physical and bioactivity comparisons with side-by-side analyses of the "old" product and qualification lots of the "new" product. When available, fully characterized reference standards for drug substance and final container material should also be used. Tests should include those routinely used for release of the bulk drug substance and final drug product in addition to tests specifically directed at fully evaluating the impact of the change on the product. Additional testing usually includes in-process assays at the manufacturing step(s) which are most likely affected by the manufacturing change(s).

Manufacturers may use the following categories of tests:

A. Analytical Testing

Analytical testing includes both chemical and physical assays. Tests should be selected which are sensitive to the full range of differences which might result from the process change. The sensitivity and breadth of analytical testing is an important determinant of the nature and extent of additional testing which should be done. These tests should include tests routinely done on all production lots, those initially used to fully characterize product structure and identity and establish product consistency from one production lot to another, and new tests if applicable.

B. Bioassays

Bioassays are functional tests which sponsors should use to assess the activity/potency of the product. These tests may also serve as measurements of the biological integrity (e.g., correct conformation) of the product and thus complement other analytical measurements. Sponsors should validate these assays and have a specific range of acceptable values for defining product activity. They may include appropriate in vitro tests (e.g. cell growth, enzymatic activity, anti-viral assays, infectivity assays) or in vivo tests in relevant animal models. If the in vivo mechanism of action of the product is known, the bioassay (when possible) should reflect this activity. Consideration should be given to in vivo and/or in vitro models as predictors of the biological effects in humans. For example, with vaccines, sponsors should evaluate the degree of correlation of the test(s) performed (e.g., assessment of immunogenicity) with clinical protection and submit such information to FDA so that it may be determined if a clinical study should be conducted following manufacturing changes. In cases where a product has multiple activities which are not completely correlated or the mechanism of action for clinical usage is unknown, manufacturers may need to consider performing more than one

functional assay. When a drug substance has more than one form and a manufacturing change shifts the distribution of forms, determination of the bioactivity of the various forms may be of value in assessing the impact of the change.

The combined precision of the analytical and functional tests and their ability to assess significant aspects of the product are important. Both sponsors and FDA should evaluate data from both types of testing modalities to determine the extent of additional tests needed.

C. Preclinical Animal Studies

In addition to the various in vitro studies, in vivo studies in animals may be used in comparability evaluations to determine pharmacokinetics parameters, pharmacodynamic activity, or toxicity endpoints. Animal pharmacokinetics data may be needed to assess comparability even in the absence of demonstrated differences in the analytical testing or the functional assays for the product. This is because analytical testing may be insensitive to changes affecting pharmacokinetics, and in vitro functional tests may not reflect the time-dependent aspects of distribution. Differences in in vivo exposure originating from differences in pharmacokinetics may lead to differences in therapeutic activity. Therefore, assessment of pharmacokinetics is often considered complementary to the functional assay. For hormones however, in vivo potency assays often take into account potential pharmacodynamics and pharmacokinetics profiles in animals. For these hormone products, when bioavailability is in question, clinical pharmacology studies may be needed to demonstrate comparability.

Adequate pharmacokinetics measurements may include determination of Cmax, Tmax, AUC and t - in either parallel or cross-over study designs. In cases where complications may arise from immune responses to heterologous proteins, cross-over design may be inappropriate. In other cases, sponsors should consider complicating factors related to binding proteins and levels of endogenous protein. In cases where animal studies may

not be relevant, clinical pharmacology studies may be needed to show comparability.

Prior to product approval, manufacturers generally should not need to repeat all toxicology studies that were performed with the product manufactured by the previous manufacturing process in order to demonstrate product comparability. In some cases, additional animal studies may only be needed if immunogenicity is the major safety concern. The necessity and extent of additional toxicity studies may depend upon the safety profile of the pre-existing product and on the magnitude of the manufacturing process change and/or effect on the product. Situations in which additional studies may be needed include those where the product has a narrow therapeutic range or where specific safety concerns are present, e.g., when the manufacturing process change raises concerns about possible toxic impurities or adventitious agents which cannot be assessed by analytical testing.

D. Clinical Studies

Clinical studies include human pharmacology studies, immunogenicity, safety, and/or efficacy trials. Although comparability testing can include some form of clinical efficacy studies, usually one of the purposes of comparability testing, not including efficacy studies, is so FDA may determine on the basis of such comparability data that additional clinical efficacy studies, of a sufficiency to support initial licensure or approval, are unnecessary. Human pharmacology studies, generally, may be needed to evaluate changes which may affect product pharmacokinetics or pharmacodynamics, e.g., change in product formulation.

In cases where a manufacturing change(s) results in a product with structural and/or bioactivity differences, and/or differences in pharmacokinetics patterns, and those differences are meaningful with respect to potential impact on the product's safety, purity, or potency (efficacy), an additional clinical study(ies) usually may be needed to evaluate the product's safety and/or efficacy. Additionally, when the analytical and other preclinical

testing is not sufficiently sensitive or broad enough to detect such meaningful differences, additional clinical study(ies) may be needed.

E. Additional considerations

In terms of comparability testing, manufacturers should generally perform extensive analytical testing complemented by functional testing if manufacturing changes occur in the process of producing the bulk drug substance. Examples of such changes include the following: a change in manufacturing site; modifications to cell or seed strains, including changes to the master cell bank; fermentation; and isolation or purification. In some cases, complementary pharmacology data or biologic response data (e.g., antibody titers for vaccines) may be needed.

Changes made to the final drug product, such as changes in storage containers, dosage forms (e.g. from a solution to lyophilized powder for reconstitution), or filling sites, may only need comparative data on final release specifications and product stability data. However, changes in the final product formulation may need comparative pharmacokinetics studies or other types of studies.

Since each manufacturing change and each product may present unique safety, identity, purity, and potency concerns, manufacturers should consider the type of manufacturing change, stage of product development, and clinical characteristics (i.e., patient population, clinical endpoints, dosing route, steepness of the dose response curve, regimen, and duration) in any comparability testing program. In-process and final product testing should focus on the manufacturing steps affected by the process change. Manufacturers should validate the modified manufacturing process and provide data on qualification lots. The appropriate process validation criteria will vary depending on the nature of the change. The ability of the manufacturer to use validated and sensitive assays to demonstrate a product's identity and structure, biological activity and clinical pharmacology provide a basis for determining whether product comparability can be

established without repeating clinical efficacy studies.

IV. Documentation of Product Comparability

This document on comparability describes testing that may be used by applicants with pending applications, licensed or approved applicants, IND sponsors, and FDA to determine the types of data that may be necessary to document product safety, purity, potency/effectiveness. FDA will determine the extent to which different types of comparability testing are necessary. For example, in some cases FDA may determine that no clinical study(ies) is necessary. In other instances FDA may determine, on the basis of comparability data, that a clinical efficacy study(ies) is necessary.

In the interest of efficient review and approval of product applications, FDA encourages sponsors of unapproved applications or products under IND to consult with FDA regarding proposed manufacturing changes before implementing such changes prior to product approval. A sponsor may provide FDA with information regarding a manufacturing change by including a description of the change, a description of corresponding comparability tests conducted, and the comparability test data and validation information in license/ new drug applications, INDs, or amendments to pending license/ new drug applications and INDs in effect. For biological products that FDA has approved, an applicant should submit information about manufacturing changes pursuant to 21 CFR REWRITE 601.12 or 21 CFR REWRITE 314.70(g), and any FDA guidance on changes to be reported.

21 CFR REWRITE 601.12 prescribes which changes must be reported to FDA and which changes require prior approval. FDA has proposed amendments to this regulation. Manufacturers should consult the current regulation and any applicable guidance to determine the need and mechanism of reporting.

In each instance, adequate information should be available in order that FDA reviewers and investigators may understand the type of change made, the stage of production at which the change was made, and the product(s) affected.

Such information should include appropriate validation of non-clinical studies and clinical studies which may vary for different products and for the manufacturing stage at which the change is implemented.

V. Conclusion

FDA may determine that manufacturers of biological products, including therapeutic biotechnology-derived products regulated as biologics or drugs, may make manufacturing changes without conducting additional clinical efficacy studies if comparability test data demonstrate to FDA that the product after the manufacturing change is safe, pure, potent/ effective.

VI. References

1. Points to Consider in the Production and Testing of Interferon Intended for Investigational Used in Humans (1983).

2. Cytokine and Growth Factor Pre-Pivotal Information Package (1990).

3. Changes to Be Reported for Product and Establishment License Applications; Guidance (April 6, 1995; 60 FR 17535).

4. FDA Guidance Document Concerning Use of Pilot Manufacturing Facilities for the Development and Manufacture of Biological Products (July 11, 1995; 60 FR 35750)

5. Changes to an Approved Application; Proposed Rule (January, 1996; 61 FR 2739).

添付資料２

Guidance for Industry

Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products

U.S. Department of Public Health
Food and Drug Administration
Center for Biologics Evaluation and Research
Center for Drug Evaluation and Research
July 1997

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Guidance for Industry[1]: Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products

I. INTRODUCTION

Sections 314.70 and 601.12 of Title 21 of the Code of Federal Regulations (21 CFR 314.70 and 601.12) prescribe the requirements for the reporting to FDA of changes to the approved applications for licensed biological products and approved drug products.

Under §§ 601.12 and 314.70(g), a change to a product, production process, quality controls, equipment, or facilities is required to be reported to FDA in: 1) a supplement requiring approval prior to distribution; 2) a supplement at least 30 days prior to distribution of the product made using the change; or 3) in an annual report, depending on its potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product. Before distributing a product made using a change, the regulations require applicants to demonstrate, through appropriate validation and/or other clinical or non-clinical laboratory studies, the lack of adverse effect of the change on the identity, strength, quality, purity, or potency of the product as they may relate to its safety or effectiveness.

The three reporting categories for changes to an approved application are defined in § 601.12 and § 314.70(g): 1) those changes that have a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product, which require submission of a supplement and approval by FDA prior to distribution of the product made using the change; 2) changes that have a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the

[1] This guidance document represents FDA's current thinking on changes to an approved application for specified biotechnology and specified synthetic biological products listed in 21 CFR 601.2(c), recombinant DNA-derived protein/polypeptide products approved under the Federal Food, Drug, and Cosmetic Act (FDCA) and complexes or conjugates of a drug with a monoclonal antibody approved under the FDCA. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both. Written requests for single copies of this document may be submitted to the Office of Communication, Training and Manufacturers Assistance (HFM-40), Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448. The document may also be obtained by mail by calling the CBER Voice Information System at 1-800-835-4709 or 301-827-1800, or by fax by calling the FAX Information System at 1-888-CBER-FAX or 301-827-3844. Persons with access to the INTERNET may obtain the document using the World Wide Web (WWW) or bounce-back e-mail. For WWW access, connect to CBER at "http://www.fda.gov/cber." To receive the document by bounce-back e-mail, send a message to "character@a1.cber.fda.gov."

product as they may relate to the safety or effectiveness of the product, which require submission of a supplement to FDA at least 30 days prior to distribution of the product made using the change; and 3) changes that have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product, which are to be described by the applicant in an annual report. Section 314.70(g) applies only to recombinant DNA-derived protein/polypeptide products approved under the Federal Food, Drug, and Cosmetic Act (FDCA) and complexes or conjugates of a drug with a monoclonal antibody approved under the FDCA.

For licensed biologics subject to § 601.12, changes to a product package label, container label, and package insert require either: (1) submission of a supplement with FDA approval needed prior to product distribution; (2) submission of a supplement with product distribution allowed at the time of submission of the supplement; or (3) submission of the final printed label in an annual report. These requirements are now harmonized fully for drugs and biologics.

Under § 601.12(f)(4), changes to advertising and promotional labeling for licensed biological products must be made in accordance with the provisions of 21 CFR 314.81(b)(3)(i), which requires the submission to FDA of specimens of mailing pieces and any other labeling or advertising devised for promotion of a drug product at the time of initial dissemination of the labeling, and at the time of initial publication of the advertisement for a prescription drug product. Mailing pieces and labeling that are designed to contain samples of a drug product are required to be complete, except the sample of the drug product may be omitted from the container. Each submission to the Center for Biologics Evaluation and Research (CBER) should be accompanied by a completed transmittal Form FDA-2567, or, when it is made available, the revised Form FDA-2253.

This guidance applies only to specified biotechnology and specified synthetic biological products, including recombinant DNA-derived protein/polypeptide products approved under the FDCA and complexes or conjugates of a drug with a monoclonal antibody approved under the FDCA, or biological products licensed under the Public Health Service (PHS) Act and outlined in 21 CFR 601.2(c). The section on labeling applies only to licensed biological products. This guidance is intended to assist manufacturers in determining which reporting mechanism is appropriate for a change to an approved application for such products.

In addition to the requirements in 21 CFR 601.12 and 314.70(g), an applicant making a change to an approved application must conform to other applicable law and regulations, including the current good manufacturing practice (CGMP) requirements of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 351(a)(2)(B)) and applicable regulations in 21 CFR parts 210, 211, 600 through 680, and 820. For example, manufacturers must comply with record-keeping requirements and ensure that relevant records are readily available for examination by authorized FDA personnel during an inspection.

Under each subsection of the guidance, FDA describes a category of changes to be reported under §§ 601.12 and 314.70(g). FDA also provides a listing of various changes that FDA currently believes fall under each category.

II. CHANGES UNDER §§ 601.12(b) AND 314.70(g)(1) - Changes requiring supplement submission and approval prior to distribution of the product made using the change (major changes).

Under §§601.12(b) and 314.70(g)(1), changes to a product, production process, quality controls, equipment, or facilities that have a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to its safety or effectiveness require submission of a supplement and approval by FDA before a product made using the change is distributed. For a change under this category, an applicant is required to submit a supplement to the license application that includes a detailed description of the proposed change; the products involved; the manufacturing site(s) or area(s) affected; a description of the methods used and studies performed to evaluate the effect of the change on the product's identity, strength, quality, purity, or potency as they may relate to its safety or effectiveness; the data derived from those studies; relevant validation protocols and data; and a reference list of relevant standard operating procedures (SOPs). The applicant must obtain approval of the supplement by FDA prior to distribution of the product made using the change.

In FDA's experience, the following changes to a product, production process, quality controls, equipment, or facilities have caused detrimental effects on the identity, strength, quality, purity, or potency of products as they relate to the products' safety or effectiveness even where applicants performed validation or other studies. FDA believes that these changes have a substantial potential to have an adverse effect on a product's identity, strength, quality, purity, or potency as they may relate to its safety or effectiveness and that the agency's continued premarket review and approval of such changes is currently necessary to protect the public from products whose identity, strength, quality, purity, potency, safety, or effectiveness may be compromised.

1. Process changes including, but not limited to,
   - extension of culture growth time leading to significant increase in number of cell doublings beyond validated parameters;
   - new or revised recovery procedures;
   - new or revised purification process, including a change in a column;
   - a change in the chemistry or formulation of solutions used in processing;
   - a change in the sequence of processing steps or addition, deletion, or substitution of a process step; or
   - reprocessing of a product without a previously approved reprocessing protocol.
2. Any change in manufacturing processes or analytical methods that
   - results in change(s) of specification limits or modification(s) in potency, sensitivity, specificity, or purity;
   - establishes a new analytical method;
   - deletes a specification or an analytical method;
   - eliminates tests from the stability protocol; or
   - alters the acceptance criteria of the stability protocol.

3. Scale-up requiring a larger fermentor, bioreactor, and/or purification equipment (applies to production up to the final purified bulk).
4. Change in the composition or dosage form of the product or ancillary components (e.g., new or different excipients, carriers, or buffers).
5. New lot of, new source for, or different, in-house reference standard or reference panel (panel member) resulting in modification of reference specifications or an alternative test method.
6. Extension of the expiration dating period and/or a change in storage temperature, container/closure composition, or other conditions, other than changes based on real time data in accordance with a stability protocol in the approved application.
7. Change of the site(s) at which manufacturing, other than testing, is performed, addition of a new location, or contracting of a manufacturing step in the approved application, to be performed at a separate facility.
8. Conversion of production and related area(s) from single to multiple product manufacturing area(s). (Addition of products to a multiple product manufacturing area could be submitted as a "Supplement - Changes Being Effected in 30 Days" if there are no changes to the approved and validated cleaning and changeover procedures and no additional containment requirements).
9. Changes in the location (room, building, etc.) of steps in the production process which could affect contamination or cross contamination precautions.

III CHANGES UNDER §§ 601.12(c) AND 314.70(g)(2) - Changes requiring supplement submission at least 30 days prior to distribution of the product made using the change.

Under §§ 601.12(c) and 314.70(g)(2), changes to a product, production process, quality controls, equipment, or facilities that have a moderate potential to have an adverse effect on a product's identity, strength, quality, purity, or potency as they may relate to its safety or effectiveness require submission of a supplement to FDA at least 30 days prior to distribution of the product made using the change. The requirements for the contents of these supplements are the same as for those requiring approval prior to distribution.

Some examples of changes to the product, production process, quality controls, equipment, and facilities that FDA currently considers to have moderate potential to have an adverse effect on a product's identity, strength, quality, purity, or potency as they may relate to its safety or effectiveness are set forth in the following list which FDA has developed based on experience gained in reviewing submissions received in the past.

1. Addition of duplicated process chain or unit process, such as a fermentation process or duplicated purification columns, with no change in process parameters.
2. Addition or reduction in number of pieces of equipment (e.g., centrifuges, filtration devices, blending vessels, columns, etc.) to achieve a change in purification scale not associated with a process change.
3. Manufacture of an additional product in a previously approved multiple product manufacturing area using the same equipment and/or personnel, if there have been no changes to the approved

and validated cleaning and changeover procedures and there are no additional containment requirements.

4. Change in the site of testing from one facility to another (e.g., from a contract lab to the applicant; from an existing contract lab to a new contract lab; from the applicant to a new contract lab).
5. Change in the structure of a legal entity that would require issuance of a new license(s), or change in name of the legal entity or location that would require reissuance of the license(s)(applies only to licensed biological products).

As described in §§ 314.70(g)(2)(v) and 601.12(c)(5), in certain circumstances FDA may determine that, based on experience with a particular type of change, the supplement for such change is usually complete and provides the proper information. Likewise, there may be particular assurances that the proposed change has been appropriately submitted, such as when the change has been validated in accordance with a previously approved protocol. In these circumstances, FDA may determine that the product made using the change may be distributed at the time of receipt of the supplement by FDA. The following are changes that in FDA's experience have been submitted properly with the appropriate information, and could be implemented under §§ 314.70(g)(2)(v) and 601.12(c)(5) at the time of receipt of the supplement by FDA without a previously approved comparability protocol.

1. Addition of release tests and/or specifications or tightening of specifications for intermediates.
2. Minor changes in fermentation batch size using the same equipment and resulting in no change in specifications of the bulk or final product.

In addition, applicants that use the protocol described in §§ 314.70(g)(4) and 601.12(e)to validate a proposed change may request that a change usually subject to supplement submission and approval prior to distribution be reported as a change subject to supplement submission at least 30 days prior to distribution of the product made using the change, or as a "Changes Being Effected" supplement submission, in which event the product made using the change may be distributed immediately upon receipt of the supplement by FDA.

IV. CHANGES UNDER §§ 601.12(d) AND 314.70(g)(3) - Changes to be described in an annual report (minor changes).

Under §§ 601.12(d) and 314.70(g)(3), changes to the product, production process, quality controls, equipment, or facilities that have minimal potential to have an adverse effect on a product's identity, strength, quality, purity, or potency as they may relate to its safety or effectiveness are required to be documented in an annual report submitted each year within 60 days of the anniversary date of approval of the application for a biological product and in the next annual report required under §-314.81(b)(2)(iv)(b) for drug products approved under the FDCA. For changes under this category, the applicant is required to submit in the annual report a list of all products involved; and a full description of the manufacturing and controls changes including: the manufacturing site(s) or area(s)

involved, the date each change was made, a cross-reference to relevant validation protocol(s) and/or SOPs, and relevant data from studies and tests performed to evaluate the effect of the change on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product.

Some examples of changes that FDA currently considers to have minimal potential to have an adverse effect on a product's identity, strength, quality, purity, or potency as they may relate to its safety or effectiveness are listed below. The list is not all-inclusive but contains items that, in FDA's experience reviewing supplements, have caused few instances in which an adverse effect on the product's identity, strength, quality, purity, or potency as they may relate to its safety or effectiveness has been observed.

1. Increase in aseptic manufacturing scale for finished product without change in equipment, e.g., increased number of vials filled.
2. Modifications in analytical procedures with no change in the basic test methodology or existing release specifications provided the change is supported by validation data.
3. Change in harvesting and/or pooling procedures which does not affect the method of manufacture, recovery, storage conditions, sensitivity of detection of adventitious agents, or production scale.
4. Replacement of an in-house reference standard or reference panel (or panel member) according to SOPs and specifications in an approved application.
5. Tightening of specifications for existing reference standards to provide greater assurance of product purity and potency.
6. Establishment of an alternate test method for reference standards, release panels, or product intermediates, except for release testing of intermediates licensed for further manufacture.
7. Establishment of a new Working Cell Bank derived from a previously approved Master Cell Bank according to an SOP on file in the approved license application.
8. Change in the storage conditions of in-process intermediates, which does not affect labeling, based on data from a stability protocol in an approved application.
9. Change in shipping conditions (e.g., temperature, packaging, or custody) based on data derived from studies following a protocol in the approved application.
10. A change in the stability test protocol to include more stringent parameters (e.g., additional assays or tightened specifications).
11. Addition of time points to the stability protocol.
12. Change in the simple floor plan that does not affect production process or contamination precautions.
13. Trend analyses of release specification testing results for bulk drug substances and drug products obtained since the last annual report.

V. COMPARABILITY PROTOCOLS UNDER §§ 601.12(e) AND 314.70(g)(4)

The comparability protocol described in §§ 601.12(e) and 314.70(g)(4) is a supplement that establishes the tests to be done and acceptable limits to be achieved to demonstrate the lack of adverse effect for

specified types of manufacturing changes on the safety and effectiveness of a product. A new comparability protocol, or a change to an existing one, requires approval prior to implementation because it may result in decreased reporting requirements for the changes covered. In general, a decrease in reporting requirement will be one reporting tier, e.g., from supplement with distribution of product in 30 days to annual report, or from prior approval supplement to supplement with distribution of product in 30 days. In some cases the decrease may be greater. The reporting category will be established at the time that the comparability protocol is approved. FDA intends to issue further guidance on the use of such protocols in the near future.

VI. CHANGES UNDER § 601.12(f) - Labeling changes.

This section applies only to licensed biological products. Under § 601.12(f), changes to labeling are required to be submitted to CBER in one of the following ways: (1) As a supplement requiring FDA approval prior to distribution of a product with the labeling change; (2) as a supplement requiring FDA approval but permitting distribution of a product bearing such change prior to FDA approval; or (3) in an annual report. Some examples of changes to labeling that CBER currently considers to be appropriate for submission in each of these three categories are listed below. These lists are not intended to be comprehensive. Pursuant to § 601.12(f)(4), promotional labeling and advertising must be submitted to CBER at the time of initial dissemination or publication.

A. Changes under §601.12(f)(1) - Labeling changes requiring supplement submission - FDA approval must be obtained before distribution of a product with the labeling change.

Under § 601.12(f)(1), any proposed change in the package insert, package label, or container label, except those described in § 601.12(f)(2) and (3), is required to be submitted as a supplement and receive FDA approval prior to distribution of a product with the label change. In such a supplement, the applicant is required to present clearly the proposed change in the label and the information necessary to support the proposed change. The following list contains some examples of changes that are currently considered by CBER to fall into this reporting category.

1. Changes based on postmarketing study results, including, but not limited to, labeling changes associated with new indications and usage.
2. Change in, or addition of, pharmacoeconomic claims based on clinical studies.
3. Changes to the clinical pharmacology or the clinical study section reflecting new or modified data.
4. Changes based on data from preclinical studies.
5. Revision (expansion or contraction) of population based on data.
6. Claims of superiority to another product.

B. Changes under § 601.12(f)(2) - Labeling changes requiring supplement submission - product with a labeling change that may be distributed before FDA approval.

Under § 601.12(f)(2), a supplement is required to be submitted for any change to a package insert, package label, or container label that adds or strengthens a contraindication, warning, precaution, or adverse reaction; adds or strengthens a statement about abuse, dependence, psychological effect, or overdosage; adds or strengthens an instruction about dosage and administration that is intended to increase the safety of the use of the product; or deletes false, misleading, or unsupported indications for use or claims for effectiveness. The applicant may distribute product with a label bearing such a change at the time the supplement is submitted, although the supplement is still subject to approval by FDA. The following list includes some examples of changes that are currently considered by FDA to fall into this reporting category.

1. Addition of an adverse event due to information reported to the applicant or Agency.
2. Addition of a precaution arising out of a post-marketing study.
3. Clarification of the administration statement to ensure proper administration of the product.

C. Changes under § 601.12(f)(3) - Labeling changes requiring submission in an annual report.

Under § 601.12(f)(3), a package insert, package label, or container label with editorial or similar minor changes or with a change in the information on how the drug is supplied that does not involve a change in the dosage strength or dosage form is required to be described in an annual report. Some examples that are currently considered by FDA to fall into this reporting category include:

1. Changes in the layout of the package or container label without a change in content of the labeling.
2. Editorial changes such as adding a distributor's name.
3. Foreign language versions of the labeling, if no change is made to the content of the approved labeling and a certified translation is included.

添付資料 3

Guidance for Industry

Changes to an Approved Application: Biological Products

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
July 1997

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GUIDANCE FOR INDUSTRY[1]: CHANGES TO AN APPROVED APPLICATION: BIOLOGICAL PRODUCTS

I. INTRODUCTION

Frequently, a licensed applicant determines that it is appropriate to make a change in the product, labeling, production process, quality controls, equipment, facilities, or responsible personnel established in the approved license application(s). Section 601.12 of Title 21 of the Code of Federal Regulations (21 CFR 601.12) prescribes the requirements for reporting such changes for licensed biological products to FDA.

Under §601.12, a change to a product, production process, quality controls, equipment, facilities, or responsible personnel is required to be reported to FDA in 1) a supplement requiring approval prior to distribution, 2) a supplement at least 30 days prior to distribution of the product made using the change, or 3) an annual report, depending on its potential to have an adverse effect on the identity, strength, quality, purity, or potency of the biological product as they may relate to the safety or effectiveness of the product. Before distributing a product made using a change, applicants are required to demonstrate, through appropriate validation and/or other clinical or non-clinical laboratory studies, the lack of adverse effect of the change on the identity, strength, quality, purity, or potency as they may relate to the safety or effectiveness of the product.

The three reporting categories for changes to an approved application are defined in § 601.12: 1) those changes that have a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the

[1] This guidance document represents FDA's current thinking on changes to an approved application for all licensed biological products, except the specified biotechnology and specified synthetic biological products listed in § 601.2(c). It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both. Written requests for single copies of this document may be submitted to the Office of Communication, Training and Manufacturers Assistance (HFM-40), Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448. The document may also be obtained by mail by calling the CBER Voice Information System at 1-800-835-4709 or 301-827-1800, or by fax by calling the FAX Information System at 1-888-CBER-FAX or 301-827-3844. Persons with access to the INTERNET may obtain the document using the World Wide Web (WWW) or bounce-back e-mail. For WWW access, connect to CBER at "http://www.fda.gov/cber." To receive the document by bounce-back e-mail, send a message to "changes@a1.cber.fda.gov."