VMF A-OT (Type II & V)

Good afternoon - my name is Renée Blosser and I am a Reviewer in the Division of Manufacturing Technologies. In my presentation today, I will be focusing on the information that should be included in an original submission to a Type V master file for sterilization process information.

Screen: 4.0 Type V Information

The first question "Are you submitting Sterile Process Validation information?" is required to activate the Type V portion of the template.

The next question allows you to select all methods of sterilization that are employed in the manufacture of the finished product. The options include moist steam sterilization, radiation sterilization, aseptic processing, and other (unclassified). Others might include processes such as ethylene oxide sterilization. You will notice as I select the different sterilization options, additional portions of the template become activated.

The next question asks if the information for your sterilization process is referenced in a Type V master file. If you have a letter of authorization to access an additional Type V master file, such as information for radiation sterilization, you should select Yes. Remember, you should already have identified the relevant Type V master file under section 1.2 above. If there are no other referenced master files related to the sterilization processes, you may select No.

If you utilize steam-in-place (SIP) processes for equipment, you should answer Yes to the next question to enable the SIP questions.

The next two questions collect information on whether you lyophilize product or use isolators in your manufacturing process. If you utilize isolators in your manufacturing process, you should answer yes and provide all relevant validation information as part of Module 3.

If you have indicated that there is an additional referenced Type V relevant to this master file, the next screen will ask you to select the relevant master file number, then add the facility name, FEI, and DUNS number, and information regarding the inspection status of that firm. If the facility has been inspected previously, you should indicate the FDA inspection status, the last inspection date, and any other additional information that may be relevant.

Screen 4.1 Moist Steam Sterilization

The next question asks you to identify which items are sterilized by moist steam: Components, Drug Product, and/or Equipment. You may select all that apply. Keep in mind that each answer should address all of the selected items.

4.1.1 Description of the Process and Product

The next set of questions relate to the description of the process and product. The first question asks what is the sterilization process and how was it developed. This section should describe the sterilization process that is utilized. An example of this is saturated steam. A description of how the process was developed should be provided. This may include information on the impact of the proposed moist steam cycle on the components or product and how the cycle parameters and acceptance criteria were developed.

Next you are asked to identify all of the autoclave(s) utilized for all moist steam sterilization processes by location and name if applicable. If you have only one autoclave, it is helpful to state this. You should then identify if the cycle(s) are bioburden or overkill based and describe any studies used to support the use of the proposed cycle(s). Additional information may be included in 4.1.1.c. related to the quality attributes of the product.

Finally you should address what container/closure system was used during cycle development. This section should identify the container and closure used for cycle development and discuss whether it is the same as is intended for the marketed product.

The next screen continues the discussion of the process and product. The first question asks if the cycle validation was performed with simulated product. This question is only relevant for moist steam sterilization of finished product. If you are describing a process for equipment or components, or if you did not use a simulated product for the validation of a finished product sterilization cycle, you may answer no. If you answer yes, you will then be asked to describe the formulation and characteristics as part of a justification for the use of a simulated product. The use of a simulated product is most common when an antimicrobial agent is present in the finished product that may impact the viability of the microorganism in a directly inoculated container.

The next question asks if a matrix or bracketing approach to validation is proposed. If you answer yes, you will be asked to provide justification for the proposed approach. If the product is filled into multiple vial sizes, the matrix or bracket should be designed to cover the worst case for vial size (for example, smallest and largest), vial shape, vial type, and load configuration (for examples, minimum and maximum load). For bracketing of component sterilization, you should provide information describing the selection of the worst case load including size, shape, materials of construction, and load configuration.

Finally, the last question asks if a filtration step is used. This is only applicable to finished drug product. If you answer yes, you should indicate the purpose of the filtration step, e.g. clarification vs bioburden reduction vs a redundant sterilization step.

The final screen in this section starts by asking if you intend to pursue parametric release for the product. Keep in mind that although parametric release may be proposed, additional information should be submitted to CVM under a separate supplemental application to address all of the requirements to support the use of parametric release. If you are considering the use of parametric release, we recommend that you come in for a meeting before submitting this information. If you answer yes, you will be asked what are the critical parameters to ensure the success of your sterilization process? Is there a risk assessment plan in place (e.g., control strategies of the cycle, risk of product failure, product manufacturing experience and knowledge)? Again, because additional information will be

required to support this type of proposal, a brief summary of information only needs to be provided here. For more information on the requirements to support parametric release, refer to GFI 194 – Submission of Documentation in Applications for Parametric Release of Human and Veterinary Drug Products Terminally Sterilized by Moist Heat Processes.

The final two questions relate to the impact of the product and sterilization process on each other. In the first question, we ask what quality attributes of the product may be impacted by the sterilization process. For example, this section should state if the product is heat labile and could be impacted by the steam sterilization.

This is followed by a question asking if there are attributes of the product that may impact the terminal sterilization process.

This is followed by an additional question asking for these attributes to be described. This section should state if there are attributes such as viscosity or density that may present a particular challenge to the steam sterilization. Responding to these questions in the Type V master file may not be the best approach to convey this information but may be more relevant to the application. In this case, you may indicate that this information can be found in the application.

4.1.2 Thermal Qualification of the Cycle

The first question asks What are the characteristics of the process that demonstrate the thermal qualification of the cycle? How were critical process parameters selected, validated, and monitored? This section should clearly state the cycle parameters that were used in validation runs and compare these to productions runs. For example, this information should include cycle time and temperature setpoints, among other cycle parameters.

The next questions are What are the acceptance criteria for the qualification of the cycle? How were these developed? This section should include F_0 acceptance criteria at a minimum as well as a justification for the proposed acceptance criteria.

Next the template asks What loading patterns were used? Were diagrams of the various loading patterns provided? This section should include a description of the load patterns. You should provide diagrams showing items in the load as well as locations of thermocouples and biological indicators. Photographs may also be helpful. Diagrams of loading patterns should be submitted in Module 3 and referred to in this response.

The final question on this screen asks how the locations of the thermocouples were selected for heat distribution studies. This section should provide a description of how the cold spots of the load were determined. References to empty chamber studies only are not sufficient to establish heat distribution within an autoclave load. Combined heat distribution and heat penetration studies may be acceptable. A full description of the combined study should be provided within eSubmitter.

The next question asks what the results of the heat distribution studies were. Again, if a combined study was performed, you may indicate where the results have been provided if they are not included in the response to this question.

This is followed by a question asking for the rationale behind the selection of monitoring locations for the heat penetration studies. If separate heat distribution/heat penetration studies are performed, the monitoring locations for heat penetration studies are typically based on the results of the heat distribution studies. If combined studies are performed, information regarding the locations selected for heat penetration monitoring should be provided. This may include a discussion of previously performed studies that have identified the hardest to heat items or areas within a load. For example, is there an area within a bag of stoppers that is hardest to heat? Or, if product vials are stacked on top of each other, which container(s) are the hardest to heat within a tray and between stacked trays.

The next question asks for the results of the heat penetration study. This should include the minimum F_0 value obtained within the load.

The final question in this section asks for the requalification schedule. This should include the frequency of requalification, the loads that are requalified and should include justification for the proposal as necessary.

4.1.3 Microbiological Efficacy of the Cycle

The first question asks what are the process controls to ensure the microbiological efficacy and consistency of the cycle and how were the critical process parameters selected, validated, and monitored. The answer should include information regarding the biological indicator used to monitor the cycle. Information regarding the species, the carrier for the spores (e.g. strip, suspension, etc.), the source of the biological indicator, and the qualification of the BI (e.g. D-value, population) should be provided. A representative COA for the BI should be included as part of Module 3.

The next question asks for the incubation conditions utilized for the BI and should include incubation temperature and time.

The next question asks for the results of the lethality studies. This should include the number of Biological indicators placed in the load and whether or not they were positive for growth.

The next question asks for the acceptance criteria for the qualification of the cycle and how these were developed. This may include acceptance criteria for the minimum BI population and whether all Biological indicators must be negative for growth at the end of the incubation period.

The next question asks for the rationale behind the selection of monitoring locations for the Biological indicators. If this information has already been included under the thermal qualification questions, you may refer back to that answer.

The final question asks how the BI was inoculated into or onto the component or equipment. This may include a description, for example, of the placement of strips into pieces or equipment or a description of how the organism is inoculated into finished product vials or onto stoppers.

4.2 Radiation Sterilization

4.2.1 Description of Process and Product

The next set of questions relate to the description of the process and product. The first question asks what is the sterilization process and how was it developed. This section should describe the sterilization process that is utilized. This should indicate, for example, gamma irradiation or ebeam. A description of how the process was developed should be provided. This may include information on the impact of the proposed irradiation cycle on the components or product and how the cycle parameters and acceptance criteria were developed.

You should then identify if the process is based on the bioburden or overkill method and describe any studies used to support the use of the proposed cycle(s). Additional information may be included in 4.2.1.c. related to the quality attributes of the product.

Finally you should address what container/closure system was used during process development. This section should identify the container and closure used for cycle development and discuss whether it is the same as is intended for the marketed product.

The next screen continues the discussion of the process and product. The first question asks if a matrix or bracketing approach to validation is proposed. If you answer yes, you will be asked to provide justification for the proposed approach. If the product is filled into multiple vial sizes, the matrix or bracket should be designed to cover the worst case for vial size (for example, smallest and largest), vial shape, vial type, and load configuration (for example, minimum and maximum load). For bracketing of component sterilization, you should provide information describing the selection of the worst case load including size, shape, materials of construction, and load configuration.

The next question asks if a filtration step is used. This is only applicable to finished drug product. If you answer yes, you should indicate the purpose of the filtration step, e.g. clarification vs bioburden reduction vs a redundant sterilization step.

The final screen in this section starts by asking if you intend to pursue parametric release for the product. Keep in mind that although parametric release may be proposed, additional information should be submitted to CVM under a separate supplement to address all of the requirements to support the use of parametric release. If you are considering the use of parametric release, we recommend that you come in for a meeting before submitting this information. If you answer yes, you will be asked what are the critical parameters to ensure the success of your sterilization process? Is there a risk assessment plan in place (e.g., control strategies of the cycle, risk of product failure, product manufacturing experience and knowledge)? Again, because additional information will be required to support this type of proposal, only a brief summary of information needs to be provided here. Although written specifically for parametric release of products sterilized by moist heat, you may refer to GFI 194 – Submission of Documentation in Applications for Parametric Release of Human and Veterinary Drug Products Terminally Sterilized by Moist Heat Processes for additional information on the requirements for parametric release of finished product.

The final two questions relate to the impact of the product and sterilization process on each other. In the first question, we ask what quality attributes of the product may be impacted

by the sterilization process. For example, this section should state if the product is sensitive to radiation and could be impacted by the sterilization process.

This is followed by a question asking if there are attributes of the product that may impact the sterilization process. This is followed by an additional question asking for these attributes to be described. This section should state if there are attributes such as density that may present a particular challenge to the radiation sterilization. Responding to these questions in the Type V master file may not be the best approach to convey this information but may be more relevant to the application. In this case, you may indicate that this information can be found in the applications.

4.2.2 Dose Mapping and Validation Studies

The first question asks What are the characteristics of the process that demonstrate the radiation qualification of the cycle? How were critical process parameters selected, validated, and monitored? This section should clearly state the parameters that were used in validation runs and compare these to productions runs. For example, this information should include the dose selected.

The next question asks if a simulated product was used. This question is only relevant for radiation sterilization of finished product. If you are describing a process for equipment or components, or if you did not use a simulated product for the validation of a finished product sterilization cycle, you may answer no. If you answer yes, you will then be asked to provide a justification for the use of a simulated product.

The next questions are What are the acceptance criteria for the qualification of the cycle? How were these developed? This section should include acceptance criteria for the minimum and maximum dose delivered as well as a justification for the proposed acceptance criteria.

Next the template asks What loading patterns were used? Were diagrams of the various loading patterns provided? This section should provide a description of the load patterns. You should provide diagrams showing items in the load as well as locations of dosimeters and (if used) biological indicators. Photographs may also be helpful. Diagrams of loading patterns should be submitted in Module 3 and referred to in this response.

Next you will be asked how the locations of the dosimeters were selected for dose mapping studies. A rationale for the dose mapping study should be included here.

The next question asks what the results of the dose mapping studies were. This should include the minimum and maximum doses obtained, the locations of those doses, and any correlation between the monitored locations for the validation studies and the proposed monitoring locations for routine sterilization processes. If a bioburden approach is proposed, this section should also include the results of the dose confirmation studies.

The final question in this section asks for the requalification schedule. This should include the frequency of requalification, the loads that are requalified, the frequency of the bioburden audit (as applicable) and should include justification for the proposal as necessary.

4.2.3 Microbiological Efficacy of the Cycle

The first question asks what are the process controls to ensure the microbiological efficacy and consistency of the cycle and how were the critical process parameters selected, validated, and monitored. If biological indicators are used, the answer should include information regarding the biological indicator used to monitor the cycle. Information regarding the species, the carrier for the spores (e.g. strip, suspension, etc.), the source of the biological indicator, and the qualification of the BI (e.g. D-value, population) should be provided. A representative COA for the BI should be included as part of Module 3.

The next question asks for the acceptance criteria for the qualification of the cycle and how these were developed. This may include acceptance criteria for the minimum BI population and whether all Biological indicators must be negative for growth at the end of the incubation period.

The final question asks for the results of the lethality studies. This should include the number of Biological indicators placed in the load and whether or not they were positive for growth. If biological indicators are not used for the validation, you may indicate "Not used" or "N/A" for each question.

4.3 Aseptic Processing

4.3.1 Buildings and Facilities

What are the critical areas and supporting clean areas used in the manufacturing operations of the product? This should be a brief description of the filling area(s) and supporting rooms and their air classifications within the aseptic processing area. The floor plans and materials/personnel flow diagrams should be provided within Module 3.

4.3.2 Process

The first question asks What are the unit operations in the aseptic process? This should include all applicable operations performed in the aseptic processing area such as filtration, lyophilization, filling, etc.

Next, the filling line or lines associated with the master file should be identified.

Next you will be asked to identify the sterile equipment. This should include items such as autoclaves, depyrogenation tunnels or ovens, lyophilizers, fillers, as applicable.

The final question on this screen asks for the normal production parameters associated with the product or products manufactured on the line. These should be critical process parameters such as filling speeds, filling times, etc. that are critical for evaluating information such as media fills or hold time studies.

The next question asks how aseptic connections are made during production. This may be a reference to the applicable SOP or area of the batch record containing the instructions. The batch record or SOP may be provided as part of Module 3. The response should also address any environmental monitoring that occurs while the connections are being made.

The next question asks if products are directly filled into vials or filtered into a surge tank or header bottle. If a surge tank or header bottle is utilized, the next question asks that the size, location, and sterilization process for the tank be identified. If it is sterilized by SIP, then additional information can be provided under section 4.3.5 below.

If the product is filled as part of a campaign, then the total duration of the campaign should be provided in response to the next question. CVM defines a campaign as the maximum number of batches produced without cleaning in between.

The final question in this section asks if lyophilization of the finished drug product or sterile API is proposed. If you answer yes, you will be asked to provide a brief description of the lyophilization process. This should include a description of the lyophilizer (a schematic and a floor plan showing flow of product from the filling area to the lyophilizer may be provided as part of Module 3). This should also include a description of any transport of the filled, partially-stoppered vials from the filling line to the lyophilizer. The lyophilization steps, such as the number of vacuum cycles performed, shelf temperatures, and how the vials are closed at the end of the cycle should be provided. SIP information for the lyophilizer may be provided here or under section 4.3.5 below.

4.3.3 Filtration

Filtration is a topic that may not be covered under a Type V master file. If this is the case, you may indicate N/A under each of the questions.

The first question asks how the product is filtered. The answer to this question should include a description of the filtration process, i.e. sterilizing vs. clarifying, number of filters as well as a description of the filters as well as any prefilters, as applicable. The description of the prefilter and/or filters should indicate the pore size, manufacturer, and composition.

The next question asks how filter integrity is examined during production. This should include the type of integrity testing performed, when it was performed (e.g. before and after filtration), and the applicable parameters and limits for integrity testing such as flow rate, bubble point or forward flow limit, etc.

The next question asks for a comparison of the filters used during validation vs. production. This may include differences in size or materials of construction.

The final question on this screen asks for the parameters used during validation. This may include the use of worst case parameters such as the time and temperature of sterilization, exposure time, or no use of a filter flush.

The next screen asks for additional information regarding the filter validation such as the method used to determine filter compatibility, filter extractables, drug absorption, and bacterial retention. The answers to each of these questions should include the parameters used for the validation and a brief summary of the results of each study. The final study reports should be provided as part of Module 3.

4.3.4 Process Simulations (Media Fills)

The first question asks "What are the parameters evaluated during the process simulations to ensure the efficacy and consistency of the process?" This should include a description of the medium used for the process simulation and a justification for the use of any alternate simulated products such as mannitol.

Next you should specify the filling line or lines utilized in the process simulation. This should be the same filling line utilized for manufacture of the finished product(s).

Next you will be asked to identify the types of sterile equipment utilized during the media fill. If multiple filter housings or surge tanks, for example, are used during the manufacturing process, a description of how these items are rotated should be incorporated into the media fill description. You are then asked to identify the number of units filled vs incubated for each media fill reported.

Finally, identify the total number of media fills performed and the dates they were conducted.

The next set of questions focuses on the microbiological processes associated with the media fills.

First, identify the incubation conditions utilized for the media fill.

Next, how does the media fill simulate the production parameters. This should include a comparison between the proposed process simulation conditions and those utilized during the filling process for all products filled on this line.

Next, identify any hold times validated by the process simulation, e.g. product hold times or filling hold times as applicable. If a matrix or bracketing approach is proposed, a description should be provided.

Finally, you should indicate what method is used to perform growth promotion (i.e. concurrent with media fill incubation vs after media fill incubation). If growth promotion is performed concurrently with the media fill incubation, describe how you confirm that the growth is due to the inoculated organism and not due to contamination.

The first question on the final media fill screen asks if there were any positive units observed. If there were positive units, a description of the investigation, including corrective and preventative actions, as well as the results of any follow-up media fills should be provided.

The next question asks about the requalification schedule for media fills. This should include both the frequency of media fills as well as any information on the containers/closures to be requalified.

You should then indicate if reprocessing of components or product is proposed. Reprocessing of aseptically processed products is generally not allowed. If reprocessing of components is proposed, this may need to be included within the media fills or through the performance of in-use or container/closure integrity testing.

The final question asks if lyophilization of the finished drug product or sterile API is proposed. If the answer is yes, a follow-up question requesting a comparison of the production conditions vs the media fill questions is required. This should include information such as if the containers were exposed to vacuum, the use of nitrogen vs compressed air, etc.

4.3.5 Steam-In-Place

The first question asks if steam-in-place is used for sterilization of equipment. If you answer yes, a series of follow-up questions are activated.

The first question asks What are the characteristics of the process that demonstrate the thermal qualification of the cycle? How were critical process parameters selected, validated, and monitored? This section should clearly state the cycle parameters that were used in validation runs and compare these to productions runs. For example, this information should include cycle time and temperature setpoints, among other cycle parameters.

To answer the next question, you should specify the equipment that is to be sterilized.

The next questions are What are the acceptance criteria for the qualification of the cycle? How were these developed? This section should include F_0 acceptance criteria at a minimum as well as a justification for the proposed acceptance criteria.

This is followed by a question asking for the rationale behind the selection of monitoring locations for the heat penetration studies.

The next question asks for the results of the heat penetration study. This should include the minimum F_0 value obtained within the load.

The final question in this section asks for the requalification schedule for the equipment to be sterilized by SIP.

Section 4.4 Other; Unclassified

This section will only be active if you have a terminal sterilization method other than moist steam or irradiation. This may include processes such as ethylene oxide or vaporized hydrogen peroxide (VHP). In this case, there are no specific question to be answered. You may provide the Quality Overall Summary Module 2 as a PDF attachment here.

Section 4.5 Component Preparation

This section of questions should provide information regarding the depyrogenation of components.

The first question asks where containers and closures are depyrogenated. You should select all that apply. In-house would be selected if you are utilizing a depyrogenation tunnel or oven for containers or a stopper processor for stoppers.

If depyrogenation is performed in-house, you should then indicate if depyrogenation is performed by washing or dry heat. Select dry heat. Supplier of component should be

selected for components that are supplied ready-to-sterilize or ready-to-use. If the supplier of a component performs depyrogenation, you may reference a Type V master file if one is available.

If depyrogenation of a component is not performed, you must provide a justification for eliminating this process.

If depyrogenation of components is performed in-house, you should provide information on the process that indicates the parameters utilized, the acceptance criteria, and a brief summary of the results of the depyrogenation studies. You should also provide information regarding the endotoxin indicators used for these studies. The hint for this question provides additional information that you may find helpful. If depyrogenation is not performed or if the information is included in a separate Type V, you may indicate that here.

The final question is for informational purposes and asks if the containers and closures are sterilized before filling. Any information regarding moist steam sterilization should have been provided under section 4.1 above.

4.6 Microbiological Monitoring of the Environment

The first question asks what monitoring programs are used in the production areas to ensure the quality attributes of the product. This should include the types of monitoring performed such as non-viable particulates, settle plates, active air monitoring, etc. Diagrams showing the monitoring locations can be included as part of Module 3. This response should also include the acceptance criteria, the frequency of monitoring and steps to be taken if the criteria are exceeded.

In the response to the next question, you should indicate when and how isolates are identified in each of the monitoring areas.

If a program is in place to control bioburden or endotoxin in the raw materials, you should indicate yes and provide a description of the program and validation information as appropriate.

If bioburden monitoring of the product is described in your Type V, you should provide a summary of this information here. Otherwise you may indicate that the information is provided in the respective applications.

4.7 Microbiological Testing Controls and Stability Considerations

The first question asks about the test methods used to support the sterility of the finished product. If this information is described in your Type V, you should provide a summary of this information here. Otherwise you may indicate that the information is provided in the respective applications.

The next question asks if there are product or component characteristics of the product or components that may be impacted by the sterilization process. If yes, you will be asked to describe the impacts and how these impacts are monitored.

The final question asks if reprocessing of components is proposed. For example, if unused bags of stoppers may be resterilized, you should provide information on the maximum exposure that component would receive and how you have incorporated this into your validation processes, such as including resterilized components within the media fill process.

4.8 Process Control Documentation

This section should describe the SOPs that support the sterilization process. You may provide a list of the relevant SOPs here.

4.9 Microbiological Testing Controls

Most of the information collected here is generally product-specific and reported under the appropriate product application or file. There is a change control requesting the deletion of sections 4.9.2 (preservative effectiveness), 4.9.3 (pyrogen or endotoxin testing), and 4.9.4 (sterility testing). Until this change control is implemented, you may respond N/A to each of these questions. If you report container closure integrity testing in the Type V master file, you should answer these questions. Otherwise, you may also respond N/A.

The first question asks for the method used to perform CCIT. The second question asks for the validation information for the CCIT method. This should include a brief description of the method, the acceptance criteria for the validation and the results of the study.