VMF-A-OT (Type II & V)

Good afternoon. My name is Elizabeth Pollina Cormier and I am a reviewer in the Division of Manufacturing Technologies. In this break out section for the CMC section, I will demonstrate how to open an original Type II VMF for a drug substance, known as the VMF A template for a Type II master files.

Renee Blosser will discuss the information included in an original submission to a Type V master file for sterilization process information. We will then have a Q&A session for the VMF templates followed by a brief break. We will resume at 3 pm with Trupti Dhami to discuss the eSubmitter templates for Post-Approval submissions. At the end of the session, there will be another Q&A portion to answer regarding these templates.

To enter a question, select the Chat tab. Ensure that the Send to: box indicates Elizabeth Cormier (Host) and type your question into the box below. Hit Send to send the question to me. You may send me questions at any time during the session. If there are questions that we are unable to answer during today's Q&A, we will hold them until the September 19th general Q&A session.

For the first screen, **Screen: 1.0 Document Information**, from the pull-down menu you select the document type as Veterinary Master File. We are submitting an original file, so there is no established file, so we select no for the second question.

To advance to the next screen, use the green arrow button at the top menu bar.
This brings you to **Screen 2.0: Firm Information**. Fill in the relevant information on this screen for the holder of the master file. If you are not an US Company, the Screen 3.0 US Agent becomes activated.

Screen 3.0 US Agent / US Employee Information – Note that a US Agent is not required for a master file. A US agent is required to register a foreign facility. Fill in the relevant information
If you are a US-based company, you will proceed to **Screen 4.0 Responsible Official Information** – and Fill in the relevant information

Screen 5.0 Submitter Information – this is information for the individual submitting to the Agency. This individual should NOT sign the eSubmitter package unless he or she is the same as the responsible official and is legally responsible for the content.

This brings us to the Submission – **Screen 6.0 Submission Type Code /Amendment Information V** (where V is for VMF). I will demonstrate the process for an original Type II VMF which is considered a CMC VMF. The submission classification code from the pull-down menu only has the option OT for other. The original submission should be directed to the Division of Manufacturing Technologies (DMF) HFV-140.

The last question on this screen is 'Is this information intended to amend a submission currently pending and under review by CVM?' And you can see that this information is disabled now since it is a new original submission.

This brings us to **Screen 1.0 General Information**. First, we select the Type of VMF, which is Type II. Then we are asked if we reference additional Master Files. If the answer is no, the rest of the screen remains deactivated. If we answer Yes, answer whether you have a reference to an additional Type II Master File. For example for an intermediate, you can provide the MF number (for either a VMF or DMF) by selecting the green plus button and input the MF number.
You are also asked if your VMF submission references a Type V VMF (this may be relevant if you have a sterile API) and again you can provide the MF number by selecting the green plus button and input the MF number.
and lastly any other type of MF (Type III or Type IV).

If you answered YES, the next screen you will provide the VMF information (**Screen: A. Type V Reference Information**) click New to provide the referenced VMF information.

- For the Type II VMF: You can select from the pull-down a DMF or VMF and then the number that you provided in the previous screen will populate the pull-down for the file number. If you do not own the Masterfile, you can attach the letter of authorization. The process is similar for the Type V and Type III references. You do the same for the Type V and Type III:

- For the referenced Type V, again, selected from the pull-down a DMF or VMF and then the number that you provided in the previous screen will populate the pull-down for the file number. Then, provide a description in less than 250 characters what information is covered in the MF. Answer whether you own the MF. If you own the MF, provide an LOA for each Master File that you do not own.
- For the Type III and Type IV VMF references, selected from the pull-down a DMF or VMF and then the number that you provided in the previous screen will populate the pull-down for the file number. Answer whether you own the MF. If you own the MF, provide an LOA for each Master File that you do not own.

This then brings us to **Screen 2.0 Type II Information**. Select the radio button for Drug Substance Information.

The information entered in response to the questions for the follow sections are intended to serve as the Module 2 Quality Overall Summary used in the Common Technical Document (CTD) format. The QOS is intended to include a summary of the critical information needed for approval of a submission, while further supporting documents and data can be attached in Module 3.

For a little background on the CMC eSubmitter, it is based on Question-Based Review - QBR which was developed to assist applicants in addressing regulatory filing requirements of the Act. The questions you will see in this template are also outlined in the Guidance for Industry 234 Question-Based Review for the Chemistry, Manufacturing, and Controls Technical Section of Animal Drug Applications.

As we go through the process of submitting an original Type II VMF, I would like to highlight that you can see the organization of this section follows CTD Module 2.

If and when you submit an CMC TS (aka (J)INAD P submission) and don't reference a separate MF for the API information, the eSubmitter template for section 2.3.S is the same as I will be describing for the VMF Type II original template.

If you reference a MF for the drug substance information, most of the questions for 2.3 S become optional. Note that some questions should still

be answered by the submitter of the CMC TS. These sections include General Information, Manufacturer, drug substances specifications, methods, and reference standards. The helpful hint provides additional guidance for sponsors/applicants. You can select the helpful hint by hoovering over this light bulb icon.

The first section, is General Information - **2.3.S.1 General Information**.
The first question is "**What are the nomenclature, molecular structure, molecular formula, CAS number, and molecular weight?"**
Answers to this question could include properties such as:

- Chemical Name:
- CAS #:
- USAN:
- Molecular Structure (including relative and absolute stereochemistry):
- Molecular Formula:
- Molecular Weight:

The second question is "**What are the physicochemical properties?"**
This may include:

Physical Description (appearance, color, physical state):
pKa:
Polymorphism (polymorph, solvate, hydrate, etc.):
Solubility Characteristics (as function of pH):
Hygroscopicity:
Melting/Boiling Point:
Partition Coefficient:
Optical Rotation:

When we proceed, we are referred back to the Type II Reference (**Screen A. Type II Referenced Manufacturer).** Select "new" and fill in the Tab "Details"
Provide facility name and then select the function of the facility (API manufacturer, intermediate, control testing laboratory, packaging, micronization, or other). Provide the facility name, FEI number, DUNS number (required as indicated by the blue dot), and the current FDA inspection status. You should provide the last inspection date and any information about the inspection.

Screen B. Manufacturer. We expect each VMF to have only one DS manufacturing site for the API.
Click the "New" button and provide the manufacturing facility information. For each additional site, you can add a new "Manufacturer" or facility that may be the (API manufacturer, intermediate, control testing laboratory, packaging, micronization, or other another process. - each proposed production site or facility involved in manufacturing and testing).
Provide the facility name, address, phone number, and contact person/US Agent.

And just as we did with the Type II MF reference, select the function of the facility (API manufacturer, intermediate manufacturer, control testing laboratory, packaging, micronization, or other). Provide the facility name, FEI number, DUNS number (required as indicated by the blue dot), and the current FDA inspection status. You should provide the last inspection date and any information about the inspection.

Proceed to the next section 2.3.S.2 for Manufacture
The next brings up to section S.2. Manufacture (**Screen 2.3.S.2 Manufacture)**

What is the starting material(s)? Provide justification.
For further guidance on determining SM, see CVM Draft Guidance for Industry #169 Drug *Substance Chemistry, Manufacturing, and Controls Information* and the general principles outlined in ICH Q7 *Good Manufacturing Guidance Practice for Active Pharmaceutical Ingredients* and Q11 Development and Manufacture of Drug Substances.
For the next question,
What are the manufacturing processes and controls and how do they ensure consistent production of the drug substance?
Include the source of the material (i.e., synthetic or natural) when both sources are available. The MF holder's COA for the registration batch(es) should be provided in the Module 3.

A complete and detailed description of the manufacturing process and controls used to produce the drug substance should be provided.

- a flow diagram,
- the batch size,

- specifications for raw materials,
- the controls performed at critical steps of the manufacturing process,
- tests and acceptance criteria for isolated and final intermediates,

Answer Yes or No to the question:
Is any component of the drug substance derived from animal origin?
If you answer yes, you should provide an explanation regarding which component are of animal origin and what information you have that will allow CVM to assess the suitability of the supplier as it relates to transmissible spongiform encefalapathy (TSE) and other adventitious agents. You should provide a risk assessment of possible adventitious agent contamination for the material in question and identify any steps adopted to mitigate the risk. A description or documentation, such as BSE/TSE certification, identifying the tissue source of the material, age of the animal, country of origin, etc. can be provided to substantiate that the source material is not a specified risk material and does not pose a significant risk to the recipient of the finished product.

The next question, **Are any additives used?** If used, provide the justification by clicking the memo pad that allows for a freeform text dialog. The character limit is also displayed...(demonstrate)

And lastly, "**What are the filling procedures for the primary container-closure system?"**

This brings us to the next section Characterization (we are now in section **2.3.S.3 Characterization).**

The first question is
How was the drug substance structure elucidated and characterized?
A list of studies performed and brief summary of the interpretation of evidence of structure should be provided. A discussion of the stereochemistry of the drug substance should be reported, if applicable. The data may include IR, UV, NMR, MS, and elemental analysis.

This is followed by the question:
What attempts were made to identify and characterize potential impurities?

List impurities (e.g., starting materials, by-products, intermediates, degradation products) observed or considered to be potentially present in the drug substance. Identify impurities by name or by other appropriate descriptor (e.g., RRT/HPLC). The structure, if known, should be provided in the supporting documents in Module 3. List analytical procedures used to detect or search for the impurity or the potential impurity. The origin of the impurities should be provided (e.g., process impurity or degradant). Indicate whether a potential impurity was actually detected in the drug substance and provide the LOQ/LOD for the analytical method.

The information can be provided inserting a table or by typing in the text box.

Note, identification of potential impurities is still needed if there is a USP monograph that includes related substances. The USP monograph provides the minimum requirements for a drug substance. Impurities not included in the monograph may arise from different manufacturing processes and should be explored.

The next question, "**Is the drug substance a chiral molecule**?" If you answer YES, that the drug substance is chiral, state whether the DS is a racemate or a specific enantiomer or diastereomer. When the drug substance is a specific enantiomer, then tests to identify and/or to quantify the enantiomer should be included. A discussion of chirality should include the potential for interconversion between enantiomers (e.g., racemization/epimerization). The same applies to diastereomers.

Are polymorphic forms are present? If you answer yes, answer the question "**How were they characterized?"**
There are a number of methods that can be used to characterize polymorphs of a drug substance. These include

- single crystal X-ray diffraction
- microscopy,
- thermal analysis
- spectroscopy.

We then move to the next section, **2.3.S.4 Control of Drug Substance**
The first question is:

What are the drug substance specifications?
You can respond using free form text, or create a table or the other options present here.

Test results and acceptance criteria should be provided as numerical values with proper units where applicable.

Then we have a Y/N question "**Do these specifications consider all the critical drug substance attributes that are related to the manufacturing process?**"

Then next questions, "**How do the specifications compare to the USP?**"
If the specifications do not conform to current USP, justify the differences. If there is no USP monograph, all specifications should be justified.

For next question, "**Are the analytical methods suitable for their intended uses and validated or verified?"**
Provide a summary of each method and its validation/verification. The method summary can include the critical parameters for the method and system suitability criteria. The validation summary can include results and acceptance criteria (including justification if necessary) for each parameter. For each analytical procedure, provide a page number to the location of the validation information in Module 3. Validation is required if a USP method is modified. If a drug substance has a USP monograph and the USP method is not used, then the method utilized should be demonstrated to be equivalent to or better than the USP method.

The analytical test method(s) for assay and impurities used in the stability program should be shown to be stability indicating.

The next question asks, "**What is the justification for the selection of impurity specifications?**
All residual solvents should be identified and limits should be established.

Applicants should develop impurity limits based on the process used.

And lastly, "**What analyses were performed on the batches?**
Provide batch analysis.

Information may include batch identity (i.e., batch number), batch size, manufacture date, manufacturing site, manufacturing process, and batch purpose. For quantitative data, the use of qualitative terms such as "conforms" or "meets specification" is generally not acceptable.

The next section is reference standards, (**2.3.S.5 Reference Standards)** There are two Yes/No questions: Is the reference standard a USP standard? and "Is there a working standard?"

Provide the expiry of the standards.

Lastly, "**How are the reference standards certified/qualified?"** If the reference standard is obtained from the USP/NF, then identify as such. A reference standard that is not obtained from USP should be of the highest purity and fully characterized.

Include a COA in Module 3, along with details of the reference standard's preparation, qualification, and characterization. This should be summarized in Module 2. Generally, the characterization information should include:

- A brief description of the manufacture of the reference standard, if the process differs from the routine manufacturing procedure of the drug substance. Any additional purification procedures used in the preparation of the reference standard should be described. The purity of the reference standard should be stated.

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- Information to substantiate the proof of structure should be provided. This may include UV, IR, NMR, MS, elemental analysis, optical rotation, X-ray crystallography, as well as applicable functional group analysis. Description of the test procedures should be submitted. Detailed interpretation of the test data in support of the claimed structure should be provided.

- An expiry/retest period should be proposed and supporting information submitted in Module 3.

If a secondary (in-house) standard is used in addition to the primary reference standard, this secondary standard should be verified against the primary reference standard.

This brings us to
2.3.S.6 Container Closure System
Select the "New" button, then answer the question:
Does your Container Closure System reference a Master File identified in the "Other Master File Table?" If you say yes, your prepopulated information will be available from the pull-down options

For the question, "**What container closure system is used for packaging and storage of the drug substance?"**
The primary and secondary containers need to be clearly identified, as do their materials of construction and manufacturer/supplier.

Then we have a Yes/No question, "**Does the primary container meet 21 CFR 177.1520 and USP <661> requirements?**"
The primary packaging material should meet CFR and USP requirements. Documentation should be provided from the supplier of the packaging materials certifying this conformance. For other information related to packaging materials, reference to a Type III DMF is acceptable, with a Letter of Authorization from the DMF holder.

And then, the question is, "**What information is included on the label?**"
The label should clearly indicate the storage conditions (with a numeric temperature range supported by long-term stability data), lot number, expiry/retest date, manufacturer's name, site of manufacture as well as Caution statements required by 21 CFR § 201.122 –such as Caution - For manufacturing, processing, or repacking''.

The final section is **2.3.S.7 Stability**
The first question asks, "**What stability studies support the retest or expiry period and the storage conditions?"**
Information for this question should include a summary of the stability data in tabular format (including ranges of results), the conclusions reached regarding stability, and the retest or expiry period.

Then, provide the conditions and tests for the stability program for the next question, "**What are the conditions and tests for the stability program?"**

The next question is "**What is the proposed commercial packaging and how does it compare with the packaging chosen for the stability program**?" Describe the packaging and how they differ as applicable.

For the question, **"What is the justification for the stability tests and specifications chosen?"**
Provide justification if there are any differences between release and stability specifications

And the final question, "**What are the stability protocol and post-approval stability commitment?"**
The stability protocol should describe the test specifications (methods, acceptance criteria, etc.), testing intervals, storage conditions, retest or expiry period, and packaging.

The post-approval stability commitment should include:

- The first three production lots followed by 3-10 % of the production lots (with a minimum of one lot per year);
- A commitment to report the stability data annually;
- A commitment to notify all authorized users of any OOS results; and
- A commitment to withdraw from the market any production lot(s) found with out-of-specification results and investigate those lots immediately before and after the lot(s) in question.

For more details, see CVM Guidance for Industry #5: Drug Stability Guidelines.

Once you complete the Module 2, the QOS questions, you return to add Type V Reference information if you have Type V information.

Then, we move to the next **Screen 5.1 Module 3** where you can attach one or multiple supporting documents. The requirements for the type of document are described in the CVM eSubmitter File Specification Quick Guide – available when you click the Quick Link.

Then, **Screen 5.2**, you can attach stability data.

Lastly, **Screen 6.0 Comments** allow you to attach any other information. This may either be entered as text in a text box and/or by selecting the green + button to upload a PDF document where you can attach items such as a cover letter.

This completes the original VMF Type II for a drug substance.

I will now go over how to submit updates to VMF, amendments to submissions pending, and General Correspondences for VMFs.

Let us go back the **CVM ONADE submission tab**, and **Screen 1.0 Document Information** and answer Yes to the question "Is this submission for a currently established file?" And then enter in the VMF number.

(Select the tab "Submission type selection)

Then I will proceed to the submission type (The Tab Submission Type Selection, **Screen 6.0 Submission Type Code/ Amendment Information VMF).** For updating the VMF select from the pull-down "C". The submission type from the pull-down menu only has the option OT for other. The original submission should be directed to the Division of Manufacturing Technologies (DMF) HFV-140. If you are not amending a submission currently pending and under review by CVM, state no. I will go over amending a submission pending in a moment.

On **Screen 1.0, General Information**, select what the update is for: annual report, response to letter, or supplemental information. Fill-in the relevant information as we discussed earlier.

You can select whether the submission is a total update or not and if you are referencing additional master files.

We proceed to **Screen 1.1, Submission Description.** Select the VMF Type. Here it is Type II. Then provide a brief overview or description of the update and then attach any documentation to support the change. This can include a change control document, affected sections for the change, etc.

You can provide this as one document or multiple. Please note that the pdf file should meet the specifications as described in the CVM eSubmitter file specification guide. The link to the guide is also provided on this page.

Then, we can attach additional information such as Stability under Screen 5.2 Stability data and for Screen 6.0 you can attach additional files such as a cover letter or any additional information you would like to include.

Now we will go back, if you have you filed a submission, and you intend to amend a submission currently pending and under review by CVM. If you have filed a submission and need to provide additional information or CVM requests additional information, you can amend an open VMF submission. Before doing so, be sure to contact CVM before amending a file to confirm that the submission is still open and is not reviewed or closed out already. Once you choose the submission type and submission classification code for the supplement, you will choose the option 'yes' for the question is the information is intended to amend a submission currently pending and under review by CVM.

Enter the CVM submission number for your currently pending submission for the submission you are amending.

The question, "Is the purpose of this amendment to direct the response to a different Web Trader Account" allows a different person or rather WebTrader account to provide an amendment. If the person creating the amendment is different (or has a different WebTrader Account) than the person who filed the submission being an amended, you can choose a YES different, or No as appropriate.

The next step is to provide the additional/amended information such as study reports, copies of raw data in pdf format and any data files. The tables, statistical analysis can be provided as .xml files or .xpt files. You will find an option to attach each file and it will display the name, date and size of the file. Select which information is being amended and attach the files.

And lastly, I will go over For General Correspondences that includes change of holder, closure, and LOAs.

We go back to the Tab **Submission Type Selection (VMF)** and from the submission selection pull-down menu – general correspondence.

The G submissions include different submission classification codes such as Ad for Administrative requests, TM to terminate file requests, and any other unclassified under OT.

The administrative requests include changes such as change in ownership
If there is change in the ownership, you will select option 'yes'
We answer no to the final question.

The administrative requests are submitted to division of business information science and management which is HFV-180.

Administrative changes include a transfer of ownership of the document. If that is the purpose the document select Yes. If no, select the purpose of the submission which could be a change in firm name, change of firm address or change in the responsible official or US agent. You have the option to apply this change to additional documents. Answer the questions as relevant.
You can add the different files this change applies to.
Add the relevant information that is updated.

On Screen 2.0 you have the option to upload a cover letter or any other relevant information for this submission.

Now we will go back and rather than have an administrative request we will have terminate file request. This should be direct to the Division of Manufacturing Technologies (HFV-140).

On the next screen, you will be required to provide the reason for the closing of the file and provide a current list of authorized users.
There is check box to affirm that you have notified other firms which are authorized to reference the MF that file will be closed. Additionally, for Type II VMF closing, you also required to check the box to affirm that the stability commitment has been fulfilled and that stability data were submitted to the VMF for all lots in the stability program through the expiry or retest date.

Again, you have the same question if this applies to other documents. Next, again is the Comments screen.

Lastly, we will go over unclassified (OT) type of submission, which you can use to provide a list of authorized users or letter of authorization. This should be direct to the Division of Manufacturing Technologies (HFV-140).

Next, you will have option to attach the pdf file and again there is the link to the quick guide on what kind of file formats are acceptable, is provided on the same page.

Again, you are asked if this submission applies to other documents.

Lastly, for all General Correspondences submission classification codes, you will have an option to include additional documents to support the submission and attach a cover letter.

That concludes my portion of the breakout session. I will now pass the presentation to Renee Blosser to discuss sterile process validation for Type V VMFs.

Renee Blosser: We are going to pause for just a minute while we switch over to the Type Vs. Just as a reminder, we do have some time built in for questions. So, we will have Type II and Type V questions at the same time. We will start again in just a minute.