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)

Table of Contents

PURPOSE

This MAPP describes the policy, responsibilities, and procedures used in the Center for Drug Evaluation and Research (CDER) for responding to requests for waivers of postmarketing safety reporting requirements submitted by applicants of new drug applications (NDAs), abbreviated new drug applications (ANDAs), and biologics license applications (BLAs)[1] regulated by CDER.

This MAPP applies to waivers of requirements for the submission of postmarketing safety reports (i.e., individual case safety reports and periodic safety reports). This MAPP does not apply to waivers of the electronic reporting requirements,[2] waivers of other electronic submission requirements covered under section 745A(a) of the Federal Food, Drug, and Cosmetic Act,[3] or waivers of the postmarketing reporting requirements

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

[2] Requesting waivers of the electronic reporting requirement is described under the 2014 final rule entitled Postmarketing Safety Reports for Human Drug and Biological Products; Electronic Submission Requirements (79 FR 33072, June 10, 2014). For more information, see FDA's Guidance for Industry Providing Submissions in Electronic Format — Postmarketing Safety Reports, available on the FDA guidance documents webpage: https://www.fda.gov/regulatory-information/search-fda-guidance-documents

[3] For more information, see FDA Guidance for Industry, Providing Regulatory Submissions in Electronic

described under 21 CFR 314.81 and 21 CFR 600.81.

BACKGROUND

Applicants of approved NDAs, ANDAs, and BLAs have postmarketing adverse drug experience reporting obligations for their products under 21 CFR 314.80, 314.98, and 600.80, respectively.

Under 21 CFR 314.90(a) for NDAs, 314.99(b) for ANDAs, and 600.90(a) for BLAs, applicants[4] may request waivers of a postmarketing safety reporting requirement. Each postmarketing safety reporting waiver request must include at least one of the following:

- An explanation why the applicant's compliance with the requirement is unnecessary or cannot be achieved[5].
- A description of an alternative submission that satisfies the purpose of the requirement[6].
- Other relevant information justifying a waiver[7].

Under 21 CFR 314.90(b) and 600.90(b), the Food and Drug Administration (FDA) has the authority to grant or deny requests for waivers of requirements described under 21 CFR 314.50 through 314.81 and 21 CFR 600.80 and 21 CFR 600.81, respectively. Similarly for ANDAs, FDA has the authority under 21 CFR 314.99(b) to grant or deny an applicant's request to waive a requirement described under 21 CFR 314.92 through 314.99 and 21 CFR 314.98(a) requires compliance with § 314.80 regarding the reporting and recordkeeping of adverse drug experiences. For a description of examples of waiver requests generally granted or routinely denied, refer to Attachment 1.

FDA is a regulatory member of the *International Council for Harmonisation* (ICH). The ICH, including FDA, adopted the ICH E2C(R2) Periodic Benefit-Risk Evaluation Report (PBRER) format as the common standard for periodic benefit-risk evaluation reporting on marketed products (including approved drugs that are under further study) among the ICH regions.[8]

Format – Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD. Specifications, available on the FDA guidance documents webpage: https://www.fda.gov/regulatory-information/search-fda-guidance-documents

[4] An applicant or their designee (e.g., U.S. Agent, contract research organization) may submit a safety waiver request.

[5] See 21 CFR 314.90(a)(1) and 21 CFR 600.90(a)(1)

[6] See 21 CFR 314.90(a)(2) and 21 CFR 600.90(a)(2)

[7] See 21 CFR 314.90(a)(3) and 21 CFR 600.90(a)(3)

[8] See FDA Guidance for Industry, E2C(R2) Periodic Benefit-Risk Evaluation Report (PBRER), available on

FDA uses the waiver provisions[9] to accept periodic postmarketing safety reports in the E2C(R2) PBRER format instead of the periodic adverse drug experience report (PADER) format or periodic adverse experience report (PAER) format required under FDA regulations.[10]

POLICY

1. The Office of Surveillance and Epidemiology (OSE) will review and respond to written waiver requests submitted under 21 CFR 314.90, 314.99(b) and 600.90 regarding postmarketing safety requirements under 21 CFR 314.80, 314.98 and 600.80, respectively.

2. OSE will issue a waiver response letter to waiver requests submitted electronically to the NDA, ANDA, or BLA.

3. The OSE Office Director, or the Office Director's designee, has authority to grant, deny, or otherwise respond to, postmarketing safety reporting waiver requests.

4. The Office of New Drugs (OND) will forward all postmarketing safety reporting waiver requests received by OND staff to OSE for a response to the applicant.

5. The Office of Generic Drugs (OGD) will forward all postmarketing safety reporting waiver requests received by OGD staff to OSE for a response to the applicant.

RESPONSIBILITIES

1. OSE Regulatory Affairs Staff (RAS):

- Reviews, tracks, and responds to all postmarketing safety reporting waiver requests and related correspondence received in the document tracking system and/or RAS mailbox account, OSE.PMKTREGS@fda.hhs.gov.

- Ensures that the waiver response letter and any supporting documentation, such as email correspondence from the requestor or

the FDA guidance documents webpage: https://www.fda.gov/regulatory-information/search-fda-guidance-documents

[9] 21 CFR 314.90, 314.99(b), and 600.90

[10] For more information, see FDA Guidance for Industry, Providing Postmarketing Periodic Safety Reports in the ICH E2C(R2) Format (Periodic Benefit-Risk Evaluation Report), available on the FDA guidance documents webpage: https://www.fda.gov/regulatory-information/search-fda-guidance-documents

CDER subject matter experts (SMEs), is archived in the appropriate electronic record keeping system.

- Serves as the point of contact for the applicant concerning the waiver request and, when relevant, the applicant's designee.

- Consults CDER staff as applicable and considers their recommendations when developing the waiver response letter.

2. **OSE RAS Director**:

   Provides direction to resolve policy questions that arise when responding to waiver requests.

3. **OSE Office Director or Designee**:

   - Reviews the draft letter, and signs the waiver response letter providing final approval of all postmarketing safety reporting waivers.

4. **OND Office of Regulatory Operations (ORO) Regulatory Project Manager (RPM):**

   - Instructs applicants to submit written waiver requests to the application, if the applicant submits a waiver request directly to the RPM by email.

   - Forwards correspondence related to postmarketing safety reporting waivers to the RAS mailbox account (OSE.PMKTREGS@fda.hhs.gov) as appropriate.

   - Ensures newly received written waiver requests are triaged properly for correct incoming document coding and reviewer assignment(s) (i.e., to RAS mailbox account) in the OND system of record.

5. **OGD RPM from either OGD/ORO or OGD/Office of Safety and Clinical Evaluation (OSCE)**

   - Instructs applicants to submit written waiver requests to the application, if the applicant submits a waiver request directly to the RPM by email.

   - Forwards correspondence related to postmarketing safety reporting waivers to the RAS mailbox account OSE.PMKTREGS@fda.hhs.gov as appropriate.

   - Ensures newly received written waiver requests are triaged properly for correct incoming document coding and reviewer assignment(s) (i.e., to RAS mailbox

account) in the OGD system of record.

6. **Subject Matter Experts (SMEs)[11] e.g., appropriate OSE and OND or OGD staff:**

   - Provide recommendations on waiver requests other than those described in Attachment 1 within the specified timeframe when consulted by RAS.

PROCEDURES

1. Receipt of the Postmarketing Safety Reporting Waiver Request

1.1. RAS verifies that the incoming submission is a request for a waiver of the postmarketing reporting requirements for a CDER-regulated product and ensures that the waiver request is submitted appropriately by the applicant or their designee (the requestor).

1.2. If applicable, RAS forwards any requests beyond the scope of postmarketing safety reporting waiver requests specified under 21 CFR 314.80 and 600.80 to the appropriate CDER office or FDA Center to issue a response to the applicant.

1.3. If applicable, OND ORO RPM and/or OGD RPM will forward postmarketing safety waiver requests and/or related correspondence to RAS.

2. Review of the Postmarketing Safety Reporting Waiver Request

2.1. RAS reviews all incoming postmarketing safety reporting waiver requests to determine if the request requires:

2.1.1. additional information from the applicant

2.1.2. input from SMEs (e.g., appropriate OSE and OND or OGD staff) for waiver consultations other than those described in Attachment 1.

2.2. For waiver requests that do not require additional information from the applicant or SME input, RAS proceeds with drafting the waiver response letter (see Step 4).

3. Obtain Additional Information or SME Input

[11] Typically, RAS consults with SMEs in the OSE Division of Pharmacovigilance team leader and the OND safety regulatory project manager, with a copy to the OND Deputy Director of Safety. Occasionally, input from other OSE or CDER groups is needed (e.g., OSE's Division of Mitigation Assessment and Medication Error Surveillance, CDER's Office of Compliance or CDER's OGD).

3.1. For waiver requests that require additional information from the applicant, RAS contacts the signatory of the waiver request letter to obtain the relevant information.

3.2. For waiver requests that require SME input, RAS consults with the appropriate SMEs in CDER for input regarding the postmarketing safety reporting waiver request.

3.3. The SMEs provide their recommendation(s) on whether the waiver request should be: granted; granted with modifications; granted with delayed implementation; denied; or deferred.

4. Prepare and Issue the Waiver Response Letter

4.1. RAS drafts a waiver response letter in accordance with OSE procedures.

4.2. The OSE Office Director or designee reviews the draft letter, approves and signs the waiver response letter.

5. Archive the Waiver Documents

5.1. RAS ensures that the waiver response letter and any supporting documentation, such as email correspondence from the requestor or SMEs, is archived in the appropriate electronic record keeping system.

REFERENCES

1. 21 CFR 314.80 *Postmarketing reporting of adverse drug experiences.* [NDAs]
2. 21 CFR 314.90 *Waivers.* [NDAs]
3. 21 CFR 314.98 *Postmarketing reports.* [ANDAs]
4. 21 CFR 314.99(b) *Other responsibilities of an applicant of an ANDA.* [ANDA Waivers]
5. 21 CFR 600.80 *Postmarketing reporting of adverse experiences.* [BLAs]
6. 21 CFR 600.90 *Waivers.* [BLAs]
7. Guideline for Postmarketing Reporting of Adverse Drug Experiences (1992)
8. Guidance for Industry: Postmarketing Adverse Experience Reporting for Human Drug and Licensed Biological Products: Clarification of What to Report (1997)
9. Draft Guidance for Industry: Postmarketing Safety Reporting for Human Drug

and Biological Products Including Vaccines (2001)

10. Guidance for Industry: E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs (1996)

11. Guidance for Industry: Addendum to E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs (2004)

12. Guidance for Industry: E2C(R2) Periodic Benefit-Risk Evaluation Report (PBRER) (2016)

13. Guidance for Industry: Providing Postmarket Periodic Safety Reports in the ICH E2C(R2) Format (Periodic Benefit-Risk Evaluation Report) (2016)

DEFINITIONS

Applicant: any person who owns an approved new drug application (NDA), abbreviated new drug application (ANDA), or biologics license application (BLA).

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" (as defined under 21 CFR 314.80(a) *Serious adverse drug experience* or 21 CFR 600.80(a) *Serious adverse experience*) outcome.

Periodic Adverse (Drug) Experience Report (PADER or PAER): the periodic safety report required under 21 CFR 314.80(c)(2) or 600.80(c)(2).

Periodic Benefit-Risk Evaluation Report (PBRER): the current E2C periodic safety report.[12] The PBRER replaced the Periodic Safety Update Report (PSUR) in 2012.

Periodic Safety Report (PSR): a report that provides a comprehensive picture of the safety of approved products marketed under ANDAs, NDAs, and BLAs focusing on a defined time period in the lifecycle of the product. The PADER, PAER, PSUR, and PBRER are examples of PSRs.

Requestor: a person who submits the request for a waiver. The requestor can be the applicant or their designee (e.g., U.S. Agent, contract research organization).

EFFECTIVE DATE

[12] See FDA Guidance for Industry E2C(R2) Periodic Benefit-Risk Evaluation Report (PBRER), available on the FDA guidance documents webpage: https://www.fda.gov/regulatory-information/search-fda-guidance-documents

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.
3/1/12	6700.5, Initial	MAPP number changed from 6004.1 to 6700.5 to place this MAPP within the OSE numbering block.
	2	Update to the MAPP to reflect changes to the ICH E2C format, the availability of new FDA guidances for industry, and changes in reporting requirement with the publication of the 2014 electronic safety reporting rule. The responsibility section was separated from the procedures section.

ATTACHMENT 1: Generally granted and routinely denied waiver requests

CDER generally grants requests to:

- Submit the International Council for Harmonisation (ICH) E2C report format in lieu of a periodic adverse drug experience report (PADER) or periodic adverse experience report (PAER) required under §§ 314.80(c)(2), 314.98(a) and 600.80(c)(2), with no proposed change in frequency of reporting.
- Change the data lock point (DLP), provided that there are no resulting gaps in reporting.
- Extend the 15-calendar day timeframe for the submission of expedited individual case safety reports (ICSRs) for annual poison control center reports or medical examiner reports. It would be a waiver of the requirement under §§ 314.80(c)(1)(i), 314.98(a) and 600.80(c)(1)(i).
- Not submit ICSRs for non-serious, labeled (NS-L) adverse experiences, *except for new molecular entities (NMEs) approved for less than 3 years.* It would be a waiver of the requirement under §§ 314.80(c)(2)(ii)(B), 314.98(a) and 600.80(c)(2)(ii)(B).

CDER routinely denies requests to:

- Discontinue all postmarketing safety reporting for active applications (e.g., not withdrawn per 21 CFR 314.152).
- Not submit ICSRs for NS-L adverse experiences under § 600.80(c)(2)(ii)(B) for biological products in the first year of approval.
- Not submit ICSRs for serious, unexpected adverse experiences, required under §§ 314.80(c)(1), 314.98(a) or 600.80(c)(1), or serious, expected or nonserious, unlabeled adverse experiences, required under §§ 314.80(c)(2)(ii)(B), 314.98(a) or 600.80(c)(2)(ii)(B).
- Grant a waiver retrospectively to bring an applicant into compliance after the applicant has failed to submit reports or has submitted reports late without prior notification to FDA.
- Submit the periodic safety report less frequently than annually.