Annex

Announcement on the Matters related to filing and Joint Review & Approval of Active Pharmaceutical Ingredients, Pharmaceutical Excipients and Pharmaceutical Packaging Materials for Drug Products

(Draft for Comments)

In order to implement the principles of the *Opinions on Deepening Reform of Review and Approval System and Encouraging Innovation of Drugs and Medical Devices* (T.Zi (2017) No. 42) issued by General Office of the CPC Central Committee and General Office of the State Council and the *Decision of the State Council on Canceling a Batch of Administrative Licensing Items* (No. [2017] 46), the former CFDA issued the *Announcement on Adjusting the Review and Approval of Active Pharmaceutical Ingredients, Pharmaceutical Excipients and Pharmaceutical Packaging Materials* (No. 146, 2017, hereinafter referred to as Announcement No. 146) on November 30, 2017. To further clarify the matters related to registration of Active Pharmaceutical Ingredients (APIs), pharmaceutical excipients and pharmaceutical packaging materials for drug products, carrying out the joint review and approval of drug products and the APIs, pharmaceutical excipients and pharmaceutical packaging materials used therein, and ensuring the smooth review and approval of drugs, it is hereby announced as follows:

I. If meeting any of the following conditions, the enterprises of pharmaceutical excipients and pharmaceutical packaging materials may conduct filing in accordance with Announcement No. 146, at its own discretion.

(I) Non-high-risk pharmaceutical excipients which have been included in Chinese Pharmacopeia, United States Pharmacopeia, European Pharmacopeia, Japanese Pharmacopeia and British Pharmacopeia, and the non-high-risk pharmaceutical packaging materials which have national standards in place.

(II) the pharmaceutical excipients, which have a history of being used in food and have national food safety standards in place, are to be used in the oral preparations.

(III) the excipients, which have a history of being used in cosmetics and have international or industry standards for cosmetics in place, are to be used in topical preparations (except ophthalmic preparations, preparations by mucosal

administration and preparations in direct contact with wounds).

(IV) the pharmaceutical packaging materials, which have evidence of being used in food packages in direct contact with food, are only used in oral solid preparations.

(V) Some corrigent, flavors, pigments, pH adjusters, and other pharmaceutical excipients (see Appendix for details).

II. For pharmaceutical excipients and pharmaceutical packaging materials other than those stated in Article I herein, it is required to conduct filing on the information disclosure platform of APIs, pharmaceutical excipients and pharmaceutical packaging materials on the web portal (website: www.cde.org.cn) of Center for Drug Evaluation, CFDA (hereafter referred to as "CDE") as required and timely submit satisfactory registration dossier before submitting marketing application for drug products.

III. When the applicant uses pharmaceutical excipients and pharmaceutical packaging materials that meet requirements of Article I and have not been filed, relevant data should be submitted in the dossiers for the drug product concerned, e.g., information on manufacturer, basic product information, information on manufacturing process, product specification, Certificate of Analyses (CoAs), notes for applications of product, Authorization Letters of or relevant agreements with enterprises of APIs, pharmaceutical excipients, and pharmaceutical packaging materials. CDE may, by sending a Deficiency Letter, require the applicant of drug product to discuss with manufacturers of pharmaceutical excipients and pharmaceutical packaging materials concerned to conduct filing or provide additional data for their products, as needed, in accordance with the Announcement No. 146 during the process of review and approval of drug product.

For pharmaceutical excipients never used in any overseas and domestic marketed drug products, and pharmaceutical packaging materials with new materials, new structures and new intended uses, filing should be conducted prior to submission of applications for drug clinical trial, or relevant dossier should be incorporated in dossiers of drug product in accordance with this Announcement and other relevant requirements.

IV. Use and filing of approved APIs, pharmaceutical excipients and pharmaceutical packaging materials.

(I) APIs, pharmaceutical excipients and pharmaceutical packaging materials, which have already obtained approval certificates, should also be registered on the website of CDE in accordance with Announcement No. 146 and the requirements for filing dossier of pharmaceutical excipients and pharmaceutical packaging materials.

(II) For pharmaceutical excipients and pharmaceutical packaging materials, which have already obtained approval certificates, it is acceptable to use such certificates, if not expired, to support new applications for drug product registration application, and new drug clinical trial applications.

If the approval certificates of pharmaceutical excipients and pharmaceutical packaging materials get expired during the process of review and approval of drug product registration application or clinical trial, appropriate approval certificates may be issued, provided that, upon review, relevant technical specifications are met.

(III) For approved pharmaceutical excipients and pharmaceutical packaging materials used in generic drug consistency evaluation, if the approval certificates thereof are still valid before August 9, 2015, they may be used for the review for consistency evaluation. If the approval certificates get expired during the process of review, the consistency evaluation may be approved, provided that, upon review, relevant technical specifications are met.

(IV) APIs, pharmaceutical excipients and pharmaceutical packaging materials with approval certificates already obtained, which have been used in drug products, may continue to be used in the original drugs, if the approval certificates thereof are expired (except those APIs, pharmaceutical excipients and pharmaceutical packaging materials prohibited from use or obsoleted as announced by the State).

(V) Enterprises of drug products should guarantee that the approval certificates of the APIs, pharmaceutical excipients and pharmaceutical packaging materials used for manufacturing their drug products are valid or the filing numbers thereof are obtained.

V. If APIs, pharmaceutical excipients and pharmaceutical packaging materials are changed in drug products, those with filing numbers may be selected, and evaluation should be conducted on the effects of such change to drug products, in accordance with relevant technical guidelines and standards, and filings or supplementary application should be submitted to CDE as required in a timely manner.

VI. After CDE finish technical review of APIs, pharmaceutical excipients and pharmaceutical packaging materials, CDE will provide the technical review comments to registrants through Applicant's Window on its website.

VII. An overseas manufacturer of APIs, pharmaceutical excipients and pharmaceutical packaging materials may appoint its representative office in China to conduct filing of its APIs, pharmaceutical excipients and pharmaceutical packaging materials as required by Announcement No. 146, and the filing dossier should be in Chinese; alternatively, it may entrust a legal institute within the territory in China to conduct the filing and perform the relevant obligations of a filing on its behalf as its authorized agent. The overseas manufacturer, as the filing holder, should be responsible for the authenticity of filing dossiers.

VIII. Registrants of APIs, pharmaceutical packaging materials and pharmaceutical excipients should be responsible for the quality of their products, organize manufacturing in compliance with relevant requirements for manufacturing quality management, and

cooperate with pharmaceutical manufacturers for audit.

IX. This Announcement shall come into effect from the date of issuance.

It is hereby announced.

Appendix: The Pharmaceutical Excipients of some Corrigents, Favors, Pigments, and pH Adjusters May Excluded from Mandatory filing of Announcement No. 146

China National Drug Administration

July dd, 2018

Appendix

The Pharmaceutical Excipients of some Corrigents, Favors, Pigments, and pH Adjusters May Excluded from Mandatory Filing of Announcement No. 146

Some pharmaceutical excipients, e.g., corrigents, flavors, pigments, and pH adjusters for drug products, may be excluded from mandatory filing as specified in Announcement No. 146, which are:

1. Corrigents (sweetening agents): sucrose, simple syrup, mannitol, sorbitol, sodium saccharin, aspartame, sucralose, stevioside, glucose, xylitol, maltitol, etc. Such excipients are limited to be used in drug products as corrigents (sweetening agents).
2. Flavors, spices: orange flavor, banana flavor, vanillin, etc. Where food standards prevail, relevant requirements of current GB 2760 *National Food Safety Standards – Standards for Use of Food Additives*, GB 30616 *National Food Safety Standards – Food Flavor*, and GB 29938 *National Food Safety Standards – General Requirements for Food Spices* should be met.
3. Pigments (colorants): iron oxide, plant carbon black, cochineal, etc. Where food standards prevail, relevant requirements of current GB 2760 *National Food Safety Standards – Standards for Use of Food Additives* should be met.
4. pH adjusters (including used for injections): malic acid, fumaric acid, acetic acid, sodium acetate, citric acid (sodium, potassium salt), tartaric acid, sodium hydroxide, concentrated ammonia solution, hydrochloric acid, sulfuric acid, phosphoric acid, lactic acid, potassium dihydrogen phosphate, dipotassium hydrogen phosphate, disodium hydrogen phosphate, sodium dihydrogen phosphate, etc.
5. Inorganic salts with simple manufacturing process and stable physicochemical properties which are only intended for being used as excipients (including used for injections): calcium carbonate, sodium carbonate, potassium chloride, calcium chloride, magnesium chloride, calcium phosphate, calcium hydrogen phosphate, calcium sulfate, sodium hydrogencarbonate, etc.
6. Benzene-free ink for printing on oral preparations.

Of the pharmaceutical excipients aforementioned, those having been included in current Chinese Pharmacopeia should conform to the requirements therein, those having not been included in current Chinese Pharmacopeia should conform to the requirements of national food standards or current United States Pharmacopeia/National Formulary, European Pharmacopeia, Japanese Pharmacopeia, and British Pharmacopeia. The other pharmaceutical excipients should conform to the requirements for pharmaceutical use.