Circular of China Food and Drug Administration on Adjusting the Review and Approval Matters of the Drug Substance, Excipients and Packaging Materials (2017 No. 146)

Released on November 30, 2017

In order to implement the *Opinions on Deepening the Reform of Review and Approval System and Encouraging the Innovation of Drugs and Medical Devices* (T.Z. [2017] No. 42) formulated jointly by the General Office of the CPC Central Committee and the General Office of State Council and the *Decision of the State Council on Cancelling a Batch of Administrative Licensing Matters* (G.F. [2017] No. 46), cancel the review and approval of excipients and packaging materials and containers that are immediately contacted with the drug (hereinafter referred to as the packaging materials), the drug substances, excipients and packaging materials will be reviewed and approved at the same time as approving the registration application of the drug product. Relevant matters are notified as follows:

I. This circular shall apply to the drug substances used for the drug registration applications filed by the applicants within the territory of the People's Republic of China for the registration category 2.2, category 2.3, category 2.4, category 3, category 4 and category 5 drug products, excipients and packaging materials used for the registration application of drug products with all types of registration categories.

II. Since the date of release hereof, the food and drug administration at all levels will no longer accept the registration application of the drug substances, excipients and packaging materials separately. The Center for Drug Evaluation, CFDA (hereinafter referred to as the CDE) will establish the registration platform of the drug substances, excipients and packaging materials (hereinafter referred to as the Registration Platform) and database. The relevant enterprises or entities may submit the registration documents of the drug substances, excipients and packaging materials according to the requirements hereof and obtain the registration number of the drug substances, excipients and packaging materials. They will be reviewed and approved after the registration application of the connected drug product is proposed.

III. The registration documents of drug substances mainly include the following: General Information, Manufacturing Information, Characterization, Control of Drug Substance, Reference Standards or Materials, Container Closure System, Stability. The detailed contents shall be in line with the requirements of CMC section of application dossiers of drug substance stated in the *Circular on the Release of Application Dossiers Requirements of New Registration Classification of Chemical Drugs (for Trial Implementation)* (CFDA circular 2016 No. 80).

IV. The registration documents of excipients mainly includes the Basic Information of Enterprise, Basic information of Excipient, Manufacturing Information, Characterization, Control of Excipient, Batch Analysis, Stability, Pharmacology and Toxicology. The detailed contents shall be in line with the requirement of application dossiers of excipient stated in the *Circular on the Release of Application Dossiers Requirements of the Packaging materials and Excipients (For Trial Implementation)* (CFDA circular 2016 No. 155).

V. Registration documents of the drug packaging materials mainly include: the Basic Information of Enterprise, the Basic Information of Drug Packaging Materials, Manufacturing Information, Quality Control, Batch Testing Report, stability study, Safety and Compatibility Study. The specific contents shall conform to the application dossiers requirements of the drug packaging materials in Circular 2016 No. 155.

VI. During the transitional period when establishing the registration platform, CDE will make public the "registration data of the drug substances", "registration data of the excipients" and "registration data of the drug packaging materials" in a tabular form on its portal website (website: www.cde.org.cn). The information to be publicized mainly includes the registration number, product name, enterprise name, registered address of the enterprise, domestic/imported product, package size, registration date, update date and approval of the connected drug product.

After filling in the basic product information at the "Applicant's Window" on the portal website of CDE, the enterprises of drug substances, excipients and drug packaging materials will submit the registration documents (including the registration form, see Attachment 1) to CDE in the form of optical disc (mailing address: Review Management Office, the Center for Drug Evaluation, No. 1, Fuxing Road A, Haidian District, Beijing). Within 5 working days after receipt of the documents, CDE will review the integrity of registration documents. If the documents are incomplete, it is needed to notify the registration documents to be supplemented at one time; if the documents are consistent with requirements, it will be publicized by CDE.

VII. With regard to the registration application of the drug substances, excipients and drug packaging materials which have been accepted, but of which the review and approval are not completed, CDE shall generate the registration number of the drug substances, excipients and drug packaging materials and import the application information into the aforesaid registration data sheet for making it public. The applicant shall submit the application registration documents to CDE in the form of light disk according to the requirements hereof. If the drug substances, excipients and drug packaging materials with approval number are used in the newly applied drug product (including the supplementary application for changing the drug substances, excipients and drug packaging materials), such drug substances, excipients and drug packaging materials shall also be registered as required.

VIII. With regard to the drug substances, excipients and drug packaging materials used by the drug product applicant only, or exclusively used by the particular marketing authorization holder, it is permitted to submit the documents of the drug substances, excipients and drug packaging materials at the same time of the drug product application (documents requirements shall be subject to this Circular), without the need of registration.

IX. The drug product applicant may select the drug substances, excipients and drug packaging materials with registration number for study and come up with marketing application or change application of the drug substances, excipients and drug packaging materials. If the drug product and drug substances, excipients and drug packaging materials do not belong to the same applicant, the drug product applicant shall provide the Power of Attorney (attachment 2) issued by the marketing authorization holder or enterprise of the drug substances, excipients and drug packaging materials

in the application documents.

X. Enterprises of drug substances, excipients and drug packaging materials already granted with registration number shall perform management according to the relevant national requirements strictly, assure the product quality and submit the product quality management report on a yearly basis after being granted with registration number; in the event of product change, relevant information shall be changed on the registration platform in a timely manner and drug product applicant of its product shall be notified actively in advance of change.

The drug product applicant shall be responsible for the quality of selected drug substances, excipients and drug packaging materials. Fully research and assess the impact of change of the drug substances, excipients and drug packaging materials on the quality of their product. Conduct research in accordance with the relevant provisions and guidelines of China Food and Drug Administration and apply for variation application or record of filing as required.

XI. After the drug product is approved for marketing, or change of drug substances, excipients and drug packaging materials is approved for the marketed drug product (including the change of drug substances supplier, type and supplier of excipients and drug packaging materials), China Food and Drug Administration will be highlight it in the public information of the drug substances, excipients and drug packaging materials. Other requirements pertaining to the bundling review and approval of the drug substances, excipients and drug packaging materials as well as drug products shall be put into implementation after relevant regulations are enacted by China Food and Drug Administration.

Relevant registration requirements of the drug substances, excipients and drug packaging materials granted with approval number prior to the release of this circular will be notified additionally after the registration platform is established.

XII. The provincial food and drug administration shall be liable for the daily supervision and management over the manufacturing enterprises of the drug substances, excipients and drug packaging materials within the administrative region. When the drug product application is in the process of review and approval, China Food and Drug Administration will organize the on-site inspection and testing of relevant drug substances, excipients and drug packaging materials if necessary.

XIII. This circular will be put into implementation since the date of release. In case of any inconsistency between the originally released relevant documents about the bundling review and approval of excipients and drug packaging materials and this circular, this circular is the only reference document if any conflict incurs.

The announcement is hereby released as above.

Attachment 1: Registration Form of the Drug Substances, Excipients and Drug Packaging Materials

2. Power of Attorney by Enterprises of the Drug Substances, Excipients and Drug Packaging Materials

China Food and Drug Administration

November 23, 2017