
Manual of Standard Operating Procedures and Policies

License Applications

Issuance and Reissuance of Licenses for Biological Products

SOPP 8403

Version #2

April 6, 1999

1. Purpose

The purpose of this document is to describe how the Center for Biologics Evaluation and Research (CBER) will issue biologics licenses. It describes the procedures and communications that should take place between the CBER offices when processing and issuing these licenses.

2. Background

Section 351(a) of the PHS Act, as amended November 21, 1997 (the Food and Drug Administration Modernization Act; Public Law 105-115) mandates in part that no person shall introduce or deliver for introduction into interstate commerce any biological product unless a biologics license is in effect for that product. In the past, both an establishment license (one per legal entity) and product license (one for each approved product) have been issued. However, as of February 19, 1998 (effective date of the Modernization Act), Biologics License certificates will be issued for all new biological products and when existing licenses are reissued.

The regulation promulgated under the PHS Act, Title 21 *Code of Federal Regulations*, Section 600.3 (t) defines the manufacturer to include any legal person or entity, including an individual, association, corporation or chartered organization, who is an applicant for a license where the applicant assumes the responsibility for ensuring compliance with applicable product and establishment standards. The applicant is not required to perform any of the manufacturing steps, but instead may contract with other firms to perform all or part of the manufacture of the product.

3. Policy

It is the policy of CBER that biologics license certificates, each with a unique U.S. License number, will be issued to the applicant as identified on the biologics or establishment license application form. Each applicant will be issued only one biologics license certificate.

4. General Information

Types of licenses

As of February 19, 1998, all U.S. Licenses issued or reissued will be in the form of a biologics license certificate. Only one biologics license certificate will be issued per applicant, no matter how many licensed products the manufacturer makes. Manufacturing sites will not be identified on the biologics license certificate; all manufacturing sites must be listed on the establishment or biologics application form and they will be identified in the license issuance/reissuance letter.

Identification of the License Holder when Issuing Licenses

Although form 3210 requests that a certificate of incorporation or other legal document be included in the package for an initial establishment license application, it is no longer mandatory to submit a certificate of incorporation or organizational chart for the 3210 or 356h forms. They are not requested as part of the Biologics License Application.

The use of the term applicant applies to all products licensed by CBER. The name of the license holder will be as it appears on the establishment license application form, or biologics license application form. If a certificate of incorporation has been submitted, and it is different from the name that appears on the application, the discrepancy should be clarified prior to issuing the license.

The address of the applicant is the address that appears on the establishment license or biologics license application form. It does not have to be a location engaged in manufacturing.

Reissuance of licenses

Whenever a license is reissued, the old license(s) will be revoked. The revocation date of the old license(s) will be the same date as the reissuance date of the new license.

When there is a change in the applicant resulting in a new name due to sale, merger, subdivision, or a name change, a new U.S license number will be issued to the new applicant. Pending supplements of the previous license holder will be transferred to the new license holder, if appropriate.

When there are changes to the operating facilities, manufacturing procedures and responsible personnel with no change in the license holder (same applicant), the license number will not be affected. New operating facilities should be reported in a prior approval supplement as prescribed in 21 CFR 601.12(b).

License Revocation and withdrawals

Voluntary revocation of a biologics, product or establishment license (or location on a license) may be requested by the license holder (applicant).

Revocation for cause will be coordinated between the Office of Compliance and Biologics Quality (OCBQ), and the product review and application divisions, as appropriate. The Office of Compliance and Biologics Quality will be the lead when there is revocation for cause.

Requests for voluntary revocation by the applicant after initiation of a compliance action (including application integrity audits) should be coordinated between the product review divisions, product application divisions and DMPQ, in consultation with the Division of Case Management, OCBQ.

All pending biologics, establishment or product license supplements will be withdrawn at the time of revocation.

Checking compliance status when issuing licenses

Prior to the issuance or reissuance of any license, a check of the compliance status of the applicant should be made by consulting the Division of Case Management, OCBQ.

If the applicant is undergoing integrity review, prior to the licensing decision, the product review office, will confer with the Division of Case Management, OCBQ, in accordance with SOPP 8407 "Compliance Status Checks."

5. Responsibilities and Procedures

New biologics license issuance

The applications division of the Office with product responsibility will be responsible for issuing the biologics license certificate.

The Center Director will sign all licenses except for blood and blood components for transfusion and source plasma. Licenses for these products will be signed by the Director, OBRR.

The approval letter will be prepared by the Office with product responsibility. The letter issued with the new biologics license certificate will identify all products and manufacturing locations covered under the license. If separate product and establishment applications were submitted prior to the effective date of the BLA provisions, one approval letter will be prepared and a biologics license certificate will be issued.

The applications division responsible for preparing the license(s) will make the appropriate entries into the CBER database system (BRMS or equivalent). Data entry should be completed in the same month that the license was issued.

A biologics license certificate will only be issued for the first product from an applicant; subsequent product approvals will not require additional license certificates. The approval letter date will serve as the effective date for licensure of subsequent products.

The license and approval letter will be dated with the same date.

Reissuance of a biologics license necessitated solely by a change in product name

These reissuances will be the responsibility of the product application division in the Office with product responsibility. A reissuance of this kind will require only an approval letter if a biologics license certificate was previously issued.

Reissuance of license due to changes in the applicant

When the applicant changes, DMPQ will prepare the new biologics license certificate in consultation with the application division in the Office having product responsibility. If revised labeling has not been submitted, DMPQ should request this from the applicant and forward it to the application division with product responsibility. DBA will prepare the new biologics license certificate for blood and blood components for transfusion and source plasma.

The Center Director signs all licenses except for blood and blood components for transfusion and source plasma. Licenses for these products will be signed by the Director, OBRR.

The letter issued with the new biologics license certificate (Appendix 1, example) will identify all products and manufacturing locations covered under the license. A request for return of previously

held licenses (establishment and product(s) or biologics) will be made so that notice of revocation may be made thereon.

The letter will be signed by the Director, OCBQ and the Director of the Office with product responsibility with the exception of blood and blood components for transfusion and plasma. The reissuance letter for these products will be signed by the Director, OBRR.

Pending supplements will be transferred from the old license number to the new. RIMS staff should be notified of the need to transfer these supplements.

Reissuance of license for revocation or addition of a manufacturing location

If an applicant has a biologics license certificate, the addition or revocation of a manufacturing location will be indicated in the letter to the applicant. A new biologics license certificate will not be issued.

If an applicant has not been previously issued a biologics license certificate, a biologics license certificate will be issued to the applicant in conjunction with the letter to the applicant. The biologics license certificate will have the same U.S. license number as the firm's previous license certificates.

The addition of a manufacturing location will require submission and approval of a prior approval supplement or supplements.

The letter issued with the new biologics license certificate (Appendix 2, example) will identify all products and manufacturing locations covered under the license. A request will be made for return of all previously issued licenses (establishment and product(s)) so that notation of revocation may be made thereon.

The letter will be signed by the Director, OCBQ and the Director of the Office with product responsibility, with the exception of blood and blood components for transfusion and source plasma. The reissuance letter for these products will be signed by the Director, OBRR.

Pending supplements which are tied to a location undergoing revocation must either be withdrawn by the firm or transferred to locations covered under the license, when feasible. RIMS staff should be notified of the need to transfer supplements.

Official license files

Copies of all license certificates issued and approval letters will be filed in the official license files, which are maintained in DMPQ.

6. Effective Date

April 6, 1999

7. Appendices

Appendix 1

[Reissuance letter due to Change in Applicant](#)

Appendix 2

Reissuance letter due to Revocation or Addition of a Manufacturing Location

8. **History**

Version 2. This version incorporates changes resulting from the creation of the Office of Compliance and Biologics Quality and revisions to 21 CFR 600.3(t) and 601.2(c). It replaces SOPP 8403 version 1 issued August 27, 1997.

Written / Revised By	Approved By	Approval Date	Version Number	Comment
CBER Application Policy Task Force	M. Beatrice	9/10/1993	#1	OD-R-3-93 reissued as SOPP 8403 in August 1997. No change to Guide content.
RMCC	Rebecca Devine	4/6/1999	#2	Incorporates changes resulting from creation of Office of Compliance and Biologics Quality and revisions to 21 CFR 600.3(t) and 601.2(c).

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