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Certifying Pharmaceutical Exports: An Introduction To FDA's Certificate Of Pharmaceutical Product

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When exporting human drugs, manufacturing facilities are often asked by foreign customers or governments to provide documentation of the facility's compliance with FDA standards. FDA issues export certificates for approved or licensed drugs and for unapproved drugs that meet certain legal requirements. Certificates of pharmaceutical product (CPP) are issued for human drugs exported from the U.S. directly to the requesting country. In Part 1 of a two-part series, we discuss the requirements for exporting U.S.-manufactured material to foreign markets leveraging a CPP issued by the FDA.

WHO, When, And Where

Let's start with the history, origins, and recommended format of the certificate of pharmaceutical product (CPP) as envisioned by the World Health Organization (WHO). To support international commerce in pharmaceuticals, the WHO developed the concept of a CPP, first in 1975, and subsequently revised in 1988, 1992, and 1997. The previous instrument used to perform this function was known as a free sales certificate, a term still used in certain countries, and for non-pharmaceutical products in the U.S.

A CPP issued by a major country (e.g., U.S.) or region (e.g., EU) with highly resourced regulatory agencies provides assurance to an importing country with less resourced regulatory agencies that the product meets international requirements for quality, safety, and efficacy (QSE). It also attests to the listed manufacturing sites' compliance with current good manufacturing practices (cGMPs). The CPP allows importing countries to perform abbreviated QSE and GMP reviews, resulting in quicker patient access to important medicines.

In order for the CPP to support registration in a new country, that country must have in its national medicine legislation or guidelines a provision to accept a CPP from the exporting country. The WHO maintains a list of participating member states and regional organizations such as the European Medicines Agency (EMA).

WHO Recommended Format And Global Supply Chain

Although the WHO does not issue the CPP itself, it provides a recommended format to follow: https://www.who.int/medicines/areas/quality_safety/regulation_legislation/certification/guidelines/en/

The WHO also developed provisions for instances where the finished product:

- is not manufactured in the certifying country but is approved in the certifying country,
- is being exported in a different dosage form, strength, or formulation from that approved in the certifying country (an explanation should be provided on the CPP),
- is approved but not available on the market in the certifying country (an explanation should be provided on the CPP),
- is not approved in the certifying country (an explanation should be provided on the CPP). This case will be discussed in further detail in the second part of this two-part series.

These provisions recognize the global nature of the pharmaceutical supply chain where different countries may contain: the API manufacturing site; the finished product manufacturing site; the finished product packaging site; API and finished product testing sites; the finished product release site; and company headquarters.

While the original intention was for the national medicine regulatory authority (NMRA) of the importing country to communicate directly with the NMRA of the exporting country to obtain a CPP, in practice the commercial entities involved with importing, exporting, and registration lead these efforts.

The WHO discourages the NMRA of the importing country from requiring more than one CPP or a GMP certificate in addition to a CPP. This is because the CPP certifies that the finished product is manufactured according to GMPs. The FDA no longer issues GMP certificates for this reason.

The WHO recommends that no further legalization is required for a CPP. However, in my experience, many rest-of-world countries have strong requirements and preferences for legalization of these documents (e.g., apostille). Therefore, many sponsors will take on legalization themselves to expedite submission in importing countries.

CPPs In The U.S.

In the U.S., CPPs fall within a subset of the FDA's Export Certification Program. Export certificates include all products subject to the Federal Food, Drug, and Cosmetic (FD&C) Act and other statutes that the FDA administers, with the exception of tobacco. Therefore, export certificates are issued by five FDA centers. See Figure 1 below for a listing of FDA centers.

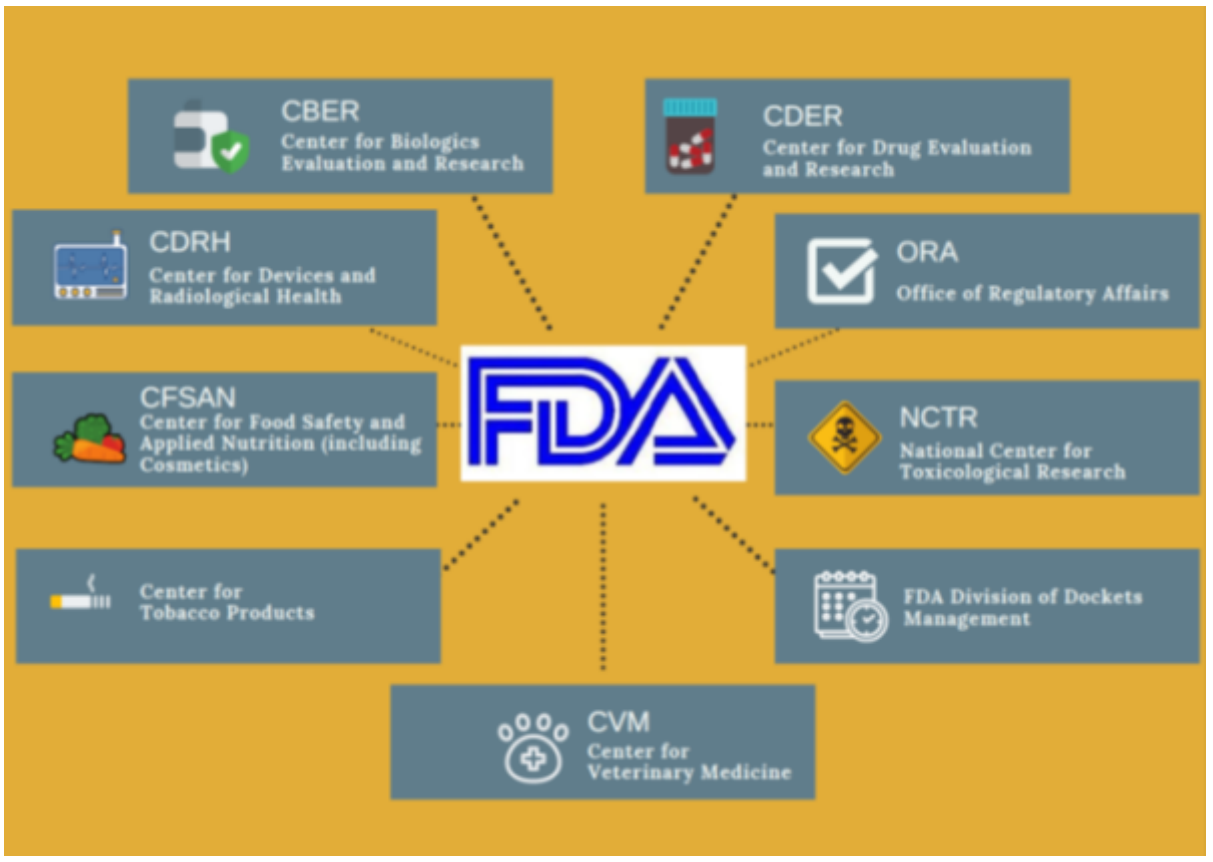

Figure 1: *FDA review centers*

The FDA issues eight types of export certificates, as detailed in Table 1.

Table 1: FDA Export Certificates

Type of Certificate	Issuing FDA Centers	Scope
Certificate of Free Sale	CFSAN	Food, including dietary supplements, and cosmetics that may be legally marketed in the U.S.
Certificate of Export for Seafood	CFSAN	Seafood that may be legally marketed in the U.S.
Health Certificates for Food/Feed	CFSAN	Primarily requested for countries in the EU. These are usually consignment-specific and contain language pertaining to "compliance" with foreign regulations. Since the FDA does not attest to compliance with another country's requirements, it will work with other governments to develop mutually acceptable language (e.g., "equivalence" rather than "compliance").
Specified Risk Materials of Bovine, Ovine and Caprine Origin Certificate	CFSAN	Issued for the export of gelatin that can be legally marketed in the U.S. to address concerns on raw material with regard to transmissible spongiform encephalopathies.

Certificate of a Pharmaceutical Product	CBER, CDER, and CVM	CPPs conform to the WHO format and are intended for use by the importing country when considering whether to license the product in question for sale.
Non-clinical Research Use Only Certificate	CBER and CDRH	These certificates are issued for export of a product, material, or component, for non-clinical research use only, not intended for human use, and which may be marketed in, and legally exported from, the U.S. Non-clinical research use only materials must be labeled per 21 CFR 809.10(c)(2) or 21 CFR 312.160, as appropriate, and exported as they are presently being sold or offered for sale in the U.S.
Certificate to Foreign Government	CBER, CDRH, and CVM	These certificates are issued for export of human drugs and biologics, animal drugs, and devices that can be legally marketed in the United States.
Certificate of Exportability	CBER, CDRH, and CVM.	These certificates are issued for export of human drugs and biologics, animal drugs, and devices that cannot be legally marketed in the United States.

The FD&C Act does not require the FDA to issue certificates for foods, including animal feeds, food and feed additives, and dietary supplements, or cosmetics. However, since foreign governments require these, the FDA provides this service as resources permit.

The 1996 FDA Export Reform amendments to the FD&C Act provided for the FDA to issue certificates for exports of certain products even if they are not allowed to be marketed in the U.S. Human drugs will receive a CPP containing special notation that the product is unapproved, instead of a Certificate of Exportability. The FDA will not issue Certificates of Exportability for foods, dietary supplements, and cosmetics.

The FDA's attestation of compliance with cGMP regulations is based on inspections of drug, biologic, medical devices, and human food/animal feed manufacturers that are registered and listed with the agency, as well as other available information. The FDA will not issue a Certificate of Exportability if:

- The product does not meet applicable requirements of the FD&C Act;
- The FDA has initiated enforcement action (e.g., seizure or an injunction);
- There is failure of the manufacturing facility(ies) to operate in compliance with cGMPs;
- The manufacturing facility(ies) is not registered or listed with FDA;
- The product is not exported from the U.S.

FDA-issued CPPs expire 24 months from the date of issue. They are printed on security paper, contain the signature of the authorized FDA official, as well as an embossed Department of Health & Human Services federal seal and ribbon. Due to these safeguards, the FDA no longer notarizes export certificates, including CPPs.

CDER Guidance On CPPs

The CDER area of the FDA website houses the majority of guidance documents related to CPPs. One difference noted against CBER requirements is that applicants are advised to use *Form FDA 3613f* if using a paper-based application. Electronic applications must be made by using the CDER Export Certification Application and Tracking System (CDER eCATS).

The cost of the first CDER-issued CPP for a country is $175, the second for the same country costs $90, and all additional CPPs for the same country cost $40. The CPP should be issued within 20 working days of receipt of a completed request.

CBER Guidance On CPPs

While CDER requires applicants to use *Form FDA 3613f*, CBER requires different forms. The responsible official of the exporting firm signs and encloses the Exporter's Certification Statement for each type.

- ***Form FDA 3613***
  - Used for the export of biologics legally marketed in the U.S.
  - There are two variations to the standard *Form FDA 3613* described below:
    - For human cells, tissues, and cellular and tissue-based product (HCT/P) procured prior to May 25, 2005, the responsible official certifies compliance with applicable requirements of 21 CFR Part 1270.
    - For HCT/P procured after May 25, 2005, the responsible official certifies compliance with applicable requirements of 21 CFR Part 1271.
- ***Form FDA 3613a***
  - This form is used for export of products not approved for marketing in the U.S. that meet the requirements of Sections 801(e) or 802 of the FD&C Act (i.e., the product is not considered adulterated or misbranded, meets requirements for labeling, is not banned in the U.S. or the intended country, is intended for export, etc.).
- ***Form FDA 3613b***
  - This form is used for export of products that are under consideration for a product license that will authorize its importation and sale or for renewal, extension, amending, or reviewing a license.
- ***Form FDA 3613c***
  - This form is used for the export of a non-clinical research use only product, material, or component that is not intended for human use which may be marketed in, and legally exported from, the U.S. under the FD&C Act.

Within CBER, the Division of Case Management (DCM) reviews CPP application requests. Any questions by applicants can be directed to CBERExportCert@fda.hhs.gov. The cost of the first two CBER-issued CPPs for a country is $175. Additional copies cost $85 each.

CBER encourages sponsors to apply for their export certificates through the Biologics Export Certification Application and Tracking System (BECATS). This is the CBER module of the eCATS system described above. At this time, only the Certificate to Foreign Government *Form FDA 3613* standard, 1270, and 1271 are available online. Other certificates (*Form FDA 3613a, Form FDA 3613b, and Form FDA 3613c)* still require paper-based application forms.

Applying For A CPP

Companies planning to request export certificates from the FDA should establish an account on the FDA's Unified Registration and Listing System (FURLS) (https://www.access.fda.gov/).

Note: this is the same platform as the CDER eCATS and BECATS systems described above, also known as the FDA Industry Systems (FIS). Although certain applications must still be made by paper, the FDA is in the process of converting all applications to electronic format.

Account holders may access all five FDA Centers to request export documentation.

From CPP To CMP…

The FDA supports manufacturers of products approved in the U.S. to obtain registration in new markets by issuing the appropriate export certificates and, in certain instances, will consider products not approved or still under review. In Part 2, we will examine the EMA's equivalent instrument, the certificate of medicinal product (CMP), and discuss exporting EU-manufactured product to foreign markets, including obtaining an EMA-issued CMP for a product not approved in the EU, under a provision known as Article 58.

Resources:

- Guidelines on the Implementation of the WHO certification scheme on the Quality of Pharmaceutical Products Moving in International Commerce: https://www.who.int/medicines/areas/quality_safety/regulation_legislation/certification/guidelines/en/
- FDA Export Certificates, Guidance for Industry, July 2004: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-export-certificates
- Certificates of Pharmaceutical Product: General Information, December 2, 2020: https://www.fda.gov/drugs/human-drug-imports/certificates-pharmaceutical-product-general-information

About The Author:

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