This page provides answers to commonly asked questions from industry regarding the technical aspects of submitting postmarketing safety reports for CDER and CBER-regulated combination products approved under an NDA, ANDA, or BLA. For a general resource on this topic, see <u>FDA's Electronic Submissions Webpage</u>. For information on the postmarketing safety reporting requirements for combination products, please refer to FDA's <u>Combination Products Webpage</u>, in particular <u>Postmarketing Safety Reporting for Combination Products Guidance for Industry and FDA Staff</u>.

1. **How do I identify my ICSR as pertaining to a combination product?**

   When submitting ICSRs through ESG identify the report as pertaining to a combination product and complete the tag A.1.FDA.15 <combinationproductreport>=1. When submitting ICSRs through SRP, identify the report as pertaining to a combination product by choosing the "Yes" option for the combination products under the "Report Identifying Information" section.

2. **When reporting an adverse event associated with the drug constituent part of a drug-device combination product (e.g., pre-filled syringe), should the information for the device constituent part also be included in the report?**

   An ICSR for a combination product such as a pre-filled syringe is a report on the product as a whole. Include information on both the device and the drug constituent parts in the report.

3. **If an applicant submits an ICSR for a drug-device combination product and the adverse event is believed to be the result of the device malfunction (e.g., the needle was dull and the patient experienced injection- site bleeding as a result) is the applicant required to provide information on the drug constituent part?**

   Please refer to the response to question 2.

4. **Does the ICH E2B tag "COMP99" refer to a prefix or suffix for an actual NDA number or a 510K?**

   The ICH E2B tag for the authorization/application number element (B.4.k.4.1) <drugauthorizationnumb> with the value "COMP99" is specific to compounded products, therefore not applicable to combination products reporting.

5. **If an applicant holds applications for both combination and non-combination products, which version of the document type definition (DTD) should the applicant use to submit their ICSRs?**

   In this scenario an applicant must submit all ICSRs for a combination product using DTD version 2.2. This version accommodates reporting for both combination and non-combination products. Please note that the use of DTD 2.2, does not prohibit the applicant from submitting ICSRs using DTD 2.1 for non-combination products.

6. **Where can we find current information on the data elements required for submission of safety reports for combination products?**

   Please refer to the current versions of the Technical Specifications Document and the Postmarketing Safety Reporting for Combination Products Guidance for Industry and Staff Guidance for Industry and FDA Staff.

7. **Is there a required or recommended format for the periodic safety reports for combination products marketed under an application?**

   The periodic safety report must address information from any initial and follow-up 5-day and malfunction reports, in addition to any from 15-day reports, submitted during the reporting interval, and should provide this information in the section that contains summary and analysis of reports submitted during the interval. Please refer to section V.B.4 of the Postmarketing Safety Reporting for Combination Products Guidance for Industry and FDA Staff for additional information on preparing the periodic safety report for combination products.

8. **If the ICSR satisfies both 15-day and 5-day reporting requirements, then should the field A.1.9 be populated for a 5-day or a 15-day report?**

   We anticipate that this will be a rare case where these are reported simultaneously, but if that situation occurs, A.1.9 should be populated for a 5-day report.

9. **How should the XML be populated for a BLA-approved combination product consisting of one vial of a biological product along with three device constituent parts to include: 1) syringe, 2) vial adapter, and 3) sterile needle?.**

   The drug section in the XML file should be repeated for each device constituent part. For the example provided in the question, see the XML below.

```
<drug>
<drugcharacterization>1</drugcharacterization>
<medicinalproduct>Bio-A</medicinalproduct>
<obtaindrugcountry>US</obtaindrugcountry>
<drugauthorizationnumb>BLA 000000</drugauthorizationnumb>
<drugauthorizationholder>Company A</drugauthorizationholder>
<drugindicationmeddraversion>20.0</drugindicationmeddraversion>
<drugindication>Chronic myeloid leukaemia</drugindication>
<brandname>Sample Brand name</brandname>
<commondevicename>Syringe</commondevicename>
<productcode>XXX</productcode>
<activesubstance>
<activesubstancename>active A</activesubstancename>
</activesubstance>
```

```
</drug>

<drug>
<drugcharacterization>1</drugcharacterization>
<medicinalproduct>Bio-A</medicinalproduct>
<obtaindrugcountry>US</obtaindrugcountry>
<drugauthorizationnumb>BLA 000000</drugauthorizationnumb>
<drugauthorizationholder>Company A</drugauthorizationholder>
<drugindicationmeddraversion>20.0</drugindicationmeddraversion>
<drugindication>Chronic myeloid leukaemia</drugindication>
<brandname>Sample Brand name</brandname>
<commondevicename>Vial Adapter</commondevicename>
<productcode>YYY</productcode>
<activesubstance>
<activesubstancename>active A</activesubstancename>
</activesubstance>
</drug>

<drug>
<drugcharacterization>1</drugcharacterization>
<medicinalproduct>Bio-A</medicinalproduct>
<obtaindrugcountry>US</obtaindrugcountry>
<drugauthorizationnumb>BLA 000000</drugauthorizationnumb>
<drugauthorizationholder>Company A</drugauthorizationholder>
<drugindicationmeddraversion>20.0</drugindicationmeddraversion>
<drugindication>Chronic myeloid leukaemia</drugindication>
<brandname>Sample Brand name</brandname>
<commondevicename>Sterile Needle</commondevicename>
<productcode>ZZZ</productcode>
<activesubstance>
<activesubstancename>active A</activesubstancename>
</activesubstance>
</drug>
```

10. **If an ICSR qualifies for adverse event reporting for both a suspect drug and a suspect combination product by the same manufacturer, which R2 file format must be used to submit the ICSR?**

    If an ICSR qualifies for adverse event reporting for both a suspect drug and a suspect combination product by the same manufacturer, then use DTD version 2.2. This version supports submissions for both non-combination drug products and combination drug products.

11. **Is A.1.9 (fulfill expedited criteria) a repeatable field and is it possible to submit multiple report types within one ICSR?**
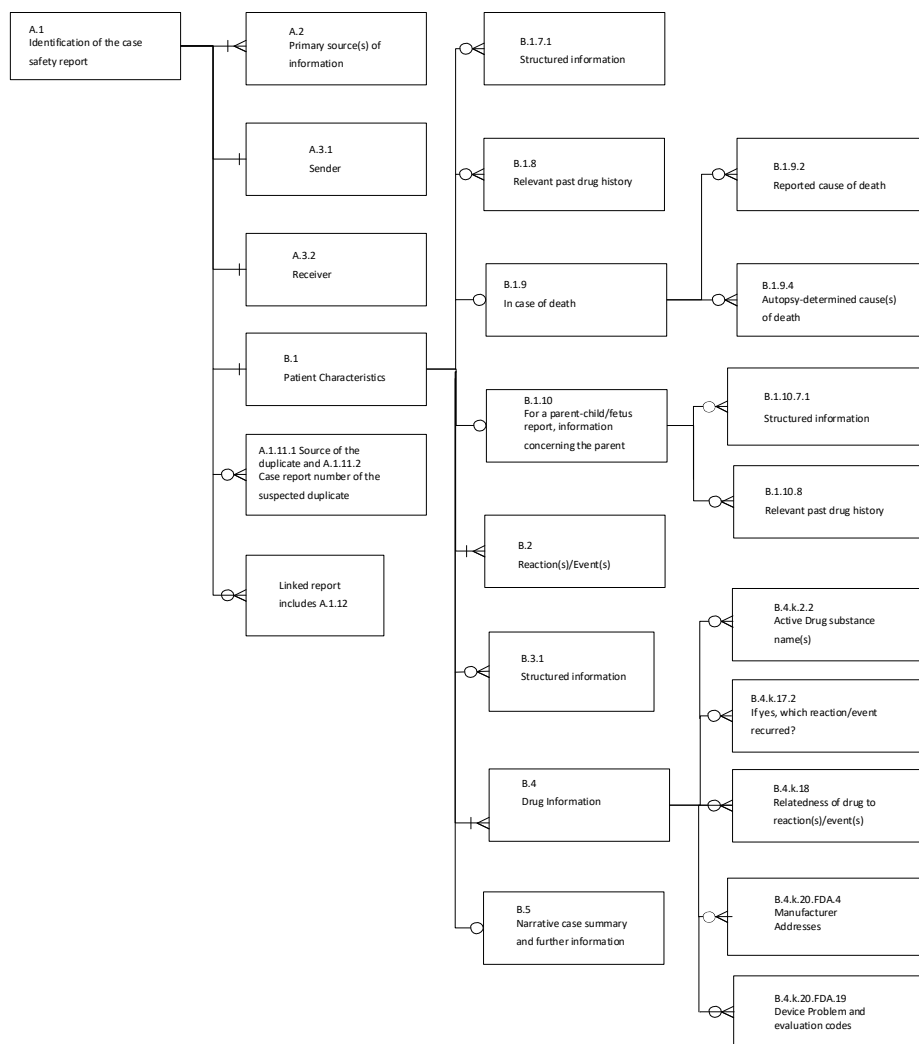
A.1.9 <fulfillexpeditecriteria> is not a repeatable field and does not support submission of multiple report types within one ICSR. You can only have one report type: either 1 for 15-Day Expedited, 2 for Periodic Non-expedited, 4 for remedial action to prevent an unreasonable risk of substantial harm to the public health, or 5 for malfunction with no associated adverse event.
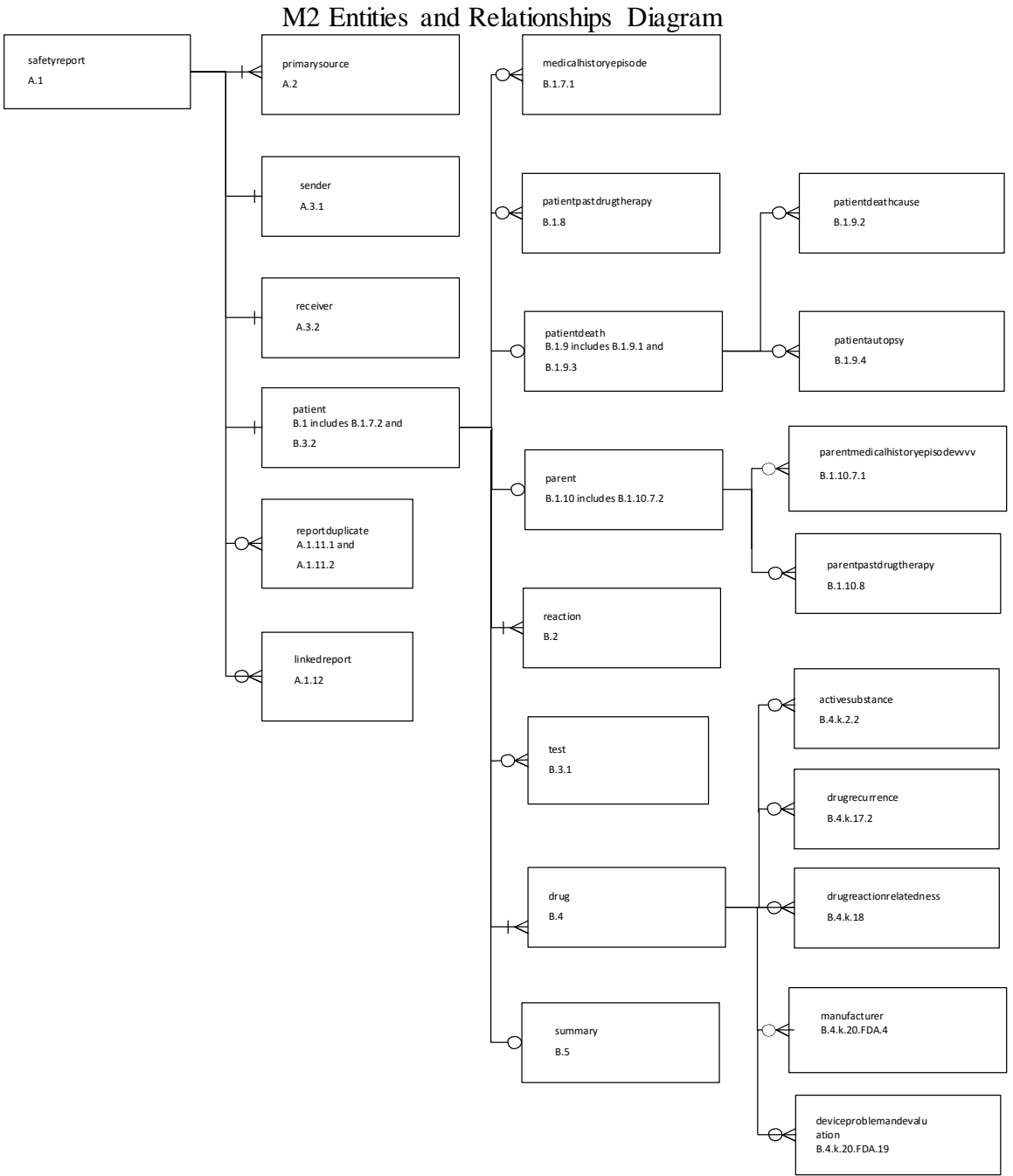
12. **Will the acknowledgement notifications be different for submissions of combination products ICSRs?**

The acknowledgement notifications for the combination products ICSRs are the same as those for ICSRs submitted for non-combination products except the value for the tag <messageformatversion> is 1.1 for an acknowledgement generated for an ICSR submitted using DTD version 2.2.

13. **Can you provide the Relational View Diagrams for ICH DTD 2.2 data elements**?

See the updated diagrams for M2 Relational View of E2B Data Elements below:

M2 Entities and Relationships Diagram

safetyreport
A.1

primarysource
A.2

medicalhistoryepisode
B.1.7.1

sender
A.3.1

patientpastdrugtherapy
B.1.8

patientdeathcause
B.1.9.2

receiver
A.3.2

patientdeath
B.1.9 includes B.1.9.1 and
B.1.9.3

patientautopsy
B.1.9.4

patient
B.1 includes B.1.7.2 and
B.3.2

parent
B.1.10 includes B.1.10.7.2

parentmedicalhistoryepisodevvvv
B.1.10.7.1

parentpastdrugtherapy
B.1.10.8

reportduplicate
A.1.11.1 and
A.1.11.2

reaction
B.2

linkedreport
A.1.12

test
B.3.1

activesubstance
B.4.k.2.2

drugrecurrence
B.4.k.17.2

drug
B.4

drugreactionrelatedness
B.4.k.18

manufacturer
B.4.k.20.FDA.4

summary
B.5

deviceproblemandevaluation
B.4.k.20.FDA.19

14.   **The FDA currently receives ICSRs using DTD version 2.1 for non-combination products and DTD version 2.2 for combination products, will the receiver identifier change for combination products?**

There is no change in the receiver identifier data elements fields for combination product reports using DTD version 2.2.

15. **If an ICSR has been submitted for multiple combination products such as (Bio-A, Syringe 1, Needle 1 and Bio-B, Syringe 2, Needle 2), how would FDA know that these are 2 separate combination products?**

In this scenario, the drug section in the XML file should be repeated for each combination product and within each combination product repeat the device constituent part. This results in four drug sections as shown below**:**

Block 1 - Bio-A, Syringe 1
Block 2 - Bio-A, Needle 1
Block 3 - Bio-B, Syringe 2
Block 4 - Bio-B, Needle 2

```
<drug>
<drugcharacterization>1</drugcharacterization>
<medicinalproduct>Bio A</medicinalproduct>
<obtaindrugcountry>US</obtaindrugcountry>
<drugauthorizationnumb>BLA 123456</drugauthorizationnumb>
<drugauthorizationholder>Company A</drugauthorizationholder>
<drugindicationmeddraversion>20.0</drugindicationmeddraversion>
<drugindication>Chronic myeloid leukaemia</drugindication>
<brandname>Sample Brand name</brandname>
<commondevicename>Syringe1</commondevicename>
<productcode>FMF</productcode>
<activesubstance>
<activesubstancename>active A</activesubstancename>
</activesubstance>
</drug>
<drug>
<drugcharacterization>1</drugcharacterization>
<medicinalproduct>Bio A</medicinalproduct>
<obtaindrugcountry>US</obtaindrugcountry>
<drugauthorizationnumb>BLA 123456</drugauthorizationnumb>
<drugauthorizationholder>Company A</drugauthorizationholder>
<drugindicationmeddraversion>20.0</drugindicationmeddraversion>
<drugindication>Chronic myeloid leukemia</drugindication>
<brandname>Sample Brand name</brandname>
<commondevicename>Needle1</commondevicename>
<productcode>FMF</productcode>
<activesubstance>
<activesubstancename>active A</activesubstancename>
</activesubstance>
```

```
</drug>
<drug>
<drugcharacterization>1</drugcharacterization>
<medicinalproduct>Bio-B</medicinalproduct>
<obtaindrugcountry>US</obtaindrugcountry>
<drugauthorizationnumb>BLA 123457</drugauthorizationnumb>
<drugauthorizationholder>Company A</drugauthorizationholder>
<drugindicationmeddraversion>20.0</drugindicationmeddraversion>
<drugindication>Chronic myeloid leukemia</drugindication>
<brandname>Sample Brand name</brandname>
<commondevicename>Syringe2</commondevicename>
<productcode>FMF</productcode>
<activesubstance>
<activesubstancename>active A</activesubstancename>
</activesubstance>
</drug>
<drug>
<drugcharacterization>1</drugcharacterization>
<medicinalproduct>Bio-B</medicinalproduct>
<obtaindrugcountry>US</obtaindrugcountry>
<drugauthorizationnumb>BLA 123457</drugauthorizationnumb>
<drugauthorizationholder>Company A</drugauthorizationholder>
<drugindicationmeddraversion>20.0</drugindicationmeddraversion>
<drugindication>Chronic myeloid leukemia</drugindication>
<brandname>Sample Brand name</brandname>
<commondevicename>Needle2</commondevicename>
<productcode>FMF</productcode>
<activesubstance>
<activesubstancename>active A</activesubstancename>
</activesubstance>
</drug>
```

16. **If an ICSR has been submitted for multiple combination products such as (Drug-A, Syringe 1, Needle 1)' with the drug having three Indications and two dose regimens, how should the XML be populated?**

The drug section should be repeated three times for each indication. The three blocks to be populated are as shown below:

Block 1 - Drug-A with indication 1 and dosage info 1, Syringe 1
Block 2 - Drug-A with indication 2 and dosage info 2, Needle 1
Block 3 - Drug-A with indication 3 and Needle 1