INAD P MC template

Good afternoon. My name is Kristen Anderson and I am a reviewer in the Division of Manufacturing Technologies. Today I will be walking you through the INAD P MC template. At the end of the INAD P presentation, there will be a brief Q&A session, if time allows, to answer any initial questions you may have regarding this template. To enter a question, select the Chat tab. Ensure that the Send to: box indicates Mike Brent (Presenter) and type your question into the box below. Hit Send to send the question to Mike. You may send questions at any time during the session. If there are questions that we are unable to answer during today's Q&A, or time does not allow us to have a Q&A, we will hold the questions until the September 19th general Q&A session.

To start the submission, you will first need to select Investigational New Animal Drug File (I) under Document Type. I won't go through the other sections of this tab as they were covered this morning in the"How to Use eSubmitter" session. Please see this recording if you have any questions about how to fill out the firm, responsible official, or submitter information. Instead, I am going to jump to the Submission Type Selection tab. First, select major technical section (P) under the submission type. Select Chemistry, Manufacturing, and Controls (MC). Select Division of Manufacturing Technologies as the review division. The next question asks if this information is intended to amend a submission currently pending and under review by CVM for which you are providing a minor amendment. This question should be answered yes only if there is an open submission already under review at CVM and is not meant to be selected yes for the reactivation of a technical section. In most cases, you will select no to this question. If you select yes, you will be asked in the next screen to provide the CVM submission number that you would like to amend. This should be the four digit submission number of an open technical section. Leading zeros are not required. With few exceptions, CVM does not accept sponsor-initiated amendments. We therefore recommend that you discuss your minor amendment with DMT, in this case, before submission. One of the exceptions to the no sponsor-initiated amendments is to identify a different WebTrader account to redirect CVM correspondence to a new responsible official. Again, the steps to redirect CVM correspondence was covered under the "How to Use eSubmitter" webinar and should be consulted for additional information.

In the next screen you will then be asked to select the section of the original submission to be amended – 1.0 General Information, 2.3.S Drug Substance, 2.3.P Drug Product, 3.0 Feed Method Trial Protocol, 4.0 Sterility, 5.0 Module 3 and Stability Information/Data, and 6.0 Comments. You should provide a separate entry for each section that is amended. For today's webinar, we will select section 2.3.S Drug Substance. You'll be asked to select the way that you intend to provide the amended information: either as text, an attachment, or both. If you only have a small amount of information to amend, you may provide it in the memo field below. For example, Update assay specification to 90-110%. If you have a significant amount of information to provide you may find it easier to provide it as an attachment. For example, if you've forgotten to include one of your analytical methods, you should attach it as a file. In this case you should select the green + to attach the appropriate PDF document. You may also find it helpful to provide information in the memo field as well as attach a file. For example, Update drug substance specifications as text, and provide a copy of the updated specifications as an attachment.

If you need to provide a minor amendment and change the responsible official, you may either submit a single amendment to cover both items or submit separate amendments.

To proceed with the remaining portion of this webinar, I will return to Screen 6.0 Submission Type Code/Amendment Information and select no to the amendment question. You will notice that it will give you a warning because any information that you have provided regarding an amendment will be deleted if you change your response here. The next set of information that you will have to fill out falls under screen 1.0 General Information. This set of questions will allow you to select phased submissions, identify incomplete submissions, or start a new technical section. Please note that the first two questions on the screen must be answered to provide the correct template. The first question asks if you are submitting a two phased submission. For additional information on the submission of two phased submissions, please see Guidance for Industry #227: Two Phased Chemistry, Manufacturing and Controls Technical Sections. If you select yes to this question, the follow-up question will ask if you are submitting phase one or phase two of the submission. If you select phased submission, all of the CMC questions will be optional. This will allow you to answer only the questions that you are prepared to answer in that particular phase. The final question on this screen asks if the submission references any master files. You should select yes if you have any master files to reference. If you select yes three additional questions will become available asking you to indicate if you have Type II, Type V, or any other type of master file. Other types of master files would include Type III for packaging or Type IV master files for novel excipients. For the purpose of today's webinar, I will select yes to each question. You will notice as I select yes, additional sections of the template will become active.

Screen 1.1 Submitted Information

The questions that will be available on this next screen will be based on the answers you have provided to the question on the previous screen regarding phased submissions. If you selected yes to the phased submission question, and indicated that this is a Phase I submission, the next question that will be available is "Is this in response to a previous CVM technical section incomplete letter?". As you can see from this screen the only possible response is no. Once you have selected no you'll be asked to select the type of submission. Again the answer to this question is required before the correct template can be loaded. Your three options are a CMC technical section, feed method trial with data only, or CMC technical section including a feed method trial study. Options two and three are applicable only for Type A Medicated Articles. The feed method trial with data only option should only be selected for Phase II of a two-phased submission. Otherwise, the CMC technical section including feed method trial study should be selected. Option one (CMC technical section) should be selected for all other types of dosage forms. If you select CMC technical section, you will then be asked if you are submitting sterility data or information. Sterility data is only required for a sterile drug product.

If you have selected Phase II, you will then be asked is this in response to a previous CVM technical section incomplete letter. In this case you must answer yes. Once you select the yes button you will be asked to provide the CVM submission number associated with the referenced technical section incomplete letter. This should be the Phase I submission. The next option is whether you will be submitting an abbreviated response or a complete QbR response. An abbreviated response means you

will only be asked to upload a PDF of the responses to the incomplete items. In most cases an abbreviated response is not an appropriate selection for a phased submission. Once you have selected complete QBR response you will then be asked to select which sections you are updating in response to CVM's incomplete letter. The possible selections are drug substance, drug product, feed method trial, and sterility. You should select all of the sections that apply. In most cases, the Phase I submission will only include the drug substance information. In this case you should be selecting a minimum of one section to be updated: the drug product. Depending on the dosage form you may also need to select feed method trial or sterility. If you had significant deficiencies in the drug substance information in Phase I, you may also need to revisit this section of questions to address the incomplete comments. You will notice as the sections are selected additional questions further in the template will become active. Finally if you respond no to "Are you submitting a two phased submission", you will then be asked "Is this in response to a previous CVM technical section incomplete letter?". Unlike the previous set of questions that we have discussed, you have the option to answer either yes or no. If this is a brand new technical section, you should select no. Again you will have the same three selections available to you: CMC technical section, feed method trial with data only, or CMC technical section including a feed method trial study. You should select the item that corresponds to the dosage form that you are describing. If you answer yes to the question is this in response to a previous CVM technical section incomplete letter, again you'll be asked to provide the submission number associated with the referenced incomplete letter. A new question is now available which asks "In the technical section incomplete letter referenced above did CVM offer a shortened review time with the resubmission of this technical section?". If you answer yes, you are asserting that you have a valid CVM technical section incomplete letter stating that upon resubmission of this technical section you may be entitled to a shortened review time. Again you'll be asked if the complete QbR response will be provided or will an abbreviated response be submitted. If you only have a small number of incomplete comments to address, it may be appropriate to select an abbreviated response and upload the PDF as described above. If you had major deficiencies, or if there have been significant changes in the information submitted previously, the complete QBR response may be a more appropriate selection. Please note that if additional information beyond what was requested in the incomplete letter is provided, it may cause a reevaluation of the shortened reactivation, if offered.

Because I selected yes to each of the types of available master files you can see that a new node has become active for each type of master file. Because the same types of information are required for each of the types of master files I will only describe the information required for the Type II master file table. For each applicable master file, you should select the green + to start a new entry. The first question asks you to select the file type: either VMF or DMF. You should then enter the file number - you do not need to include leading zeros. The next question asks for a brief description of the information covered in this master file. This could include items such as drug substance manufacturing information, analytical controls, sterilization information etc. For Type II master files, the description should include the name of the active pharmaceutical ingredient. The next question asks if you own the master file. If you have a DMF, you must include a letter of authorization regardless of whether you own the master file or not. If you have a VMF, you only need to include a letter of authorization if you do not own the

master file. To attach the letter of authorization, press the green + and select the appropriate PDF file. You should repeat these procedures for each applicable master file.

Once you have entered all of the information for the master files, the next screen is 2.0 Product Description. The first question asks if the drug product has a USP monograph. The next two pieces of information are the product established name and the proposed proprietary name. For the established name for a new product, you should enter the title of the USP monograph if one is available. If the drug product does not have a USP monograph, and the drug is already approved, then enter the approved product established name. If this is a new or novel drug product, where a USP monograph does not exist, the drug product established name should follow the USP nomenclature naming convention as described in USP <1121> Nomenclature. As a general rule, the titles for drug product established names shall appear in the following format:

[active moiety] [route of administration] [dosage form]

For the proprietary name, be sure that you have included the entire name including copyright, trademark or registered symbols. You may do this by copying and pasting the proprietary name from another document such as a Word document (Proprietary2®) or by clicking the symbol button on the right hand side. This will allow you to select the appropriate symbol for insertion into your proprietary name. Again, for feed or drinking water combinations, the proprietary names for each drug product and the combination should be included.

In the next screen you'll be asked to identify all of the active ingredients for this finished drug product. Once you have identified all of the active ingredients, you can move to the next screen. Because I've entered multiple APIs, you will notice that at the top of the 2.3.S.1 General Information there is a box that indicates that this information will apply to API2. You may switch between the APIs by clicking the arrow button on the right hand side of the box. You will notice that the information under 2.3.S.1 General Information is required for all APIs. The first question asks what are the nomenclature, molecular structure, molecular formula, CAS number, and molecular weight of the API? It also asks for the physicochemical properties of the API. In the next screen you'll be asked to identify the manufacturer of that API. This includes the facility name, address, and phone number. You will also be asked to identify a contact person or US agent for this facility if the facility resides outside of the U.S. You should next select the functions of that facility. You may select multiple functions if that applies. You should then enter the FDA establishment identifier (FEI) and the DUNS number. 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 if available.

The next set of screens includes information regarding each active pharmaceutical ingredient. Because of time constraints, this webinar will be focused on the drug product information only. If you would like information regarding the submission of drug substance or sterilization information, please listen to the recording for the Chemistry, Manufacturing, and Controls 2 webinar covering the VMF-A-OT template for both Type II and Type V master files. This recording will cover the types of information that should be submitted for each of these topics. Before moving to the drug product screens, I would like to point

out that at the top of each of the drug substance screens there is an initial question that asks is the subject matter for that screen included in a referenced master file. If you select yes, you'll be asked to identify the Type II master file that references, in this case, the manufacture information. Once you have selected a master file, all of the remaining questions on that screen will become optional. This will allow you to input any additional information not included in the master file for that API. The same system is in place for sterilization information that may be covered in a referenced Type V master file.

The first set of drug product screens asks for information regarding the description and composition of the drug product. The first question asks "What is the physical description of the drug product? What are the available strengths, routes of administration, release mechanisms, as well as any other distinguishable characteristics?" For solid oral dosage forms, for example, you may include information such as the drug product is an oval, immediate – release, aqueous film coated tablet in three strengths, 5 mg, 10 mg, and 20 mg. The next question asks what is the function of each component in the drug product? The answer to this question should include all of the components used in the manufacture of the drug product. It should also include solvents and processing aids even if removed during processing. An example of this is nitrogen which may be used as a blanket for oxidation-sensitive drug products. You should also indicate which components are Compendial, e.g. USP/NF. If the product contains various strengths, list the quantitative composition of the finished dosage form. The grade of materials should be discussed in Section 2.3.P.4 Control of Excipients. The amount of material in the pilot and production batches should be included in Section 2.3.P.3 Manufacture.

Does this product have multiple processing steps? If you answer yes to this question you will be asked to identify the composition of the significant intermediates. This question is most applicable to tablets in which the completed tablet contains tablet cores or beads, and, as such, are likely to be manufactured in multiple processing steps.

Are there any overages in the formulation of the product? If you answered yes to this question, you should identify and justify any formulation overage that occurs in the final product. Note that overages should only include losses identified from manufacturing processes, not from losses that occur over stability. P&P 1240.4130 can be consulted for additional information on overages.

The final question asks if this product contains any materials with sizes in the nanometer range? You should select yes or no, based on whether the product contains nanomaterials.

The next screen references the pharmaceutical development report. The pharmaceutical development report is not required but can be helpful in providing background information and demonstrating process knowledge for your product. If you choose to submit a pharmaceutical development report, select yes to the first question and then the plus sign to attach the PDF file.

The next set of three screens collects information regarding the manufacture of the drug product. The first question asks what manufacturing processes and controls are used for production of the finished drug product? This question is asking for a general description of the manufacturing process. The description should include the sequence of steps undertaken to produce the finished drug product and should provide more detail than is provided in a flowchart. The description should include the following

items: 1. The complete manufacturing process for each drug product, for example, strength, packaging configuration, and scale production. 2. Identification of equipment by type and working capacity where relevant. This is most relevant for tableting and sterile operations. 3. A detailed description of any novel processes or technologies and packaging operations that directly affect product quality. 4. Identification of all process controls, including the critical process controls and the associated numeric ranges, limits, or acceptance criteria.

Is a flowchart of the manufacturing process provided in module three? The flowchart gives the steps of the process and shows where materials enter the process. The entire manufacturing process from the weighing of components through finished product release is generally pictured. The flowchart often includes the following: description of each manufacturing setup, identification of the material being processed, identification of the critical process controls and point at which they are tested, and identification of the types of equipment used.

Is a batch formula provided for the drug product composition? In general, a batch formula should be provided. An example of a product that may not require a batch formula is one that contains only repackaged active pharmaceutical ingredient. If you select yes, then you should also answer the following question: “What are the amounts of the components including overages used in the manufacturing process?” All ingredients should be included in the batch formula whether or not they remain in the finished product. Any explanatory notes, for example actual amount added based on purity, should be described. The batch formula included in the batch record should be the same as the batch formula included in the product composition section. You may also attach a file containing this information by pressing the add button and selecting the PDF file that contains the information.

The next question asks what are the in-process controls that ensure each step is successful. In-process controls are tests and controls used during production to monitor and, if appropriate, adjust process parameters and/or ensure an in-process material meets established acceptance criteria. As you answer this question, you should consider which in-process controls are used to monitor critical process parameters.

What in-process specifications were established? Specifications should include the tests and acceptance criteria used to monitor and assess the performance of the process and the quality attributes of in-process materials.

Which in process controls are used to monitor critical process parameters? A critical process parameter is one whose variability impacts the quality attributes of the drug product, and therefore needs to be controlled to ensure that the process produces the desired quality of drug product. Tests and acceptance criteria, with justifications for acceptance limits, performed at the critical steps of the process should be provided to ensure it is under control. These controls may include things such as operating parameters, environmental conditions, or quality attributes of In-Process Materials. Keep in mind, particular process parameters may or may not be critical depending on the drug product and the manufacturing process.

What is the reconciliation of the batch? Reconciliation is a comparison of the actual yield to the theoretical yield of the batch. The reconciliation includes an account of materials, (e.g. labels), a description of the accounting for such items as discards, breakage, etc. and the criteria used in accepting or rejecting batches of drugs in the event of an unexplained discrepancy.

What is the difference in size between commercial scale and pilot batches and does the equipment use the same design and operating principles? The equipment used for each scale should be briefly described and any differences in operating principles should be indicated.

Were developmental studies used to justify limits or identify critical parameters prior to execution of the pilot batch? If you select yes, a follow-up question will be available which asks what differences between equipment used in developmental studies and pilot batches are relevant to quality attributes of the material generated.

What is the rationale for differences in equipment, critical or quality related steps and controls? For some changes the rationale may be as simple as "due to larger batch size a larger bin blender was required", whereas more complex changes, such as a change in operating parameters, should be supported by data. A reference to the pharmaceutical development report is acceptable if the report supports the rationale.

The next set of questions addresses scale-up processes. If your registration batches were manufactured at full scale, you may indicate this in the responses. The first question is what evidence supports the plan to scale up the process to commercial scale, and what operating parameters will be adjusted to ensure the product meets all in-process and final product specifications? Information to address these questions may be supported by understanding of formulation, manufacturing process, and equipment or by information that was generated during the drug development phase.

Do you have prior experience with other products using the same unit operations, literature references or scale-up factors, or modeling and dimensional analysis to support scale-up? If you select yes, you'll be asked to describe your prior experience. If this or similar information is available, it may provide valuable information to support your process knowledge. If this information is available as part of your product development report, you may reference that here.

Are the process description and the in-process release specifications likely to be changed during scale-up? There is some flexibility to adjust operating parameters, (such as mixing times, flow rate, temperature) to meet these constraints during scale-up. For commercial scale-up, a sponsor may either propose fixed ranges for these operating parameters in a proposed master batch record or indicate that an operating parameter will be adjusted to reach a desired end-point.

The final question in this section is what additional rationale supports scale-up? All rationale should be provided and should focus on critical steps in the manufacturing process. This rationale should build on your experience, (including problems that were identified and resolved), obtained during development and/or the production of the pilot batch or batches.

The last item you'll be asked to identify is the manufacturer. You should press the green + to begin adding manufacturer items. The Manufacturer screen utilizes the address book functionality. The address book functionality was described in the "How to use eSubmitter" webinar and should be consulted for additional information. The information required for each facility includes the name of the facility, address, phone number, and a contact person or US agent if the facility is located outside of the US. You should select all of the functions performed in each facility. These functions include drug product manufacturer, control testing laboratory, packaging, sterilization, micronization, or other. If you select other you should describe the facility function in the box below. You should include the FDA establishment identifier or FEI, the DUNS number, and some information regarding the current FDA inspection status if known. This includes the outcome of the last inspection or allows you to identify if the facility has never been inspected. If available please include the last inspection date. You may enter any date that falls within the timeframe of the last FDA inspection of this facility. If you have any additional information about the inspection status of the facility you may enter it in the box below. You should fill out this form for each proposed facility to be used in the manufacture or testing of this product including finished product manufacturer, contract sterilizers, testing facilities, and any other facility that performs an operation for the finished drug product.

2.3.P.4 Control of the Excipients

In this first screen you'll be asked some questions that will activate other sections of this template based on the types of excipients you will be utilizing. The first question is does the product contain excipients. If your product does not contain excipients you'll be able to move onto the next section for Control of Drug Product. If you select yes to this question, you'll see some additional questions activate. The first question is "Are USP/NF excipients being utilized?" The next question is "Are non-USP/NF excipients being utilized?" This is followed by "Are any novel excipients being utilized?" Novel excipients are those that have not been previously used in veterinary drug products. Novel excipients are generally not used in an ANADA product as safety and effectiveness information is not available. These excipients may require additional details including manufacture, characterization, controls, or a DMF/VMF reference. Are there any excipients derived from animal origin? If you answer yes, you should provide an explanation regarding which excipients 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 encephalopathy 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. For example, cattle-derived material may be subject to prion contamination, amongst other things. To mitigate this risk, you could source non-specified risk materials. 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.

Finally we ask what is your vendor qualification program? The answer to this question should include a description of your vendor qualification program or a reference to the appropriate SOP which can be provided as part of Module 3. Initial qualification should include analysis of the first three lots received

from a vendor to confirm all of their COA results, and the drug product manufacturer should perform requalification testing for the excipients periodically, e.g. at least once per year.

If you selected yes to does this product contain USP/NF excipients, you will next be asked to identify information for each of the relevant excipients. First "What are the USP/NF specifications". To answer this question you may provide a listing of the specifications in the box. Alternatively, you may attach a copy of the current USP/NF monograph by clicking the green + to attach the PDF file. The next question asks are there any additional specifications that are in excess of those included in the USP/NF. If you answer yes you should identify the specifications under the next question and also include the justification for the additional specifications. For example, if micronization is required, a specification for particle size may be included. The next question asks if there are any differences between the provided specifications and the USP/NF specifications. In this section you should describe and provide justification for any differences between the provided specifications and the USP/NF specifications. This may include the addition of alternate degradants that may result from APIs manufactured using a different synthetic route.

If you selected yes to non- USP/NF excipients, you should identify each excipient utilized. You should provide the specifications for this non-USP/NF excipient. In addition, you should provide a justification for the proposed specifications utilized for this excipient. You may reference the appropriate section of the PDR for the justification if available. The grade of the material should also be included.

If you select yes to the novel excipients question you should then identify the novel excipient utilized. You should select yes or no to the question does the component reference a Type IV master file, and select the master file identifier that includes the excipient information. What additional details are available to support the use of this novel excipients? Because these excipients are novel you may need to provide additional details including manufacture, characterization, controls, or a DMF/VMF reference. What information supports the suitability of this excipient for its intended functions? The known functions of common excipients are sufficient to determine suitability. For novel excipients or novel uses of common excipients, describe studies that identify the critical attributes of the excipient. A reference can be made to the pharmaceutical development report if one has been provided. Currently, the template requires the addition of at least one manufacturer of an excipient if you answer yes to the question "does the drug product include excipients". This is a bug in the template logic. The addition of manufacturer information is intended only to be collected for novel excipients. Until this template can be updated, you may provide the information for one excipient manufacturer to fulfill this requirement. This includes the facility name and address, phone number, a contact person or US agent, and an identification of the excipients manufactured at this facility.

2.3.P.5 Control of Drug Product

What is the drug product specification and does it include all of the critical drug product attributes? The drug product manufacturer should include the full release specifications. Acceptance criteria should be provided as numerical values with proper units where applicable. Dosage form specific tests should be included as appropriate. For example, dissolution, uniformity of dosage units, water content, microbial

limits etc. may be applicable for a tablet. Guidance for Industry #176 Specifications: Test Procedures and Acceptance Criteria for New Veterinary Drug Substances and New Medicinal Products: Chemical Substances provides guidance on the setting and justification of acceptance criteria and the selection of test procedures for new medicinal products.

Does the drug product conform to a USP monograph? If you answer yes, you will need to address the following question: How do the specifications compare to the USP? If the specifications do not conform to current USP, justify the differences. If you answer yes that the drug product conforms to a USP monograph, you should address how the specifications compare to the USP. If they are identical to the USP you may state this here. If there is no USP monograph available for the drug product, you should select No to the first question.

The next group of questions refer to the analytical methods. Are the analytical method suitable for their intended uses and validated or qualified. What is the justification for the validation acceptance criteria? Provide a summary of each method and its validation/qualification, as applicable. The method summary should include the critical operational parameters for the test method. The validation summary should include results and acceptance criteria for each validation or qualification parameter. For each analytical procedure that requires validation or qualification, provide a page number to the location of the validation information in Module 3. Validation is required if the USP method is significantly modified or if there is no USP method. For example, USP General Chapter <621> provides some information on chromatography conditions that may be modified within a USP method. Use of modifications as indicated in this chapter would only need to be qualified. You may reference VICH GL2 aka Guidance for Industry #64: Validation of Analytical Procedures: Methodology for additional information regarding validation of methods. If a USP method exists and is not used, the proposed method should be demonstrated to be equivalent to or better than the USP method. For each analytical test method for assay used in the stability program, what information demonstrates that it is a stability indicating method. You should provide the results of any stress-testing performed to demonstrate it is a stability-indicating method.

The next question asks if impurities are quantified using impurity reference standards. If impurities are quantified using the impurity standard for impurity methods, provide information regarding the relative response factors for impurities. For this question, you can clarify if a relative response factor is used or whether a relative response factor of 1 is assumed in the calculation.

What is the batch control numbering system for the finished product? What are the batch analysis results for all pilot and clinical batches, including those used for stability studies? Batch analyses should include at a minimum, release testing results. Test results should be expressed numerically or qualitatively, as appropriate. Quantitative results should not be reported in general terms such as “complies”, “conforms”, or “meets limit”. Results below the limit of detection or limit of quantitation for validated methods should not be reported as zero but rather as less than the value of the LOD or LOQ.

What are the potential drug product impurities? Information on the drug product impurities should be provided. See VICH GL11 aka Guidance for Industry #93 - Impurities in New Veterinary Medicinal Products (Revised) for additional information. All potential drug product impurities should be discussed in this section of the application whether or not the impurities are included in the finished drug product specification. The next question asks you to address which potential impurities are included in the drug product specification. Provide justification for any potential impurities not included in the drug product specifications. For example, an impurity that has been isolated and characterized or is specified in a USP monograph but is not included in the drug product specifications. The final question asks you to describe what characterization studies i.e. structural characterization were performed for the impurities.

2.3.P.6 Reference Standards and Materials

Is the reference standard a USP standard? Is there a working standard? How are the reference standards certified or qualified? In this set of questions, we ask you to provide information about reference standards used to test the finished product (e.g. assay for API or relevant excipient such as benzyl alcohol). Information for the drug substance reference standard can be incorporated by reference back to section 2.3.S.5. If the reference standard is obtained from the USP/NF or EP, identify it as such. If the reference standard is not obtained from USP or EP, it should be of the highest purity and fully characterized. Include a COA as a supporting document in Module 3, along with details of the reference standard preparation, qualification, and characterization. Generally, the characterization information should include a brief description of the manufacture of the reference standard, if it differs from the routine manufacturing procedure of the drug substance. Any additional purification procedures used and the preparation of the reference standard should be described and the purity of the reference standard should be stated. Information to substantiate the proof of structure may need to be provided if the source of the material is not the drug substance manufacturer and the information is not available for review in a master file. This includes information such as NMR and MS for chemical entities or amino acid sequencing data and amino acid composition for biotechnological/biological product reference standards. Detailed interpretation of the test data in support of the claimed structure should be provided. If a secondary or working standard is used in addition to the primary reference standard that was characterized as described above, this secondary standard should be qualified against the primary reference standard. The answer should also discuss reference standards for impurities, if used.

2.3.P.7 Container Closure System

For each item utilized for the container closure system you should answer the following questions: identify the component that is proposed for packaging and storage of the drug product. This may include items such as stoppers, vials, syringes, or bags. Does the component reference Type III or IV master file? If a master file is referenced you should select the master file identifier that references that information. You should then provide a description of the component and identify if the container closure system has been qualified for use with this drug product and if the material meets FDA and USP requirements. The next screen contains a follow-up question addressing this topic.

What testing or certification supports the safety of the packaging with the drug product? Examples include those tests described in the USP or a reference to the supplier's VMF or DMF may be appropriate if that is where the test results can be located. Provide any other testing or certification such as 21 CFR references, if applicable. For example federal regulations under 21 CFR sections 174-186 provide a list of materials that are safe for use in direct or indirect food contact. Other references such as USP <660> may also be appropriate. A statement may be provided referencing products that have been approved using the same packaging system. A copy of the test results that qualify the container closure system as safe should be provided as part of Module 3.

The final question in this section asks are copies of the label provided. If the label is not final, provide a draft label to indicate CMC relevant information, such as storage conditions, active ingredients, how supplied, space for expiration date and lot number, and any special instructions such as the stopper may only be punctured XX times. In some cases, the language proposed for use in the draft label may be an acceptable alternative to providing the draft label.

2.3.P.8 Stability

The first question asks what are the specifications for stability studies, including justification of acceptance criteria that differ from the drug product release specification. The description and stability specifications should include the test methods, acceptance criteria, etc. If there are any differences between release and stability specifications, provide justification.

What stability studies support the proposed shelf life and storage conditions? Information should include a summary of the stability data in tabular form, the conclusions regarding stability, and the expiry period. Include the results of the accelerated stability studies. This may also include the results of any one-time studies such as photostability, in-use, or freeze-thaw studies, as applicable.

What are the post approval stability specifications, methods, acceptance criteria, etc. What are the stability storage conditions and testing intervals? This should include all stability storage conditions including label storage, intermediate, and accelerated, as applicable. If a bracketing or matrix approach was used for the registration batches or is proposed for ongoing commercial stability batches, you may describe the approach here.

What packaging is used for stability samples? To answer this question, you may indicate that the proposed market container will be used. If something other than the proposed market container is used, you should fully describe all packaging here.

What is the proposed post-approval stability commitment? The post approval stability commitment should include the following: a commitment to place the first three production lots followed by 3 to 10% of the production lots on stability, with a minimum of one lot per year. A commitment to report the stability data to CVM in a Minor Changes and Stability Report annually. A commitment to withdraw from the market any production lot or lots found to be out of specification and to investigate those lots manufactured immediately before and after the lot or lots in question. For more information see Guidance for Industry #5: Drug Stability Guidelines.

If information regarding a Feed Method Trial is to be submitted, an additional series of questions must be addressed.

3.1 Protocol.

The first question asks if you have previously submitted a Feed Method Trial Protocol to CVM for review. You should then attach the protocol by selecting the green + button to upload the appropriate PDF document.

3.2 Method

In the first question, you should provide a summarized description of your feed method. This should include information such as the method used for analysis and the sample preparation information. You should then attach the method by selecting the green + button to upload the appropriate PDF document.

3.3 Single Laboratory Validation

You should first indicate if a company laboratory or a contract laboratory was utilized for the single laboratory validation. The company laboratory would be the sponsor of the investigational drug. You should then attach the method validation by selecting the green + button to upload the appropriate PDF document.

3.4 Method Transfer Study

In the box, provide the names and addresses of all participating laboratories.

3.5 Feed Samples

The first question asks how many batches were used. You should indicate the number of batches used for the feed method trial. To answer the next question, you should indicate the sizes of the batch or batches. For the next question you may select either mash form or pellet form, or both if applicable. You should then select Yes or No to indicate if any Type B feeds were analyzed.

3.6 Permitted Analytical Variation

In the next screen, you should indicate the Permitted Analytical Variation (PAV) that you are requesting. You should then describe how the PAV was determined. This should include the equation used to calculate the PAV. Equations can be copied and pasted in from Word documents. You should then describe the data that supports the PAV.

3.7 Feed Method Trial Study

You should attach the Feed Method Trial Study report by selecting the green + button to upload the appropriate PDF document.

3.8 Supporting Data/Information

You should attach the supporting study data or information here by selecting the green + button to upload the appropriate PDF document. This should include all documentation associated with the transfer study such as chromatograms, worksheets, etc.

We will now move on the final sections of the template. In section 5.0 Module 3 and Stability Information/Data, you will be asked to upload all Module 3 information as well as relevant stability data.

In screen 5.1, you are asked to attach the Module 3 information by selecting the green + button to upload the appropriate PDF document or documents. Although you may attach multiple files, it is best to keep the total number of files small for the ease of the reviewer. Each file should include a table of contents. Bookmarks within the documents are helpful for ease of navigation through long documents.

In screen 5.2, you are first asked if the submission contains stability data. If you select yes, you will be asked to attach the supporting stability information. For this question, you may attach the stability data by selecting the green + button to upload the appropriate PDF or XML document.

Section 6.0 Alternate Facility asks if you are adding an alternate facility. This section is relevant for reactivations in which an alternate facility may need to be substituted for one proposed previously. If you select yes, you will then be asked to identify all of the relevant information for the alternate facility. The information required for each facility includes the name of the facility, address, phone number, and a contact person or US agent. Although this question is available for all technical section submissions, it should not be used for the initial CMC submission to the file. For the first CMC submission, this information should be contained in the Manufacturer section under 2.3.P.3.c above.

Section 7.0 allows you to include additional comments. This may either be entered as text in the text box or by selecting the green + button to upload a PDF document.

This concludes the demonstration of the INAD-P-MC template. We will now address comments that were received during the talk. As a reminder, if you have any questions that are not answered during this Q&A or if there are additional questions that you did not enter during this talk, we can address them during the general Q&A scheduled for September 19. Since we are a little ahead of time, we will put the sound on mute for a moment and look at the questions that have been received and come back to answer them. It looks like we only have one question received. The question asked for an example of the Manufacture section of the template similar to one that was received by GADA members during a meeting with CVM. I am not familiar with this meeting, so we will look into this and provide a response in the September Q&A. If you have any questions that you think of after this webinar concludes, feel free to bring them to the September 19 Q&A session.

This concludes the INAD-P-MC template demonstration. The next talk will feature the JINAD-P-MC template which is essentially identical to the INAD-P-MC template with a few identical questions so feel free to move on to a different webinar if you wish.