POLICY AND PROCEDURES

Office of Surveillance and Epidemiology

Responding to Requests For Waivers of Postmarketing Safety Reporting Requirements under 21 CFR §§ 314.80 (NDAs), 314.98 (ANDAs), and 600.80 (BLAs)

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PURPOSE

This MAPP explains the policy and procedures to be used in the Center for Drug Evaluation and Research (CDER) for handling requests for waivers of postmarketing safety reporting requirements in 21 CFR §§ 314.80, 314.98, and 600.80, which pertain to new drug applications (NDAs), abbreviated new drug applications (ANDAs), and biologics license applications (BLAs),[1] respectively. These waiver requests are handled by CDER's Office of Surveillance and Epidemiology (OSE) according to the policy and procedures outlined in this MAPP.

BACKGROUND

Regulations for postmarketing safety reporting requirements

Applicants of approved NDAs and approved ANDAs have postmarketing adverse drug experience reporting obligations for their products under 21 CFR §§ 314.80 and 314.98, respectively. Licensed manufacturers of approved BLAs (licensed manufacturers) have similar postmarketing adverse experience reporting obligations under 21 CFR § 600.80.

Regulations for waivers of postmarketing safety reporting requirements

Under 21 CFR § 314.90(a), applicants may request waivers of any postmarketing safety reporting requirement under 21 CFR § 314.80. Similarly, under 21 CFR § 600.90(a),

[1] For purposes of this MAPP, BLAs include only the therapeutic biological products regulated by CDER.

licensed manufacturers may request waivers of any postmarketing safety reporting requirement under 21 CFR § 600.80. Applicants of ANDAs may request postmarketing safety reporting requirement waivers under 21 CFR § 314.99(b), which requires them to comply with the waiver regulations under 21 CFR § 314.90. The waiver requests must include one of the following justifications for a waiver: (1) an explanation as to why compliance with the requirement is unnecessary or cannot be achieved, (2) a description of an alternative submission that satisfies the purpose of the requirement, or (3) other information justifying the waiver.

Under 21 CFR §§ 314.90(b) and 600.90(b), the Food and Drug Administration (FDA) has the authority to grant or deny the waiver requests made by applicants and licensed manufacturers.

Guidances for Industry

Considerations in requesting waivers of postmarketing safety reporting requirements are described in several guidances for industry.

Guidance for Industry: Postmarketing Adverse Experience Reporting for Human Drug and Licensed Biological Products: Clarification of What to Report (1997). This guidance informs applicants and licensed manufacturers that FDA is willing to consider requests for waivers of the requirement for periodic submission of individual case safety reports (ICSRs) for adverse experiences that are determined to be both non-serious and labeled (NS-L waiver request).

Draft Guidance for Industry: Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines (2001). This guidance includes information on NS-L waiver requests. In addition, it states that applicants and licensed manufacturers may request waivers of the requirements under 21 CFR §§ 314.80(c)(2) and 600.80(c)(2) to submit postmarketing periodic safety reports in the periodic adverse (drug) experience report format and to base the reporting interval on the U.S. application approval date. Alternatively, applicants and licensed manufacturers may request to prepare these reports using the International Conference on Harmonisation (ICH) Periodic Safety Update Report (PSUR) format and to base the reporting interval on a harmonized date (PSUR waiver request). The 1996 ICH guidance entitled *E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drug*s and the February 2004 ICH guidance entitled *Addendum to E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs*[2] provide information on the format and content of the PSUR to aid in preparation of these reports.

[2] This guidance was developed within the Expert Working Group (Efficacy) of the ICH Technical Requirements for Registration of Pharmaceuticals for Human Use and has been subject to consultation by the regulatory parties, in accordance with the ICH process. This document has been endorsed by the ICH Steering Committee at *Step 4* of the ICH process, November 1996. At *Step 4* of the process, the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan, and the United States. This guidance was published in the *Federal Register* on May 19, 1997 (62 FR 27470), and is applicable to prescription drug and biological products.

Although these guidance documents focus on two specific types of waivers under 21 CFR §§ 314.90(a) and 600.90(a), applicants and licensed manufacturers may request a waiver of any postmarketing safety reporting requirement under 21 CFR §§ 314.80 and 600.80, respectively.

POLICY

1. OSE is responsible for reviewing and responding to written waiver requests submitted under 21 CFR §§ 314.90, 314.99(b) and 600.90 regarding postmarketing safety reporting requirements under 21 CFR §§ 314.80, 314.98, and 600.80, respectively.

2. The OSE Office Director, or the Office Director's designee, has authority to grant or deny, or otherwise respond to, such waiver requests.

3. The OSE/Immediate Office (IO) will collaborate with other OSE divisions and CDER offices, as appropriate, to respond to waiver requests.

4. Generally, waivers requesting permission to submit periodic safety reports in PSUR format and waivers requesting permission not to submit ICSRs for NS-L adverse experiences will be granted, unless a waiver is not justified because of a product-specific, safety-related concern.

RESPONSIBILITIES AND PROCEDURES

1) Verifying the information provided in the incoming waiver request letter

a) The OSE/IO regulatory analyst will ensure the waiver request has been submitted appropriately by the applicant, licensed manufacturer, or an appropriate designee (the requestor) and will obtain additional information from the requestor, if needed.

i) Only waiver requests received in writing, and that have been submitted to each application for which the waiver is being requested will be reviewed (one waiver request letter may reference multiple applications, but a copy of that letter should be submitted to each of those applications).

b) If OSE receives a request for a waiver (for a CDER-regulated product) of a requirement outside of 21 CFR § 314.80 or 21 CFR § 600.80, the OSE/IO regulatory analyst will forward the request to the appropriate CDER office. Similarly, if OSE receives a waiver request pertaining to a product regulated by another FDA center, the OSE/IO regulatory analyst will forward the request to the appropriate center. In both cases, the OSE/IO regulatory analyst will inform the requestor that the waiver request has been forwarded.

2) Coding and tracking of waiver requests

a) The OSE/IO regulatory analyst will ensure that the incoming waiver request letter is accurately archived and coded in the appropriate data management system(s). This step includes logging the request in the OSE waivers spreadsheet for internal tracking purposes.

3) Reviewing the waiver request

a) The OSE/IO regulatory analyst will review all waiver requests and determine whether the request requires input from CDER reviewers (see Attachments 1 for examples).

i) For waiver requests that do not require reviewer input (see Attachment 1 for examples):

(1) Before OSE issues a response letter, the OSE/IO regulatory analyst will send an e-mail to the appropriate OSE safety evaluator team leader (SE TL) in OSE's Division of Pharmacovigilance (DPV) I or II and to the safety regulatory health project manager (SRPM) in the appropriate review division in OND to inform them (1) of the details of the request being made, (2) that the request does not require review because it will be routinely granted or routinely denied, and (3) that a response letter will be issued within the next two weeks. The OND review division Deputy Director of Safety (DDS) will be copied on this e-mail.

(2) Reviewers who are in agreement do not need to send a reply back to the OSE/IO regulatory analyst. The OSE/IO regulatory analyst will draft a response letter as described under Procedures/Step 4 below.

(3) Reviewers who do not agree that the waiver request that should be granted, will need to transmit their reasons by e-mail to the OSE/IO regulatory analyst within the timeframe specified in the e-mail (generally one week). The OSE/IO regulatory analyst will discuss the objection with the OSE Office Director and work with CDER staff (as appropriate) and the OSE Office Director to reach alignment on the response.

ii) For waiver requests that require reviewer input:

(1) The OSE/IO regulatory analyst will send an e-mail to the relevant CDER reviewers to (1) inform them of the details of the request, and (2) ask for their feedback on whether the request should be granted, granted with modifications, or denied. Typically the e-mail is sent to the OSE SE TL and OND SRPM, with a copy to the OND DDS, but input from other CDER groups is sometimes needed (e.g., CDER's Office of Compliance, OSE's Division of Medication Error Prevention and Analysis, or CDER's Office of Generic Drugs (OGD)).

(2) The reviewers will provide feedback by e-mail to the OSE/IO regulatory analyst within the specified timeframe.

(a) The timeframe is typically two weeks, but may be sooner if warranted (e.g., requests pertaining to the submission of 15-day "Alert reports").

(b) If there is disagreement among the reviewers on the response, the OSE/IO regulatory analyst will work with CDER staff (as appropriate) to reach alignment.

(3) If the reviewers' decision is to grant the requested waiver but with modifications to the original request, the OSE/IO regulatory analyst will notify the requestor by telephone or e-mail and find out whether or not they agree to the modifications.

(a) If the requestor agrees to the modifications, the response letter will be drafted, granting the requested waiver with the reviewers' modifications.

(b) If the requestor disagrees with the modifications, they may propose an alternative or withdraw the request.

(i) If the requestor proposes an alternative, the review process will be repeated.

(ii) If the requestor withdraws the request, a response letter acknowledging the withdrawal will be issued.

(iii) If the requestor chooses neither, a letter denying their original waiver request will be issued.

(4) If the reviewers' decision is to deny the requested waiver, the OSE/IO regulatory analyst will prepare the denial letter.

4) Preparing and signing the waiver response letter

a) The OSE/IO regulatory analyst will draft a response letter, once all the necessary input is received.

b) The OSE Office Director, or the Office Director's designee, will review the draft letter.

c) Once any outstanding issues are resolved, the OSE Office Director, or the Office Director's designee, will sign the letter.

i) For all waiver response letters, a copy of the letter will be provided to the OSE SE TL, the OSE ADRA, and CDER's Office of Compliance. For waivers pertaining to NDAs and BLAs, a copy of the letter will be provided to the

OND DDS and OND SRPM. For waivers pertaining to ANDAs, a copy of the letter will be provided to OGD.

5) Archiving waiver documents

a) The OSE/IO regulatory analyst will ensure that the waiver response letter is accurately archived in the appropriate data management system(s).

REFERENCES

- 21 CFR § 314.80 *Postmarketing reporting of adverse drug experiences.* (NDAs)
- 21 CFR § 314.90 *Waivers.* (NDAs)
- 21 CFR § 314.98 *Postmarketing reports.* (ANDAs)
- 21 CFR § 314.99(b) *Other responsibilities of an applicant of an abbreviated application.* (Waivers)
- 21 CFR § 600.80 *Postmarketing reporting of adverse experiences.* (BLAs)
- 21 CFR § 600.90 *Waivers.* (BLAs)
- Guideline for Postmarketing Reporting of Adverse Drug Experiences (1992)
- Guidance for Industry: Postmarketing Adverse Experience Reporting for Human Drug and Licensed Biological Products: Clarification of What to Report (1997)
- Draft Guidance for Industry: Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines (2001)
- Guidance for Industry: E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs (1996)
- Guidance for Industry: Addendum to E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs (2004)

DEFINITIONS

Non-serious, labeled (NS-L) adverse experience – an adverse experience that is both included in the current version of the product labeling and has not resulted in a serious outcome ("serious" as defined under 21 CFR § 314.80(a) *Serious adverse drug experience* or 21 CFR § 600.80(a) *Serious adverse experience*).

NS-L waiver request – a request to be waived of the requirement to submit ICSRs for NS-L adverse experiences (21 CFR § 314.80(c)(2)(ii)(*b*) or 21 CFR § 600.80(c)(2)(ii)(B)).

Periodic adverse (drug) experience report – the periodic safety report required to be submitted under 21 CFR §§ 314.80(c)(2) and 600.80(c)(2).

Periodic Safety Update Report (PSUR) – the international periodic safety report whose format and content are specified by the ICH guidance *E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs*.

PSUR waiver request – a request to submit a PSUR in lieu of a periodic adverse (drug) experience report as described under 21 CFR §§ 314.80(c)(2) and 600.80(c)(2).

"Other" waiver request – a request for a waiver of a postmarketing safety reporting requirement under 21 CFR § 314.80 or 21 CFR § 600.80 that is not an NS-L waiver request or a PSUR waiver request.

EFFECTIVE DATE

This MAPP is effective upon date of publication.

CHANGE CONTROL TABLE

Effective Date	Revision Number	Revisions
11/16/1999	Initial	N/A
5/6/11	1	This revision modifies the roles of CDER staff and adds new and more detailed instructions for coding and the coordination of the waiver response, and includes an attachment that lists examples of waiver requests that do not require CDER reviewer input (these requests are either routinely granted or routinely denied).
3/1/12	6700.5, Initial	MAPP number changed from 6004.1 to 6700.5, to place this MAPP within the OSE numbering block.

ATTACHMENT 1
Examples of waiver requests that do not require input.

These waiver requests are routinely granted or routinely denied. Typically, requests not included in the lists below will require input from reviewers before a response is issued.

Examples of waiver requests that are routinely granted; CDER has allowed firms to:

- Submit a PSUR in lieu of a periodic adverse (drug) experience report, with no proposed change in frequency of reporting. A one-time shift in the reporting interval to align to the PSUR data lock point is permitted (waiver of the requirement under 21 CFR §§ 314.80(c)(2) and 600.80(c)(2));

- Extend the 15-day timeframe for the submission of expedited ICSRs (15-day "Alert reports") from annual poison control center reports or medical examiner reports (waiver of the requirement under 21 CFR §§ 314.80(c)(1)(i) and 600.80(c)(1)(i)); and

- Electronically submit non-expedited ICSRs on an ongoing, real-time basis, rather than in a single batch at the time the periodic report is submitted (waiver of the requirement under 21 CFR §§ 314.80(c)(2)(ii)(*b*) and 600.80(c)(2)(ii)(B)).

- No longer submit ICSRs for NS-L adverse experiences (waiver of the requirement under 21 CFR §§ 314.80(c)(2)(ii)(*b*) and 600.80(c)(2)(ii)(B)). This waiver, however, is not routinely granted for new molecular entities that have been approved for less than three years.

Examples of waivers requests that are routinely denied; CDER has not permitted firms to:

- Discontinue all postmarketing safety reporting for active (i.e., not withdrawn) applications (waiver of requirements under 21 CFR §§ 314.80 and 600.80);

- Not submit ICSRs for serious adverse experiences or unlabeled adverse experiences (waivers of the requirements under 21 CFR §§ 314.80(c)(1), 314.80(c)(2)(ii)(*b*) and 600.80(c)(1), 600.80(c)(2)(ii)(B)); and

- Submit domestic ICSRs on the Council for International Organizations of Medical Sciences) (CIOMS) I form instead of FDA Form 3500A.