Oracle Argus Safety

CDER E2B(R2) Combination Product Best Practices

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Oracle Argus Safety CDER E2B(R2) Combination Product Best Practices, Release 8.4.1

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Contents

Preface

This preface contains the following sections:

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Documentation accessibility

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Revision history

Argus version	Description
8.4	First release
8.4.1	Republished

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Introduction

This document provides the best practices and recommendations to configure Combination Products and generate PMSR reports for Combination and Non-Combination Products using FDA E2B(R2) 2.2 profile.

FDA has published a Final Guidance on the Post-Marketing Safety Reporting (PMSR) for Combination Products guidelines in July 2019 regarding reporting of Combination Products marketed in the United States.

FDA has also published a Technical Specification Document for Preparing and Submitting Electronic ICSRs and ICSR Attachments in February 2020, which covered the following requirement on Similar devices reporting:

Combination Product Applicants for combination products containing device constituent parts should submit Malfunction reports to FDA for otherwise reportable malfunctions, for both devices and device constituent parts of combination products marketed outside the U.S. by that applicant that are the same as, or similar to, the device constituent part of the applicant's U.S.-marketed combination product if the malfunction is likely to occur in the U.S. marketed combination product.

As per FDA, Combination Product Applicants should submit PMSRs consistent with the requirements of the combination product with compliance date July 31, 2020 for reporting ICSR to FDA Adverse Event Reporting System (FAERS) and Electronic Medical Device Reporting System (eMDR) to report ICSRs.

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Configure Single Entity Combination Products

A product comprised of two or more regulated components (e.g. drug/device, biologic/device, drug/biologic, or drug/device/biologic) that are physically, chemically, or otherwise combined and produced as a single entity is known as a Single Entity Combination Product. Insulin Pen is one of example for single entity combination product, as the product comprises of insulin (drug) and an injector pen (device).

In Oracle Argus Safety, drug and device components can be within the same product to configure Single Entity Combination Products:

1. Click **Business Configuration** > **Products and Licenses** > **Add New Family**.

2. Enter the required mandatory data and save the family.

3. Click **Add New Product**.

4. Enter the required mandatory data and save the Product, ensuring that the 3-character Device Code is entered for the Product.

5. Create a Primary mode of action product License by clicking **Add New License**.

6. Enter the required mandatory data for creating a Drug license as below and save the License.

   a. Authorization country = UNITED STATES

   b. License Type = Marketed Drug

   c. License Number can be entered in either of the following ways:

      i. License # = NDA<License number>

      ii. Application type=NDA

      iii. License # = <License number>

7. Create a Constituent Device License by clicking **Add New License**.

8. Enter the required mandatory data for creating a Drug license as below and save the License.

   a. Authorization country = UNITED STATES or WORLD

   b. License Type = Marketed Device

   c. License # = <License number>

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Configure Co-packaged Combination Products

Two or more separate products packaged together in a single package or as a unit comprising of drug and device products, device and biological products, or biological and drug products, is known as Co-Packaged Combination Products.
Inhaler with filled drug cartridge is one of example for co-packaged combination product, as it comprises of 2 components, an inhaler device and drug that are within a single package.

In Oracle Argus Safety, drugs and devices can be added to products belonging to different families to then configure a Co-Packaged Combination Product:

1. Click **Business Configuration** > **Products and Licenses** > **Add New Family**, for creating family for the Drug.

2. Enter required mandatory data and save the family.

3. Click **Add New Product**.

4. Enter the required mandatory data and save the Product.

5. Create a Primary mode of action product License by clicking **Add New License**.

6. Enter the required mandatory data for creating a Drug license as below, and save the License.

    a. Authorization country = UNITED STATES

    b. License Type = Marketed Drug

    c. License Number can be entered in either of the following ways:

        i. License # = NDA<License number>

        ii. Application type=NDA

        iii. License # = <License number>

7. Click **Business Configuration** > **Products and Licenses** > **Add New Family**, for creating family for the Device.

    The N/A value can be added in the Ingredient codelist and the same can be selected for the Device family.

8. Enter required mandatory data and save the family.

9. Click **Add New Product**.

10. Enter the required mandatory data and save the Product, ensuring that the 3-character Device Code is entered for the Product.

    The N/A value can be added in the Formulation codelist and the same can be selected for the Device Product.

11. Create a Constituent Device License by clicking **Add New License**.

12. Enter the required mandatory data for creating a Drug license as below, and save the License.

a. Authorization country = UNITED STATES or WORLD

b. License Type = Marketed Device

c. License # = <License number>

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Configure World License for Similar Product

If MAH has devices that are marketed outside of US which are similar to the Devices marketed in US, then, it is required to configure World Similar License Product to aid in scheduling of E2B Reports to CDER.

1. Click **Business Configuration** > **Products and Licenses** and select the Product which has Devices that marketing license outside of US.

2. Create a World license for Similar Device by clicking **Add New License**.

3. Enter the required mandatory data for creating a Drug license as below and save the License:

   a. Authorization country = WORLD

   b. License Type = Marketed Device

   c. License # = <blank>

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Set up Reporting Destinations

To enable reports to be sent in the FDA E2B(R2) 2.2 format, we recommend you configure the existing reporting destination that was configured for the FDA E2B(R2) 2.1 profile as follows:

Open the reporting destination that Argus Safety uses to send ICSRs to the FDA using the FDA E2B(R2) 2.1 profile. Make the following updates in the EDI tab.

- For Message Profile, select ICH-ICSR V2.2 MESSAGE TEMPLATE – FDA (standard profile).

- For ACK Profile, leave ICH-ICSR V1.1 ACKNOWLEDGMENT TEMPLATE – FDA.

- Set the URL for Message Schema to https://www.accessdata.fda.gov/xml/icsr-xml-v2.2.dtd.

- For URL for Ack Schema, leave http://www.accessdata.fda.gov/xml/icsrack-xml-v1.1.dtd.

- Set the Encoding parameter to ISO-8859-1.

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Set up Reporting Rules

We recommend you retain the existing expedited reporting rules (#1, #2) for 15-day and periodic report types, and create the other new expedited reporting rules, below are the suggested reporting rules:

Country	License Type	Agency	Rule Name	Time Frame	Report Form	Condition
United States	Marketed Drug	FAERS	15-day	15	E2B	Serious (Event) = Yes and Listedness (Event) = No
United States	Marketed Drug	FAERS	Periodic	60	E2B	Case Serious = No or Case Serious = Yes Criteria using Advance conditions: Case Listedness = Yes Any other condition as per your company's business process
United States	Marketed Drug	FAERS	5-day	5	E2B	Criteria using Advance conditions • Remedial Action exists • Case Classification = Combination Product Any other condition as per your company's business process
United States	Marketed Drug	FAERS	30-day	30	E2B	Case Serious = No Criteria using Advance conditions • Malfunction = Yes • Case Classification = Combination Product Any other condition as per your company's business process

Country	License Type	Agency	Rule Name	Time Frame	Report Form	Condition
World	Marketed Drug	FAERS	30-day	30	E2B	Case Serious = No Criteria using Advance conditions: - Case Classification = Combination Product - Malfunction = Yes - Product type = Treatment/Other - Drug not administered = Yes - Similar Device = Yes

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Configure Combination Product in Flexible Re-categorization Codelists

Flexible re-categorization codelist is enhanced to include a new COMBO_PRODUCT_RELATIONSHIP codelist for maintaining list of combination products that are marketed in US.

1. Click **Code lists** > **Flexible Data re-categorization** > **Flexible re-categorization** > **COMBO_PRODUCT_RELATIONSHIP**.

2. Use the **Add New** button to enter the information for the combination products.

> ✎ **Note:**
>
> Flexible re-categorization codelist does not validate the correctness of the Product Name, License name and Country of authorization, it is required to enter the below information by copying respective data from the Product and License configuration screen.

Column Name	Recommended Data Length	Comments
PMOA_PROD_NAME	250	Enter the Primary mode of action product's Product Name (not Trade Name) as Configured in Business Configuration > Product a and Licenses
PMOA_LIC_NUMBER	40	Enter the primary mode of action product's license number
PMOA_COUNTRY	50	Enter the primary mode of action product's Authorization Country
CONS_PROD_NAME	250	Enter the constituent product's Product Name (not Trade Name) as Configured in Business Configuration > Product and Licenses
CONS_LIC_NUMBER	40	Enter the constituent product's License number
CONS_COUNTRY	50	Enter the constituent product's Authorization Country

3. Click on the ✔ icon and then click **Save**.

4. If a combination product has multiple device constituent products, then add additional records with the same data for PMOA related fields along with other constituent product details.

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Single Entity Combination Product Case Processing

These are the steps for creating/processing cases with Single entity Combination Products:

1. Book-in a case with information received as per Source documents.

   If the Suspect Product involved is a Combination Product, on selection of the Product from Product browser, the system enables Drug and Device tabs.

2. Enter Drug and Device data in the corresponding tabs.

3. Select Combination Product in the **General** > **Case Classification** field.

4. Save the case and ensure all the mandatory data is entered that is required for CDER submission.

5. Perform Auto-scheduling and system schedules an E2B report to CDER agency using FDA 2.2 DTD Profile.

6. Click the **Draft** link to preview the report in XML view.

7. The <combinationproductreport> element is populated with value 1 indicating ICSR contains Combination Product.

8. The <fulfillexpeditedcriteria> element is populated with one of these values below indicating the type of report:

   - 1 = 15-day

   - 2 = Non-Expedited

   - 4 = 5-day

   - 5 = Malfunction (30-day)

   The Device data is embedded within the <drug> block pertaining to the Primary mode of action product as below.

   ```
   <drug>
   <drugcharacterization>1</drugcharacterization>
   <medicinalproduct>ADYPHREN</medicinalproduct>
   <obtaindrugcountry>US</obtaindrugcountry>
   <expirationdateformat>102</expirationdateformat>
   <expirationdate>20190201</expirationdate>
   <productavailableforevaluation>2</productavailableforevaluation>
   <productreturndateformat>610</productreturndateformat>
   <productreturndate>201804</productreturndate>
   <brandname> ADYPHREN</brandname>
   <commondevicename>Convenience Kit</commondevicename>
   <productcode>006</productcode>
   <modelnumber>Model1234567</modelnumber>
   <catalognumber>CatalogABCD1234</catalognumber>
   <serialnumber>SerialNumber1234</serialnumber>
   <udinumber>UDI1234</udinumber>
   ```

```
<dateimplantedformat>102</dateimplantedformat>
<dateimplanted>20180201</dateimplanted>
<dateexplantedformat>102</dateexplantedformat>
<dateexplanted>20180201</dateexplanted>
<deviceage>2</deviceage>
<deviceageunit>801</deviceageunit>
<labeledsingleusedevice>1</labeledsingleusedevice>
<devicemanufacturedateformat>102</devicemanufacturedateformat>
<devicemanufacturedate>20180201</devicemanufacturedate>
<remedialactionrecall>1</remedialactionrecall>
<remedialactionrepair>2</remedialactionrepair>
<remedialactionreplace>1</remedialactionreplace>
<remedialactionrelabel>2</remedialactionrelabel>
<remedialactionnotify>1</remedialactionnotify>
<remedialactioninspection>2</remedialactioninspection>
<remedialactionpatientmonitor>1</remedialactionpatientmonitor>
<remedialactionmodifyadjust>2</remedialactionmodifyadjust>
<remedialactionother>1</remedialactionother>
<deviceusage>2</deviceusage>
<devicelotnumber>DevLot1234</devicelotnumber>
<malfunction>1</malfunction>
<followupcorrection>1</followupcorrection>
<followupadditionalinfo>2</followupadditionalinfo>
<followupresponsetofda>1</followupresponsetofda>
<followupdeviceevaluation>1</followupdeviceevaluation>
<operatorofdevice>Lay User</operatorofdevice>
<manufacturer>
<manufacturername>Aster Devices Inc</manufacturername>
<manufactureraddress>11 Crown Towers</manufactureraddress>
<manufacturercity>Bridgewater</manufacturercity>
<manufacturerstate>NY</manufacturerstate>
<manufacturercountry>US</manufacturercountry> </manufacturer>
<deviceproblemandevaluation>
<evaluationtype>01</evaluationtype>
<evaluationvalue>1396</evaluationvalue> </
deviceproblemandevaluation>
</drug>
```

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Similar Device Case Processing (Single Entity Combination Products)

These are the steps for creating/processing cases with Non-US marketed devices that involve reportable malfunction and have similar devices marketed in the US as part of Single entity Combination Product:

1. Book-in a Case with information received as per Source documents.

2. If the Suspect Device had caused a reportable malfunction, then check for the **Product Portfolio** for Similar devices marketed in the US as Combination Product.

3. If such a product exists, then add the Product from the **Product** browser and enter the following data in the **Drug** tab:

   a. Product type = Treatment / Other

   b. Drug not administered = Ticked

4. Enter the following data in the **Device** tab:

   a. Similar Device = Ticked

5. Select **Combination Product** in the **General** > **Case Classification** field.

6. Save the case and ensure that all mandatory data required for CDER submission is entered.

7. Perform Auto-scheduling and system schedules an E2B report to CDER agency using FDA 2.2 DTD Profile.

8. Click the **Draft** link to preview the report in XML view.

   The <combinationproductreport> element is populated with value 1, indicating ICSR contains Combination Product.
   The <drugcharacterization> element is populated with value 5, indicating Similar Device.

   The Similar Device data is populated in the ICSR as shown in below example:

```
<fulfillexpeditecriteria>5</fulfillexpeditecriteria>
<combinationproductreport>1</combinationproductreport>
<drug>
<drugcharacterization>5</drugcharacterization>
<medicinalproduct>INSULIN</medicinalproduct>
<brandname> SYRINGE</brandname>
<commondevicename>Syringe Piston</commondevicename>
<productcode>DXT</productcode>
</drug>
```

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Co-packaged Combination Product Case Processing

These are the steps for creating/processing cases with Co-packaged Combination Products:

1. Book-in a Case with information received as per Source documents.

2. If the Suspect Product involved is a Combination Product, ensure the Primary mode of action (PMOA) product is selected first using the Product browser and the drug data is entered.

3. Add the Constituent Device Product using the Product browser.

4. Enter the Device data in the Constituent Product.

5. Select **Combination Product** in the **General** > **Case Classification** field.

6. Save the case and ensure all the mandatory data required for CDER submission is entered.

7. Perform Auto-scheduling and the system schedules an E2B report for the PMOA Product to CDER agency using the FDA 2.2 DTD Profile.

8. Click **Draft** link to preview the report in XML view.

9. The <combinationproductreport> element is populated with value 1 indicating ICSR contains Combination Product.

10. The Device data is embedded within the <drug> block pertaining to the Primary mode of action product as per the example provided in the Single Entity Combination section.

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Similar Device Case Processing (Co-Packaged Combination Products)

These are the steps for creating/processing cases that have Non-US marketed device that involves reportable malfunction and similar devices marketed in the US as part of Co-packaged Combination Product:

1. Book-in a Case with information received as per Source documents.

2. If the Suspect Device had caused a reportable malfunction, then check the **Product Portfolio** for Similar devices marketed in the US as Combination Product.

3. If such product exists, then add the PMOA Product from the **Product** browser and enter the following data:

   a. Product type = Treatment / Other

   b. Drug not administered = Ticked

4. Add the **Constituent Device Product** from the **Product** browser and enter the following data:

   a. Product type = Treatment / Other

   b. Drug not administered = Ticked

   c. Similar Device = Ticked

5. Select **Combination Product** in the **General** > **Case Classification** field.

6. Save the case and ensure that all mandatory data required for CDER submission is entered.

7. Perform Auto-scheduling and system schedules an E2B report to CDER agency using the FDA 2.2 DTD Profile.

8. Click the **Draft** link to preview the report in XML view.

   a. The <fulfillexpeditedcriteria> element is populated with value 5 indicating a 30-day Malfunction Only report.

   b. The <combinationproductreport> element is populated with value 1 indicating that ICSR contains Combination Product.

   c. The <drugcharacterization> element is populated with value 5 indicating Similar Device.

   The Similar Device data is populated in ICSR as in the example below.

```
<fulfillexpeditecriteria>5</fulfillexpeditecriteria>
<combinationproductreport>1</combinationproductreport>
<drug>
<drugcharacterization>5</drugcharacterization>
<medicinalproduct>ADYPHREN</medicinalproduct>
<brandname> ADYPHREN</brandname>
<commondevicename>Type 1: Convenience Kit of Co-Package</commondevicename>
```

```
<productcode>006</productcode>
</drug>
```

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Other Considerations

1. For submitting a Malfunction report to CDER, these are the recommendations for data entry:

   - **Patient tab**: No data needs to be entered, Patient Initial element gets populated as **None**.

   - **Product tab**: Set the Malfunction field to **Yes**, enter one or more Malfunctions in the **Malfunction Information** section and enter the Device Problem codes in the **Device** tab of the Constituent Product.

     > **✎ Note:**
     >
     > If there are multiple malfunction reports, it is recommended to provide a summary of malfunction information in the Narrative.

   - **Event tab**: Enter **No Adverse Event as Reported** term to get the properly coded corresponding MedDRA term.

   - **Analysis tab**: Case Serious is set to **No**.

2. For submitting a Malfunction Similar Device report to CDER, the following are the recommendations for data entry:

   a. FDA recommends providing the following data for Similar Device Combination Products. Hence the FDA E2B(R2) 2.2 DTD report populates this data for Similar Device Combination Products.

Element ID	Element Description
B.4.k.4.1	Authorization/Application Number
B.4.k.4.2	Country of authorization/application
B.4.k.4.3	Name of holder/applicant
B.4.k.20.FDA.4	Manufacturer
B.4.k.20.FDA.4a	Device Manufacturer Name
B.4.k.20.FDA.4b	Manufacturer Address
B.4.k.20.FDA.4c	Manufacturer City
B.4.k.20.FDA.4d	Manufacturer State
B.4.k.20.FDA.4e	Manufacturer Country

   b. The following elements are not required for Similar Device Combination Products as the product was not administered, hence it is recommended to leave these fields blank:

Element ID	Element Description
B.4.k.2.4.FDA.1a	Expiration Date Format
B.4.k.2.4.FDA.1b	Expiration Date

Element ID	Element Description
B.4.k.2.FDA.5	Product available for evaluation
B.4.k.2.6.FDA.1a	Product return date format
B.4.k.2.6.FDA.1b	Product return date
B.4.k.20.FDA.5	Model Number
B.4.k.20.FDA.6	Catalog Number
B.4.k.20.FDA.7	Serial Number
B.4.k.20.FDA.8	Unique Identifier UDI#
B.4.k.20.FDA.9a	Implanted Date Format
B.4.k.20.FDA.9b	Implanted Date
B.4.k.20.FDA.10a	Explanted Date Format
B.4.k.20.FDA.10b	Explanted Date
B.4.k.20.FDA.11a	Approximate age of device/product
B.4.k.20.FDA.11b	Approximate age unit of device / product
B.4.k.20.FDA.12	Single Use Device
B.4.k.20.FDA.13a	Device Manufacture Date Format
B.4.k.20.FDA.13b	Device Manufacture Date
B.4.k.20.FDA.14.1a	Recall
B.4.k.20.FDA.14.1b	Repair
B.4.k.20.FDA.14.1c	Replace
B.4.k.20.FDA.14.1d	Relabeling
B.4.k.20.FDA.14.1e	Notification
B.4.k.20.FDA.14.1f	Inspection
B.4.k.20.FDA.14.1g	Patient monitoring
B.4.k.20.FDA.14.1h	Modification / Adjustment
B.4.k.20.FDA.14.1i	Other
B.4.k.20.FDA.15	Device Usage
B.4.k.20.FDA.16	Device Lot Number
B.4.k.20.FDA.18.1a	Correction
B.4.k.20.FDA.18.1b	Additional Information
B.4.k.20.FDA.18.1c	Response to FDA request
B.4.k.20.FDA.18.1d	Device Evaluation
B.4.k.20.FDA.19	Device Problem and evaluation codes
B.4.k.20.FDA.19.1a	Evaluation Type
B.4.k.20.FDA.19.1b	Evaluation Value
B.4.k.20.FDA.20	Operator of the Device

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FAQ

What type of product configuration is recommended for Combination Products?

If the PMOA Product is a single device constituent, then the product can be configured according to the steps suggested for the single entity combination products. However, if there is a requirement to perform assessment of drug and devices separately in the case, then it is recommended to configure the PMOA and device constituents under different products.

If the PMOA Product has a multiple device constituents, then the product can be configured as per the steps suggested in the co-packaged combination products.

In the COMBO_PRODUCT_RELATIONSHIP flexible codelist, is it required to enter Product Name or Trade Name for PMOA and Constituent Products?

It is required to specify the Product Name, not the Trade Name.

Does the Combination Product solution provided by Oracle Argus Safety allow a configuration of Combination Product that comprises of multiple device constituents?

If the Combination Product comprises of multiple device constituents, then it is required to create separate entries for each of the device constituent in the COMBO_PRODUCT_RELATIONSHIP codelist with the same PMOA Product.

For which type of Combination Products is the flexible codelist configuration required?

You can use the flexible re-categorization codelist to specify combination products that belong to the following categories:

- Company Drug / Biologic (PMOA Product) and Company Device (Constituent Product)
- Company Vaccine (PMOA Product) and Company Device (Constituent Product)

If Device is PMOA Product, is it required to configure the combination products in the flexible codelist?

For the products with Device as a PMOA Product, eMDRs are required to be submitted. eMDRs do not require configuration of flexible re-categorization codelists for combination products since the eMDR profile maps suspect drugs present in the case to Block C of the report.

Is MAH required to report cases that contain combination products that include a non-company product as PMOA?

MAH is not required to report cases that contain combination products that include a non-company product as PMOA to the FDA.

Do the entries populated in the CASE_PMOA_CONS_RELATION table for a case get copied on performing a Case Copy?

No, Case Copy does not copy the data from the CASE_PMOA_CONS_RELATION table. The data present in this table is neither printed in Case Form Print, nor is it audit logged.

If a case with drug and device data submitted using E2B(R2) 2.1 DTD to FDA and now if the follow-up data is received and requires to be processed as Combination Product, what needs to be done from the data entry perspective?

These are the steps to follow to ensure that the case is treated as a Combination Product ICSR:

- Case Classification needs to be set to Combination Product.

- Ensure that the appropriate device information is entered for the device constituents.

- Generate the draft E2B report to the FAERS agency to check if the case qualifies to be Combination Product Case.

If a PMOA Product has multiple device constituents associated, is it required to enter all the device constituents in the case in order to recognize the product as Combination Product?

If the case has PMOA Product along with at least one device constituents present, then it is considered as a Combination Product, and the system does not expect all device constituents to be entered in the case.

If a foreign (Non-US) case has a combination product which has equivalent US licensed combination products, will the system be able to determine that case qualifies for combination product reporting in US?

Yes, the system evaluates the products within the case and compares all licenses associated with the product with the entries in the flexible codelist, and determines if it is a combination product or not.

Will there be any impact on any reports submitted outside of US for a case that has Similar device Products?

Similar device products are entered with product type as **Treatment/Other**, hence this product is not reflected in any other expedited or periodic reports.

If multiple combination products similar to the device constituent marketed outside of the US resulted in reportable malfunction, is it required to provide the details of the combination product in the E2B report?

Yes, FDA recommends that the report for a foreign malfunction identifies each US combination product (using the Similar characterization) for which the malfunction event being reported is relevant.