efficacy.

(ii) If the usage or dosage of the new efficacy exceeds the scope originally approved, the existing non-clinical and clinical data must be evaluated to see if it is sufficient to support the new usage or dosage; otherwise, additional safety data must be provided for evaluation.

III. Pharmacokinetics/pharmacodynamics

(i) The pharmacokinetic characteristics of the patient population for the new indications, including blood concentration and exposure, shall be evaluated on a case-by-case basis.

(ii) Is there sufficient pharmacokinetic/pharmacodynamic data to clarify the rationale for the new usage and dosage?

(iii) Are evaluations performed regarding special populations, drug interactions and food effects, and are proper recommendations given?

IV. Clinical and statistical aspects

(i) Is the clinical data submitted sufficient to support the efficacy of the stated new indications, usage and dosage?

(ii) Is the clinical data submitted sufficient to support the safety of the stated new indications, usage and dosage?

(iii) If the drug is a long-term drug, is there sufficient information to support the efficacy and safety of long-term use?

(iv) The rationale for the usage and dosage recommended by the manufacturer.

(v) Is there a post-marketing Periodic Safety Update Report?

(vi) Is there racial disparity in the efficacy and safety of the stated new indications, usage and dosage?

(vii) If there are other approved therapies for the new indications, are there any comparisons with other therapies?

(viii) Benefit-risk assessment

V. General considerations

Is the manufacturer's provided draft Chinese package insert appropriate?

C. Key points of review for new compound drugs

I. CMC

(i) API

Are the API specification, batch analysis and Analytical Procedures sufficient to support the quality and consistency of the API? If submission of technical data is required for the API, the key points of review of the API are the same as those for the new drugs with new ingredients.

(ii) Preparations

1. Compatibility between APIs, and between excipients and APIs, must be evaluated.

2. Are the source and controls of excipients, processes for finished products, control, process validation, and specifications for finished product, Batch Analyses, Validation of Analytical Procedures, rationale for specification and Container Closure System sufficient to support the quality and consistency of the drug? Are the design, data and/or statistical analysis data of the drug stability testing sufficient to support the shelf life?

II. Drug toxicology

(i) If all ingredients of the new compound have been approved for marketing but have not been used together clinically, the pharmacodynamics, pharmacokinetics, toxicology and chemical interactions between each of the ingredients (prescribed preparation) and the up to 90 day report on the additional compound bridging toxicity study must be evaluated to see if they are sufficient to support the safety and efficacy of the drug.

(ii) If all ingredients of the new compound have been approved for

marketing, but (1) each ingredient (prescribed preparation) in the compound has similar toxic effects on the organs or mechanisms;

(2) any ingredient (prescribed preparation) causes severe or undetectable toxicity under near-clinical exposure conditions in human or animal experiments; or (3) interactions between ingredients (prescribed preparations) results in safety concerns, an up to 90 day repeated dose toxicity study and/or phase II embryo-fetal development test for the compound shall be evaluated to see if they are sufficient to support the safety of the drug.

(iii) If all ingredients of the new compound have been approved for marketing and they are commonly used together in a clinical setting, there are no safety concerns regarding the interactions between the ingredients (prescribed preparations), and the indications and approved dosage are similar to those of the new compound drug, the additional non-clinical trial and bridging repeated dose toxicity study for the new compound can be waived.

III. Pharmacokinetics/pharmacodynamics

If all ingredients have been approved for marketing and the clinical efficacy and safety data of the prescribed preparations are to be given continued applicability,

(i) the drug interactions between individual prescribed preparations shall be evaluated.

(ii) Are special populations evaluated and are appropriate recommendations given?

(iii) Have drug interaction and food effects been evaluated for the new compound product, and have appropriate recommendations been provided?

(iv) Evaluate the bioequivalence report between the new compound product and the individual prescribed preparations.

IV. Clinical and statistical aspects

(i) Is the pivotal test report of the new compound sufficient to support the efficacy and safety?

(ii) What are the clinical contributions of the individual prescribed preparations? Does the design of the pivotal test present the contributions of the individual prescribed preparations?

(iii) If each prescribed preparation is approved and can be used alone, is there sufficient data to support the superior efficacy of the new compound over the individual prescribed preparations?

(iv) If each prescribed preparation has been approved and can be used individually, does the new compound have clinical and public health value in addition to improved drug compliance, especially when the individual prescribed preparations were originally approved for different indications?

(v) If one of the prescribed preparation cannot be used alone clinically and the purpose of such a prescribed preparation is to improve the medical efficacy of another active ingredient (e.g., increase absorption, decrease drug resistance), is sufficient data provided to support the efficacy and safety of the new compound?

(vi) If the new compound has different doses, has the pivotal test covered all doses?

(vii) If the drug is a long-term drug, is there sufficient information to support the efficacy and safety of long-term use?

(viii) Are the stated indications compliant with medical practice (e.g., first-line or later-line therapy)?

(ix) Is there any doubt about ethnic differences?

(x) Benefit-risk assessment

V. General considerations

Is the manufacturer's provided draft Chinese package insert appropriate?

D. Key points of review for new drugs with new routes of administration

I. CMC

(i) API

1. Overall consideration shall be given to the physical and chemical properties of API relevant to drugs with new routes of administration. For example:

(1) If the crystal form of the API affects the bioavailability of the drug having a new route of administration, it must be controlled.

(2) If the particle size distribution of the API is the key quality attribute of the drug having a new route of administration, it must be controlled.

2. Are the API specification, batch analysis and Analytical Procedures sufficient to support the quality and consistency of the API? If submission of technical data is required for the API, the key points of review of the API are the same as those of the new drugs with new ingredients.

(ii) Preparations

1. Overall consideration shall be given to characteristics that may affect the quality and safety of the drug having a new route of administration. For example:

(1) If the drug having a new route of administration is an injection, particles, sterility and endotoxin tests must be controlled.

(2) If the drug having a new route of administration relaxes the impurity specifications, the basis for the specifications' rationale shall be provided.

2. The selection of excipients, formula development, Manufacturing Process Development, Container Closure Systems, and microbiological properties of the drug having a new route of administration must be

understood in order to evaluate the appropriateness of in-process controls and finished product controls.

3. Are the source and controls for excipients, processes for finished products, controls, process validation, specifications, Batch Analyses, Validation of Analytical Procedures, rationale for specification and Container Closure System sufficient to support the quality and consistency of the drug? Are the design, data and/or statistical analysis data of the drug stability testing sufficient to support the shelf life?

II. Drug toxicology

Is the non-clinical safety data sufficient to support the use of the drug having a new route of administration, and does it reflect the intervals and duration of expected use? If the applicant can provide scientific information for drugs with the same composition to support the systemic exposure of the drug having a new route of administration, the information provided will be evaluated for citation and for level of support. This will help to determine whether a partial bridging test is required, or that only the safety of the local tissues where the drug is administered needs to be evaluated.

III. Pharmacokinetics/pharmacodynamics

(i) The bioavailability test of the new drug having a new route of administration shall be tested at the maximum usage and dosage.

(ii) If the route of administration is changed from intravascular to extravascular, the metabolism related to absorption, drug interaction, food effects and special ethnic groups must be reassessed, and proper recommendations shall be given.

(iii) If the route of administration is changed from extravascular administration to intravascular administration, the sufficiency of the in vivo linear pharmacokinetic properties, absorption, distribution,

metabolism, excretion data, drug interactions, special ethnic groups and other pharmacokinetic information must be checked, and proper recommendations shall be given.

(iv) If the bioavailability of the new route of administration is higher than the original route of administration, it is necessary to evaluate whether there is a need to conduct trials on drug interaction that cover the exposure of the new route of administration and special populations.

(v) Is there sufficient pharmacokinetic/pharmacodynamic data to clarify the rationale for dosage?

IV. Clinical and statistical aspects

(i) Is the pivotal test report of the new route of administration sufficient to support the efficacy and safety?

(ii) Compared with the route of administration originally approved, is the new route of administration attended by new safety issues?

(iii) Compared with the dosage for the route of administration originally approved, is the dosage selected for the new route of administration reasonable given reference to pharmacokinetic data?

(vi) Are there any concerns regarding ethnic differences?

(v) Benefit-risk assessment

V. General considerations

Is the manufacturer's provided draft Chinese package insert appropriate?

E. Key points of review for new drugs with new dosage forms

I. CMC

(i) API

Are the API specification, batch analysis and Analytical Procedures sufficient to support the quality and consistency of the API? If submission of technical data is required for the API, the key points of review of the API are the same as those for the new drugs with new ingredients.

(ii) Preparations

1. The selection of excipients, formula development, Manufacturing Process Development, the Container Closure System, and microbiological properties of the drug having a new dosage form must be understood in order to evaluate the appropriateness of in-process controls and finished product controls.
2. Are source and control of excipients, processes for finished products, control, process validation, specifications, Batch Analyses, Validation of Analytical Procedures, rationale for specification and Container Closure System sufficient to support the quality and consistency of the drug? Are the design, data and/or statistical analysis data for the drug stability testing sufficient to support the shelf life?

II. Drug toxicology

(i) Immediate-release dosage form

1. Proper pharmacokinetic evaluation is recommended to compare the maximum blood concentration (Cmax), area under the blood drug concentration/time curve (AUC), and shape of blood drug concentration/time curve for the new dosage form and the approved dosage form, to serve as a basis for whether there is a need for

additional preclinical trials. If the exposure of the new dosage form is significantly different, or the safety information of the approved dosage form is insufficient to support the exposure of the new dosage form, it may be necessary to evaluate whether the altered drug exposure supports the stated efficacy, and to conduct additional non-clinical safety tests.

2. Compared with the approved dosage form, if new impurities are formed or new excipients are used in the chemical production and control process of the new dosage form, additional non-clinical safety tests may be required.
3. If the usage of the new dosage form is significantly different from the approved dosage form, additional non-clinical data may be required to prove its efficacy and safety.

(ii) Controlled release dosage forms

1. Proper pharmacokinetic evaluation is recommended to compare the maximum blood concentration (Cmax), area under the blood drug concentration/time curve (AUC), and shape of blood drug concentration/time curve for the new dosage form and the approved dosage form, to serve as a basis for whether there is a need for additional preclinical trials. If the exposure of the new dosage form is significantly different, or the safety information of the approved dosage form is insufficient to support the exposure of the new dosage form, it may be necessary to evaluate whether the altered drug exposure supports the stated efficacy, and to conduct additional non-clinical safety tests.
2. Compared with the approved dosage form, if new impurities are formed or new excipients are used in the chemical production and control process of the new dosage form, additional non-clinical safety tests may be required.
3. If the usage of the new dosage form is significantly different from the approved dosage form, additional non-clinical data may be required to prove its efficacy and safety.

(iii) Nano-dosage form

1. Nanoparticles in the drug may penetrate physiological barriers, resulting in toxicity different from that of the originally approved dosage form. Therefore, a drug in nano-dosage form is considered to be a new drug, and proper safety tests shall be carried out on the representative nano-products.

Assessment priority shall be given to the organs/systems that may be penetrated. Potential target organs/systems include the liver and organs containing reticuloendothelial tissues; the kidneys; central nervous system; reproductive organs; cardiovascular system; etc.

2. The structure and properties of nanoparticles can have an impact on the immune system. Therefore, proper assessment regarding potential immunotoxicity is recommended for products in nano-dosage form.
3. Nanoparticles may aggregate into agglomerates that affect various organs in the body. In particular, they may induce thrombus formation in small blood vessels. This type of risk must be evaluated through appropriate techniques (e.g., histological techniques).
4. Nanoparticles can directly or indirectly induce severe irritation and inflammation, so the topical effects of nano-products (e.g., skin and eye irritation; lung inflammation; hemolysis) shall be evaluated in accordance with the route of administration.

5. Due to the special physicochemical properties of nanoparticles, their genotoxicity is quite unpredictable. Therefore, proper assessment on genotoxicity must be performed for nano-products. 6. Nanoparticles may cross the umbilical placental barrier, so embryo toxicity and teratogenic risks must still be assessed for nanoform products.

7. Due to the special nature of nanomedicines, additional safety assessment requirements will apply depending on drug type.

III. Pharmacokinetics/pharmacodynamics

(i) In principle, a bioequivalence (BE) test report or bioavailability (BA) test report must be provided.

(ii) Have food effects, special populations and drug interactions been re-evaluated, and are proper recommendations given?

IV. Clinical and statistical aspects

(i) Immediate-release dosage form

1. In principle, the BE test report for the new dosage form and the originally approved dosage form must be submitted. This is usually applicable when both the new dosage form and the originally approved dosage form are of the immediate-release dosage form. If the new dosage form and the originally approved dosage form cannot achieve bioequivalence (e.g., if the new dosage form is of the immediate-release dosage form and the originally approved dosage form are of the controlled release dosage form; or both the new dosage form and the originally approved dosage form are of the immediate-release dosage form but the bioequivalence is not achieved), a pivotal test report for the new dosage form shall be submitted.

2. If the originally approved dosage form is applicable to more than one indication, and the new dosage form and the originally approved

dosage form cannot achieve bioequivalence, in principle, individual pivotal test reports shall be submitted for all stated indications of the dosage form product, to support its efficacy and safety.

3. Is a risk management plan required?

4. Benefit-risk assessment

(ii) Controlled release dosage forms

1. In principle, the BE test report for the new dosage form and the originally approved dosage form must be submitted. This is usually applicable when both the new dosage form and the originally approved dosage form are of the controlled release dosage form. If the new dosage form and the originally approved dosage form cannot achieve bioequivalence (e.g., if the new dosage form is of the controlled release dosage form and the originally approved dosage form is of the immediate-release dosage form; or both the new dosage form and the originally approved dosage form are of the controlled release dosage form but bioequivalence is not achieved), a pivotal test report for the new dosage form shall be submitted.
2. If the originally approved dosage form is applicable to more than one indication, and the new dosage form and the originally approved dosage form cannot achieve bioequivalence, in principle, individual pivotal test reports shall be submitted for all stated indications of the dosage form, to support its efficacy and safety.
3. Special attention shall be paid to the description of the usage and dosage in the package insert when designing controlled release dosage form products; these must be able to be adjusted for dosage and meet special population requirements.
4. Is a risk management plan required?
5. Benefit-risk assessment

(iii) Nano-dosage form

1. A pivotal test report shall be submitted for the new nano-dosage form. Refer to new drugs having new ingredients for the key points of review.
2. Safety is the point of review for nanomedicines, and at present, review is discussed on a case-by-case basis.
3. Is a post-marketing study required?
4. Is a risk management plan required?
5. Benefit-risk assessment

V. General considerations

Is the manufacturer's provided draft Chinese package insert appropriate?

F. Key points of review for new drugs with new doses/new unit content

I. CMC

(i) API

1. The specifications for drugs with new doses/new unit content and the specifications of the API for the approved drug shall be evaluated.
2. Are the API specification, batch analysis and Analytical Procedures sufficient to support the quality and consistency of the API? If submission of technical data is required for the API, the key points of review of the API are the same as those for the new drugs with new ingredients.

(ii) Preparations

1. When a drug having the new dose/new unit content is the result of adjusted API proportions or is proportional to the formula of the drug originally approved, the drug originally approved can be used as a reference for comparison.
2. If the maximum daily dose of the API is increased, the impurity specification of the finished product shall be evaluated. When specification of the impurity exceeds the qualification thresholds, safety data shall be provided for the evaluation of the rationale for the specification.
3. When the same Analytical Procedures is applied to the drug having multiple new doses/new unit content, the applicability of the Analytical Procedures and Validation of Analytical Procedures shall be evaluated.
4. Are the source and control of excipients, processes for finished products, control, process validation, specifications, Batch Analyses, Validation of Analytical Procedures, rationale for specification and Container Closure System sufficient to support the quality and consistency of the drug? Are

the design, data and/or statistical analysis data of the drug stability testing sufficient to support the shelf life?

II. Drug toxicology

The non-clinical efficacy and safety data of the approved drug shall be provided as a reference for assessment.

(i) With regard to pharmacology, proof of validity must be provided, including pharmacological test results for the drug, or the relevance to the dose and efficacy of the marketed drug established in accordance with pharmacokinetics.

(ii) With regard to toxicology, check whether the non-clinical safety data of the marketed drug is sufficient to support the clinical exposure safety of the drug having the new dose or new unit content. If it is insufficient, additional assessment or non-clinical safety tests are required regarding the insufficiency.

III. Pharmacokinetics/pharmacodynamics

(i) New dose

1. The bioavailability (BA) test report for the maximum usage and dose shall be provided.
2. If the amount of in vivo exposure for the new dose is higher than that for the previously approved product, re-assessment shall be conducted to determine whether tests on drug interaction, food effects and special populations are required.
3. Is there sufficient pharmacokinetic/pharmacodynamic data to clarify the rationale for new dose?

(ii) New unit content

In principle, a bioequivalence (BE) test report or bioavailability (BA) test report must be provided.

IV. Clinical and statistical aspects

(i) New dose

1. A pivotal report for the new dose shall be submitted.

2. For general cases it is rare to change only the dose, and thus the following shall be considered:

(1) What is the purpose of the dose increase or decrease, or usage change?

(2) The design and quality requirements of the pivotal test shall follow those of the new drug with new ingredients.

3. Benefit-risk assessment

(ii) New unit content

1. The indications, usage and dosage must be the same as those of the approved drug.

2. In principle, the bioequivalence (BE) test report of the new unit content and the original unit content shall be submitted. If bioequivalence cannot be achieved, the bioavailability test report and pivotal test report (BA+clinical) shall be submitted for the new unit content.

3. Benefit-risk assessment

V. General considerations

Is the manufacturer's provided draft Chinese package insert appropriate?

G. Key points of review for prodrugs

I. CMC

The key points of review for the API and preparation are the same as those for the new drug with new ingredients.

II. Drug toxicology

Regardless of whether it is a prodrug or an active metabolite, if one of them has already been approved for marketing and the other is to be developed, then in principle, the key point of reviews are the same as those for the new drug with new ingredients.

However, because the prodrug or active metabolite has been on the market, if appropriate scientific linkage data can be provided and is approved by the regulatory agency after discussion and review, some of the preclinical safety tests may be exempted by citing the information of the marketed drug. For test exemption, the following information shall be provided:

(i) The results of relevant pharmacological tests are required to indicate whether the prodrug is active and the relationship between the efficacy of the prodrug and active metabolite shall be evaluated.

(ii) Preclinical pharmacokinetic data shall be provided to clarify the conversion rate and conversion time of the prodrug and active metabolite both in the human body and in the animal species undergoing the preclinical safety tests. The exposure of the approved drug in the human body shall also be evaluated to see if it is sufficient to support possible exposure of the new drug in the human body.

(iii) If the new drug can be completely converted to the approved drug, the complete assessment data or experimental data mentioned in point 1 and point 2 above can be provided. This allows discussion with the

regulatory agency regarding whether the longer-term general animal test can be replaced with a bridging animal study. If it cannot be completely converted, it shall be considered on a case-by-case basis. Long-term toxicological tests that meet the regulatory requirements may still be required.

(iv) If the exposure of the approved drug does not fully support the safety of the new drug, toxicological tests that meet the regulatory requirements shall again be conducted for the prodrug.

(v) In vitro hERG assays, genotoxicity tests and local tolerance tests for the prodrug must be performed or evaluated.

(vi) The regulatory agent may have different test requirements or recommendations based on the overall data presentation of the case.

III. Pharmacokinetics/pharmacodynamics

(i) In principle, the prodrug is considered to be a drug with new ingredients. Therefore, the technical data requirements are the same as those for a new drug with new ingredients, and the pharmacokinetic data of the prodrug and the active metabolite must be evaluated simultaneously.

(ii) If the active metabolite of the prodrug is a drug approved in Taiwan or is the same as the active metabolite of the approved product, the following shall be considered:

1. Is there sufficient data to clarify the bioavailability of the prodrug and the active metabolite?

2. The metabolic pathways in which the prodrug is converted to the active metabolite must be clarified, and the subsequent metabolism and elimination shall be evaluated. If existing data is cited, the rationale shall be explained.

3. Are special populations evaluated, and are appropriate recommendations given? If existing data is cited, the rationale shall be explained.

4. Are the drugs interactions fully evaluated and are appropriate recommendations given? If existing data is cited, the rationale shall be explained.

5. Is there sufficient pharmacokinetic/pharmacodynamic data to clarify the rationale for dosage?

IV. Clinical and statistical aspects

(i) For a chemical preparation, whether it is a prodrug or active metabolite, if the active ingredient is different from that of the approved chemical preparations in Taiwan, it is regarded as a drug with new ingredients.

(ii) If the chemical preparation is the prodrug or active metabolite of an approved drug in Taiwan and proper data for scientific links (e.g., exploration and explanation of pharmacokinetic characteristics) are provided, then in some cases, the publicly available data of the approved drugs can be cited as a partial reference to support the quality, safety and efficacy required for marketing approval in Taiwan. Some clinical data may be waived as well.

(iii) In the above two cases, the key points of review from the clinical and statistical aspects are as follows:

1. Clinical:

(1) Is the clinical data submitted sufficient to support the efficacy of the stated indications, usage and dosage?

(2) Is the clinical data submitted sufficient to support the safety of the stated indications, usage and dosage?

(3) If the drug is a long-term drug, is there sufficient information to support the efficacy and safety of long-term use?

(4) Is there a post-marketing periodic safety update report?

(5) If there are other approved therapies for the indication, are there any comparisons with such other therapies?

(6) Is a post-marketing study required?

(7) Is a risk management plan required?

(8) Benefit-risk assessment

2. Statistical

(1) Is there an appropriate pivotal test for the stated indications, usage and dosage?

(2) Are the design and statistical methods of the pivotal test appropriate?

(3) Can the results of the pivotal test support the efficacy of the stated indications, usage and dosage?

(4) Can the overall evidence of efficacy support the efficacy of the stated indications, usage and dosage?

V. General considerations

Is the manufacturer's provided draft Chinese package insert appropriate?

H. Points of review for expedited review

I. CMC

(i) Chemical drugs:

1. API

(1) A complete review shall be conducted in accordance with that of the drug having new ingredients.

(2) However, if a statement affirming that the manufacturer, process, specifications and container closure system of the API are the same as those required by FDA, EMA or MHLW/PMDA is provided, the review can be simplified; in such case, only the physical and chemical properties, specifications, and Certificate of Analysis (CoA) will be reviewed (in accordance with the expedited review procedures for new drug registrations). Content relevant to the above (e.g., Manufacturing Process Development, rationale for specification) is also the key point of review.

2. Preparation

(1) A complete review shall be conducted in accordance with that of the drug having new ingredients.

(2) The key points of review are the development/origin and discovery process, process, specifications, CoA, container closure system, and stability of the preparation (in accordance with the expedited review procedures for new drug registrations). Content relevant to the above (e.g., excipient controls, rationale for specifications, etc.) is also the key point of review.

(ii) Biological drugs:

1. API

(1) A complete review shall be conducted in accordance with that of the

drug having new ingredients.

(2) However, if an appropriate statement is supplied affirming that the manufacturer/process control, specifications and container of the API are the same as those required by FDA, EMA or MHLW/PMDA, the key points of review are Manufacturing Process Development, CoA, and the results of stability testing.

(3) If there are significant changes during the manufacturing process development phase, corresponding comparative tests must be performed, including batch analysis, characteristic analysis and acceleration/pressure tests.

2. Preparation

(1) A complete review shall be conducted in accordance with that of the drug having new ingredients.

(2) However, if an appropriate statement is supplied affirming that the manufacturer/process control, specifications and packaging of the drug are the same as those required by FDA, EMA or MHLW/PMDA, the key points of review are development of the preparation, CoA, and the results of stability testing.

(3) If there are significant changes in the development of the preparation, corresponding comparative tests must be performed, including batch analysis, characteristics analysis and acceleration/pressure tests.

II. Drug toxicology

In terms of non-clinical pharmacology and toxicology, in principle, the review comments of the FDA, EMA or MHLW/PMDA are acceptable. The non-clinical safety data will be reviewed based on the drug toxicity summary report or review comments to see if it is sufficient to support the safety of the clinical population. The key points of review are the same as those for the new drug with new ingredients.

III. Pharmacokinetics/pharmacodynamics

A full review shall be conducted in accordance with the principles for the new drug with new ingredients. If the drug has been approved for marketing in any two countries/regions among the United States, Europe and Japan, the key points of review are:

(i) Is the data sufficient to evaluate differences between ethnic groups in the East and West?

(ii) When the formula/process is different or when primary and secondary changes are involved, is there corresponding linkage data for the product-to-be-marketed in Taiwan and the clinical trial drug?

(iii) When two regions among the United States, Europe and Japan have different opinions on special populations and drug interactions, is there sufficient data for evaluation, and are proper suggestions provided?

IV. Clinical and statistical aspects

(i) Are the stated indications different from the indications approved by the US FDA, EU EMA or MHLW/PMDA?

(ii) Is the clinical data submitted sufficient to support the efficacy and safety of the stated new indications, usage and dosage?

(iii) Has the bridging study evaluation been waived, and are there racial disparities in the efficacy and safety of the claimed indications, usage and dosage?

(iv) Have US FDA, EU EMA or MHLW/PMDA of Japan made phase IV commitment or requirement? Are the reasons for such requirements in line with the requirements, or additional requirements for implementation of other post-marketing studies?

(v) Is a risk management plan required?

(vi) Is there a post-marketing Periodic Safety Update Report?

(vii) Benefit-risk assessment

V. General considerations

Is the manufacturer's provided draft Chinese package insert appropriate?