

III.D.2. Information Sufficient To Consider Product Administration Changes

Proposed §§ 310.305(c)(2)(ii), 314.80(c)(2)(ii), and 600.80(c)(2)(ii) would require that manufacturers and applicants submit to FDA information, received or otherwise obtained, whether foreign or domestic, that would be sufficient, based upon appropriate medical judgment, to consider changes in product administration. Manufacturers and applicants would be required to submit this information to the agency as soon as possible, but in no case later than 15 calendar days after the manufacturer or applicant determines that the information qualifies for expedited reporting. Examples of such information include any significant unanticipated safety finding or data in the aggregate from an in vitro, animal, epidemiological, or clinical study, whether or not conducted under an IND, that suggests a significant human risk, such as reports of mutagenicity, teratogenicity, or carcinogenicity, or reports of a lack of efficacy with a drug or biological product used in treating a life-threatening or serious disease. The proposed rule would require that manufacturers and applicants maintain records of their efforts to determine whether information that they have received or otherwise obtained would qualify for expedited reporting under this proposed requirement. This proposed requirement is consistent with the proposed revisions to the premarketing expedited safety reporting regulations at proposed § 312.32(c)(1)(ii) (see section III.B.2.c of this document) and with the ICH E2A guidance (60 FR 11284 at 11286). The proposed amendment would further clarify some of the types of safety information that must be submitted to FDA in an expedited manner.

III.D.3. Unexpected SADRs With Unknown Outcome

FDA expects that, in most cases, manufacturers and applicants will be able to determine the outcome for an SADR (whether the SADR is serious or nonserious). However, in those few cases where a determination may not be possible, FDA would require submission of unexpected SADRs with unknown outcome in an expedited manner (proposed §§ 310.305(c)(2)(iii), 314.80(c)(2)(iii), and 600.80(c)(2)(iii)). Expedited safety reports for unexpected SADRs with unknown outcome would be submitted to FDA within 45 calendar days after initial receipt by the manufacturer or applicant of the minimum data set for the unexpected

SADR. FDA is proposing this action to expedite review of potentially serious SADRs.

The proposed rule would require that manufacturers and applicants reporting an unexpected SADR with unknown outcome include in the expedited safety report the reason(s) for their inability to classify an SADR as either serious or nonserious (*i.e.*, unknown outcome). For this purpose, manufacturers and applicants should include in the expedited report a chronological history of their efforts to determine the outcome of the SADR.

Manufacturers and applicants reporting an unexpected SADR with unknown outcome must exercise due diligence to determine the expectedness for the SADR and to acquire at least the minimum data set for the individual case safety report. For this purpose, these persons would be required to use active query to acquire this information (see section III.C.5 of this document). These persons should include in postmarketing expedited safety reports a chronological history of their efforts to acquire this information if there is a delay in obtaining it.

III.D.4. Always Expedited Reports

Proposed §§ 310.305(c)(2)(iv), 314.80(c)(2)(iv), and 600.80(c)(2)(iv) would require manufacturers and applicants to submit to FDA individual case safety reports for SADRs, received or otherwise obtained, whether foreign or domestic, that are the subject of an always expedited report. These always expedited reports would be submitted to the agency as soon as possible, but in no case later than 15 calendar days after receipt by the manufacturer ("applicant" for proposed §§ 314.80(c)(2)(iv), and 600.80(c)(2)(iv)) of the minimum data set for the report. The following medically significant SADRs, which may jeopardize the patient or subject and/or require medical or surgical intervention to treat the patient or subject, would be subject to an always expedited report:

- Congenital anomalies,
- Acute respiratory failure,
- Ventricular fibrillation,
- Torsades de pointe,
- Malignant hypertension,
- Seizure,
- Agranulocytosis,
- Aplastic anemia,
- Toxic epidermal necrolysis,
- Liver necrosis,
- Acute liver failure,
- Anaphylaxis,
- Acute renal failure,
- Sclerosing syndromes,
- Pulmonary hypertension,
- Pulmonary fibrosis,

• Confirmed or suspected transmission of an infectious agent by a marketed drug or biological product,

• Confirmed or suspected endotoxin shock, and

• Any other medically significant SADR that FDA determines to be the subject of an always expedited report (*i.e.*, may jeopardize the patient or subject and/or require medical or surgical intervention to treat the patient or subject).

These SADRs would be submitted to the agency in an expedited manner whether unexpected or expected and whether or not the SADR leads to a serious outcome. The medical gravity of these SADRs requires expedited reporting.

The agency is proposing that a confirmed or suspected transmission of an infectious agent by a marketed drug or biological product would be the subject of an always expedited report. Examples of such transmissions include human immunodeficiency virus (HIV) transmission by anti-hemophilic factor, hepatitis C transmission by intravenous immunoglobulin, bacterial contamination of albumin leading to sepsis, and parvovirus contamination of anti-hemophilic factor causing an SADR. These SADRs indicate a public health problem that requires expedited review by the agency.

The proposal provides that the agency could make a new SADR the subject of an always expedited report. Such an SADR would only become the subject of these reports if FDA determines that the SADR is medically significant (*i.e.*, may jeopardize the patient or subject and/or require medical or surgical intervention to treat the patient or subject). New SADRs that become the subject of always expedited reports would be included in the agency's current guidance for industry on postmarketing safety reporting for human drugs and licensed biological products.

Proposed §§ 310.305(c)(2)(iv)(B), 314.80(c)(2)(iv)(B), and 600.80(c)(2)(iv)(B) would require that if a full data set is not available for always expedited reports at the time of initial submission of the report to FDA, manufacturers and applicants would submit the information required under proposed §§ 310.305(c)(1)(iv), 314.80(c)(1)(iv) and 600.80(c)(1)(iv) as described in section III.C.5 of this document and also submit a 30-day followup report as described in section III.D.6 of this document. FDA is proposing this action to clarify the importance of acquiring complete information for medically significant SADRs that are the subject of always expedited reports.