Power-point slide: 1

Good afternoon. My name is Trupti Dhami, 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 the eSubmitter templates for Post-Approval submissions. I will mainly be talking about Minor Changes and Stability Report and Supplemental applications. At the end of this presentation, there will be a brief Q&A session, if time allows, we will answer any question you have regarding these templates. otherwise we will hold them until the September 19th general Q&A session.

Annual report: CVM ONADE Submissions walkthrough

Let's start with the Minor Changes and Stability Report (MCSR) template. In the morning session, you were given the information on creating an electronic submission, and the general information you are required to fill out. We will start by selecting the document type 'A' here. I will focus on the ANADA templates since it has additional questions which are not included in the NADA template. Otherwise, NADA templates are similar to ANADA templates. The next question asks 'Is this submission for a currently established file? since the MCSR is for an already established file, you will select 'Yes' here. As your answer is yes, it will ask you to include the document number of your ANADA application. You will fill out the firm information and responsible official information and you then you will land on screen 6.

Screen 6:

The first question here is 'Are you submitting to an ANADA application that has received a prior approval of a section 512(b)(1) supplement?'. If your ANADA does not fall under B1 generic drug product, then you will select the answer 'No'. Under the supplemental applications, I will discuss further regarding the B1 generic drugs and different submission codes.

Then select the ANADA submission type: here you will see several options to choose from, such as supplement, reactivation of a supplement, annual report, general correspondence, meeting request, and request for changes to MOC. Since we are going through the MCSR template, you will select Chemistry Annual Report which is your B submission.

You will select the submission classification code Chemistry annual report (CA) here. Please note that these two questions on the screen must be answered to provide the correct template.

Since the CMC information goes to the Division of Manufacturing technologies, you will select DMT (HFV-140) here.

The next question asks ‘is this information intended to amend a submission currently pending and under review by CVM’. This question should be answered ‘yes’ only if there is a submission already under review at CVM and is not meant to be selected ‘yes’ for the reactivation of an incomplete MCSR. In most cases, you will select ‘no’ to this question.

Screen 1.0 for amendments: General information

If you select ‘yes’, then 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 MCSR. If the purpose of this amendment is to direct the response to a different web trader account, then select ‘yes’. This will allow the gateway to redirect the response to this submission to the person identified as the responsible official in the amendment. 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. With few exceptions (for example, identification of a new responsible official), CVM does not accept sponsor-initiated amendments. We recommend that you discuss your minor amendment with CVM before submission.

Screen 2.0 for amended information

. In the next screen, you will then be asked to select the section of the submission to be amended. You’ll be asked to select the way that you intend to provide the amended information: either it is a 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. If you have a significant amount of information to provide, you may find it easier to provide as an attachment. In this case, you can press on this green ADD button to attach the appropriate PDF document.

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.

Screen: 1.0 Chemistry Annual Report

When you will select ‘No’ to this question, the next set of information that you will have to fill out falls under screen ‘1.0 General Information’. You will fill out the reporting period of the MCSR where you are required to include the correct start and end date of the reporting period.

The next two questions ask if the product was manufactured or marketed during the reporting period? You will select option ‘Yes’ if the product was manufactured during the reporting period.

The next question is ‘Does this submission include information for Animal Drug Availability Act (ADAA) combinations?’. In ADAA combinations the multiple new animal drugs are used in the same medicated feed. You should answer ‘Yes’ if the MCSR is for a product that is also approved in ADAA combinations that you own and the same information or a reference to the information is going to be submitted in the MCSRs for those combinations.

Screen 1.1 Document Types and number table

When you select Yes, you will have to fill out a table that identifies the combination applications that will be relying on the data in the single product MCSR. Please note that including combination applications in the table does not automatically create submissions to the combination NADAs. You will be providing this information to each combination applications separately. This table helps CVM to keep track of which combination MCSRs contain duplicate data and information. You will answer ‘yes’ only if you have CMC information to drug combinations. You can select the light bulb icon to get more information which will help you answer this question.

In most of the cases, you will select ‘No’. The next question asks you to select yes if the drug product has a USP monograph. You will also be required to include product established name and proprietary name, so make sure you include the entire proprietary 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. For feed or drinking water combinations, the proprietary names for each drug product in the combination should be included. Once you fill out this screen for section 1.0, it will take you to screen 1.2.

Screen 1.2

Screen 1.2. collects the information regarding the reference listed product or RLNAD. where you will be required to fill out the information on reference listed product, such as RLNAD product document number, RLNAD product proprietary name, name of the RLNAD product owner firm, and finally you are asked to fill out the RLNAD product established name. Your product established name should match the RLNAD product established name. Please note that this screen will not be available for the post-approval submissions for NADA applications.

Screen: 2.0 Manufacturing changes

Once you entered all the information for RLNAD product, the next screen is 2.0 includes details on Manufacturing changes. The first question asks if the submission contains manufacturing changes? If you click your answer to be ‘No’ then the option to summarize the manufacturing changes gets disabled. When you select ‘yes’, then you will be required to summarize all the manufacturing changes either as a text, an attachment, or both. If you only have a small

amount of information to include, you may provide it in the memo field below. If you have a significant amount of information to provide you may find it easier to provide as an attachment. In this case, you should select the green + to attach the appropriate PDF document.

This screen will also ask you if the application references a master file? You should reference ALL master files that your application relies on in each MCSR, i.e., your answer should always be yes if there are any MFs at all that support your application If you select the answer 'yes' to this question, it will take you to section 2.1 to fill out the Master file table.

Screen 2.1 Master file table:

For each applicable master file, you should select 'New' to start the 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 if the MF has been updated during the reporting period. Please note that you should know this information even if you don't own the master file, because the MF holder should be notifying you each time they submit something to the Master file. If you answer yes to this question, the next question asks if you own the master file. If you have a VMF, you only need to include a letter of authorization if you do not 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. 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. If you click on 'List' here, you will find the list of all the Master files you have included and under details you will find all the detailed information for each MF you have included. You have the option to delete file from the list as well. Once the MF file information is included, you move on the next screen 3.0. You will rarely answer the question 'if MF has been updated during the reporting period' to be "no", because the MF holder should be updating their file at least annually to report minor changes and stability data or to report that there were no changes and no new stability data. If you answer no to this question it turns off the next question about MF ownership and turns off the ability to attach a LOA.

Screen 3.0 Stability Data

You will select 'Yes' if you are submitting the updated stability data to the file. As you select 'Yes', it will ask you the number of new lots placed on stability during the reporting period and the total number of updated stability lots reported in the submission. Here I want to remind you to make sure that these numbers are accurate. We get a lot of submissions where the numbers of lots in the template don't match up with what's in the attachments, sometimes the sponsors forget to include data or submit data they weren't supposed to. If you are not submitting stability data at all or if you have not put any new lots on stability, that should be

explained in the submission. E.g If back in Section 1.0 if you said the product was not manufactured during the reporting period, that would address why no new lots were placed on stability. If they you did manufacture during the reporting period we would expect to see at least one new lot on stability. Here you will find an option to include stability data either in .xml or pdf file format. You can also include stability protocols, commitments or any other information such as OOS investigation reports or if you want to include the discussions and conclusions as pdf documents. For more information see Guidance for Industry #5: Drug Stability Guidelines.

When all the information is included, you will click on green arrow here, it will confirm that you have reached the end of the submission form. If any of the required information is missing in the submission, you will notice that that a pop up window will appear with the message that the report is incomplete due to the missing data/validation issues. It will direct you to click on Output menu to easily identify all questions with missing responses and validation issues. You can go back to each incomplete section in the eSubmitter template and fill out the missing information to complete the submission form.

For the reactivation of MCSR, on screen 6.0 you will select the ANADA submission type to 'Reactivation of a chemistry annual report (F) and all other questions will remain the same. This ends our Chemistry annual report template. Next we will discuss supplemental submissions.

Supplements:

CBE-0:

Now we will move on to next reporting category for post-approval CMC changes. i.e. Change-Being-Effected Supplement or Chemistry Immediate Change Being effected (CBE-0).

I will focus on the ANADA template since it has additional questions which are not included in the NADA template. Otherwise, NADA templates are similar.

Screen 6: Submission type code/Amendment information

To start the submission, as we discussed earlier, you will answer the first question 'yes' or 'no' based on your product if it falls under B1 generic drug product category or not. If your ANADA falls under B1 generic, which basically includes an innovative change to a true generic product, you will select 'yes' to this question. The products approved under section 512(B)(1) get assigned the ADUFA review times, that is why it is important for you to provide the correct information here. Once you select 'yes' to this question, you will select the ANADA submission type and since we are going through supplement template, you will select the submission type to be Supplement 'C'. When you click on the submission classification code, here you will find

several options to choose from especially for generic with B1, such as AI for CBE 0, AS for CE-30, AP for PAS and AC for comparability protocol. Please choose the option correctly. If you choose CA/CI/CS/CP instead of the sub-class codes for the B1 ANADA, they will get assigned the AGDUFA review time instead of the ADUFA review time.

For now we will select the answer 'no' to the first question on this screen. Then you will select the answers for next two questions on submission type which is supplement (C) here and the submission classification code to be CI which is for Chemistry Immediate Change Being effected. Please note that these two questions on the screen must be answered to provide the correct template.

Since the CMC information goes to the Division of Manufacturing technologies, you will select DMT (HFV-140) here.

The next question asks 'is this information 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 a submission already under review at CVM and is not meant to be selected 'yes' for the reactivation of an incomplete MCSR. In most cases, you will select 'no' to this question.

Screen 1.0 for amendments: General information

If you select 'yes', then 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 MCSR. If the purpose of this amendment is to replace the eSubmitter responsible official, select 'yes'. This will allow the gateway to redirect the response to this submission to the person identified as the responsible official in the amendment. If you need to provide a minor amendment and change the responsible official,

Screen 2.0 for amended information

you may either submit a single amendment to cover both items or submit separate amendments. With few exceptions (for example, identification of a new responsible official), CVM does not accept sponsor-initiated amendments. We recommend that you discuss your minor amendment with CVM before submission. In the next screen, you will then be asked to select the section of the submission to be amended. You'll be asked to select the way that you intend to provide the amended information: either it is a 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. If you have a significant amount of information to provide, you may find it easier to provide as an attachment. In this case, you should select the green + to attach the appropriate PDF document.

Screen 1.0 General information

The first question on this screen asks you to provide the purpose of the submission; here you can provide a descriptive purpose of the submission. If you are reporting the same supplemental change to multiple applications, you will have to create a separate supplement for each application (until we get linking) but you can use the same text for purpose of submission in each supplement.

The next question here is regarding the CBE30 which is 'Is this CBE-30 is a resubmission of an incomplete Prior Approval Supplement?' This question is here by an error. We are currently working on fixing the template to remove this un-related question. So for now we will just answer 'No' here and will move on to the next question which asks you to fill out more general information related to this change if it affects other NADAs or ANADAs? You will make a proper selection of the answer 'yes' of 'no' for that. Similarly, you will answer 'yes' or 'no' for the question if the submission references a master file. If your answer to this question is 'Yes' then in the next screen you will be required to provide details on each affected ANADA or each referenced master file. For a supplement, we only want sponsors to reference master files that are directly involved with the supplement. E.g., if the purpose of the supplement is to report a change to DS manufacturing then you would reference the MF containing the DS information. If the purpose of the supplement is to report a change to the DP mfg site with no change in the approved API suppliers, the sponsor does not need to/should not reference the MFs for their API suppliers.

The next question on this screen is if the submission includes a change to the labeling of your product. If you answer 'no' to this question then the remaining questions on that screen will become optional. If you select yes to this question and yes to the next question which is 'if the drug used in a Medicated animal feed', then you will be required to complete section 3.0 for Animal feed labeling. So for now we will select yes for affected ANADAs and no to Master files and label and now you will see next screen 1.1 for affected ANADA becomes active now. For each applicable ANADA, you should select 'New' to start the new entry. The first question asks you to select the Application type: either ANADA or NADA. You should then enter the Document number - you do not need to include the leading zeros. Referencing other application affected by this supplemental change helps improve the efficiency of the review process and allows the same change to be consistently reviewed across multiple applications. However, list only those applications which you will submit identical information. Please note that listing an application in this table does not create a submission to that application. At this time, CVM requires you to create and submit a separate submission for each listed (A)NADA. We are working on a linked submission option where the supplement can be linked to all the (A)NADAs and separate submissions not required. You are also required to certify that the

information provided in that A(NADA) application is identical to the information you are submitting with this supplement. You check the box if you agree. You should repeat these procedures for each applicable (A)NADA. If you click on 'List' here, you will find list of all the (A)NADA applications you have included and under details you will find all the detailed information for each (A)NADA you have included. You have the option to delete file from the list as well. Once the (A)NADA file information is included you move on to the next screen 1.3. If you had selected 'yes' to the affected Master files, then it would have asked you to include MFs details in the table.

Screen 1.3

Screen 1.3 collects information regarding the reference listed product or RLNAD. where you will be required to fill out the information on reference listed product, such as RLNAD product document number, RLNAD product proprietary name, name of the RLNAD product owner firm, and finally you are asked to fill out the RLNAD product established name. Your product established name should match the RLNAD product established name. Please note that this screen will not be available for the post-approval submissions for NADA applications.

screen 2.0

The next screen includes the Product description which is the screen 2.0, where you can list if the drug product has a USP monograph and must include a product established name and proprietary name.

Now here on next screen 3.0 for animal feed labeling, all the options are disabled since in section 1.0 we had answered that no animal feel label is included. Since there is no labeling information included in the submission, it will skip section 4.0 for other labeling and we will land on to screen 5 for alternate facility.

Screen 5.0

If you are requesting an approval of ANY new facility as part of this supplement, then should identify the facility here. This includes DS mfg, DP mfg, testing labs, micronizers, contract facilities, etc.

For the new entry, you will click on 'New', and you will be required to provide details of the alternate facility such as purpose of the facility (You may select multiple functions if that applies), name of the facility and address. 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 enter the FDA establishment identifier 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.

Screen 6.0

Next screen is 6.0 where you can include details of the affected facility, where you can select yes or no to the question 'is there a change in the manufacturing process at an approved facility?' The purpose of this section is to report a change at an already approved facility, for example, if you are changing a test method, you should identify here the facility or facilities where that test method is performed. If your answer is no then it will take you to the screen 7 but if your answer is 'yes' to this question, then you will be required to complete the facility details on screen 6.1

Screen 6.1:

You should enter facility name.

You should next select the functions of that facility. You may select multiple functions if that applies.

then enter the FDA establishment identifier 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 a Master file is associated with this facility, then you will include the MF type and master file document number for our reference.

Screen 7.0 Proposed change

On screen 7.0 you will provide a brief description of the proposed change. You can attach documentation to support your supplemental changes. Again you can click on quick guide to check the eSubmitter file specifications.

Screen 8.0 Stability data

On Screen 8.0 you can include supporting stability data and attach data in xml or in pdf format and as I mentioned earlier, you can attach stability protocols, commitments or OOS investigation reports, and your conclusions in pdf file format.

Screen 9.0 Environmental impact

The screen 9.0 includes the information on Environmental impact. As it is a requirement for an original submission, every supplemental (A)NADA package must include an Environmental

Impact technical section because under the National Environmental Policy Act, federal agencies are required to evaluate the environmental impacts of the proposed actions to determine whether they will have a significant impact on the environment. So even for CMC supplements, you must submit either an environmental assessment or a claim of categorical exclusion. Typically, CMC supplements will qualify for a categorical exclusion under 21 CFR 25.33(a) because the action will not increase the use of the drug. You would fill check the "claim of categorical exclusion" and "21 CFR 25.33(a)" boxes on this page. If you think that the effect of the supplement does not qualify under 21 CFR 25.33(a), you could still qualify for a different categorical exclusion that is listed in the regulations, and you could enter that citation on this page here. But you can contact us before you submit your application if you have any questions.

Also, when you submit a categorical exclusion, you are required to certify that to the best of your knowledge, no extraordinary circumstances exist that may significantly impact the quality of the human environment for the proposed action. This requirement is also in the regulations, so you must check this box in order to complete your submission. Failure to certify, by checking the box, will prevent the completion of the submission.

Screen 10 Comments

Screen 10 is to include any additional comments you have to support your submission.

This will complete your submission. Again, if any of the required information is missing in the submission, you will notice that that a pop up window will appear with the message the report is incomplete due to the missing data/validation issues. It will direct you to click on the Output menu to easily identify all questions with missing responses and validation issues. You can go back to each incomplete section in the eSubmitter template and fill out the missing information to complete the submission form.

CBE-30

Now we will move on to the next reporting category for post-approval CMC changes. i.e. Change being effected in 30 days (CBE-30). To start the submission, as we discussed earlier, you will answer the first question 'yes' or 'no' based on your product if it falls under B1 generic drug product category or not.

Then you will select the answers for next two questions on submission type which is supplement (C) here and the submission classification code to be CS which is for Change being effected in 30 days. Please note that these two questions on the screen must be answered to provide the correct template.

Since the CMC information goes to the Division of Manufacturing technologies, you will select DMT (HFV-140) here.

The next question asks 'is this information 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 a submission already under review at CVM and is not meant to be selected 'yes' for the reactivation of an incomplete MCSR. In most cases, you will select 'no' to this question.

Screen 1.0 General information

The first set of questions on Screen 1 includes the general information. The first question asks you to provide the purpose of the submission, here you can provide a descriptive purpose of the submission. If you are reporting the same supplemental change to multiple applications, you will have to create a separate supplement for each application (until we get linking) but you can use the same text for purpose of submission in each supplement.

The next question is 'Is this CBE-30 is a resubmission of an incomplete Prior Approval Supplement?' If you answer 'yes' to this question you are asserting that you have a valid CVM incomplete letter from a Prior Approval supplement stating that the supplement may be resubmitted or the response to incomplete letter can be submitted as a CBE-30 Supplement. You will be required to provide a submission number associated with this incomplete prior approval supplement (which can take maximum 4 digits). where the CVM offered you to the option of resubmitting this supplement as a CBE-30 supplement.

Rest of the questions on this screen are similar what we have seen for CBE-0 submission such as 'if the proposed change affects other NADAs or ANADA?', 'If the submission references an MF' or 'change in label' etc. Since we have gone through these answers earlier, I will move on to the questions which are only applicable to CBE-30 supplement. I will not discuss the common questions which were discussed in other supplemental submissions. You will see that since I have selected the answer 'no' to both affected ANADAs and MFS, these sections 1.1 and 1.2 are not active anymore. We are on screen 1.3 now where you will be required to include the information on reference listed new animal drug. The next screen includes the Product description which is the screen 2.0, where you can list if the drug product has a USP monograph and must include a product established name and proprietary name.

Now here on the next screen 3.0 for animal feed labeling, all the options are disabled since in section 1.0 we had answered that no animal feel label is included. Since there is no labeling information included in the submission, it will skip section 4.0 for other labeling and we will land on to screen 5 for alternate facility.

In section 5 you will include information on alternate facilities, if you are requesting the approval of an alternate facility. ALL alternate facilities that you are seeking approval for need to be listed here We will click yes to this question and you will see you will be required fill out the information of the alternate facility. On the next screen 5.1, For the new entry, you will click on 'New', you will be required to provide details of the alternate facility such as purpose of the facility (You may select multiple functions if that applies)., name of the facility and address. 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 enter the FDA establishment identifier 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.

Next screen 6 is for affected facility, if there is a change in manufacturing process at an approved facility then you will click yes or else no. This screen is for reporting a change at an already approved facility, for example that if you are reporting a change in API mfg, you should list the API mfg site here, if you are reporting a change in equipment or scale for the DP you should identify the DP mfg facility or facilities where the change applies here. Here I have selected 'no', so you now you can see the screen which asks for the details of affected facility, is no more active.

Again the next screens for 7.0 to 10.0 are common to what we saw in CBE-0 application, hence I will not discuss it here again. But if you have any particular questions regarding these screens, you can ask me in the Q & A at the end of this session.

PAS:

Now we will move on to next reporting category for post-approval CMC changes. i.e. Prior Approval Supplement (PAS).

To start the submission, as we discussed earlier, you will answer the first question 'yes' or 'no' based on your product if it falls under B1 generic drug product category or not. For the submission type selection, you will select ANADA submission type to be supplement (C) and submission classification code to be Chemistry Prior Approval (CP). Since the CMC information goes to the Division of Manufacturing technologies, you will select DMT (HFV-140) here. The next question asks is this information 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 a submission already under review at CVM and is not meant to be selected yes for the reactivation of the technical section.

Screen 1.0 General information

The first question on this screen asks you to provide the purpose of the submission, here you can provide a descriptive purpose of the submission. You can use the same text for all submission in a multiple application supplement. The next question here is regarding the CBE30 which is 'Is this CBE-30 is a resubmission of an incomplete Prior Approval Supplement?' This question is here by an error. We are currently working on fixing the template to remove this un-related question. So for now we just answer 'No' to this question.

Other than this, you will be required to fill out a similar information which you did in other types of supplemental applications. Rest of the chemistry supplement information for PAS submission is same as what you filled in CBE-30 application.

Comparability Protocols

a CP describes the specific tests and studies to be performed as well as the acceptance criteria used to demonstrate that the proposed CMC change(s) do not adversely affect the product's quality.

The eSubmitter template applies to comparability protocols that would be submitted in new animal drug applications (NADAs), or abbreviated new animal drug applications (ANADAs), or supplements to these applications. These protocols submitted to A(NADA)s can include changes related to drug master files (DMFs) and veterinary master files (VMFs) that are referenced in these A(NADA)s applications. CVM also accepts comparability protocols submitted under J/INADs, which are E submissions with 50-day (for INAD) review time.

On screen 3.0 for information on comparability protocol, the first question asks you to provide a brief description of the proposed change clearly identifying all differences from the conditions approved in the application.

The next question is to provide description on specific test and studies performed. Here a list should be included of the specific tests e.g. release, in-process etc. Under studies, such as characterization, stability, removal of impurities, laboratory-scale adventitious agent removal or inactivation etc. you will provide information on how you assess the effect of the change on the drug substance, or product and or/or if appropriate, the intermediate, in -process material, or component (e.g. container closure system) directly affected by the change. Studies performed to assess the feasibility of the proposed change can often be helpful in determining whether the current approved analytical procedures will be appropriate for assessing the effect of the change on the product

Next, you are required to provide a brief description of the analytical procedure used. Here you can specify the analytical procedures that you intend to use to assess the effect of the CMC changes on the product or intermediate material. Analytical procedures should be chosen

capable of detecting new impurities or the other changes in a product that can result from the change.

Finally, you will provide a brief description of the Acceptance criteria. You should include the acceptance criteria (numerical limits, ranges or other criteria) for each specified test and study that will be used to assess the effect of the CMC changes on the product or other material and/or demonstrate equivalence between pre- and post change material. In general, the drug substance and drug product specifications would be identical to that in the approved application.

The next screen 3.1 is to provide more details on the comparability protocol. First, You should identify the type (e.g. release, long-term or accelerated stability data) and the amount of data (e.g. 3 months accelerated stability) that will be submitted. If available, you can include any data from studies performed to assess the feasibility of the proposed change with the proposed comparability protocol. Development or feasibility studies can provide insight into the relevance and adequacy of the choice of the battery of tests you have identified to assess the product.

Next, you are required to provided what is your proposed reporting category, you can choose from any of the following categories, PAS, CBE-30, CBE-0, or AR). We recommend you include a proposal for the reporting category that you would use for changes implemented using the approved comparability protocol. FDA will evaluate your proposed reporting category as part of its review of the comparability protocol and communicate any concerns about your proposal. Agreement by the applicant and FDA on the reporting category for the specified CMC changes will be part of the process of approving the comparability protocol.

On screen 3.2, you will provide a brief description of the steps taken if equivalence is not demonstrated using the approved comparability protocol. Some changes in the manufacturing process will result in a post-change product that cannot be demonstrated to be equivalent to the pre-change product without more extensive physiochemical, biological, pharmacology, PK/PD, efficacy, or safety testing or in a product that does not meet the pre-specified acceptance criteria in the protocol. You should identify in the protocol the steps you will take in such circumstances.

You should also include a commitment in your comparability protocol that you will update or withdraw your protocol when it becomes obsolete. If you do not commit, then you will be required to provide a reasoning for not providing this commitment.

You can also attach documentation which includes any other pertinent information to support a change covered under the comparability protocol. Here you have option to submit a single or multiple pdf files.

On Screen 4.0 under environmental impact, As it is a requirement for an original submission, every supplemental (A)NADA package must include an Environmental Impact technical section because, under the National Environmental Policy Act, federal agencies are required to evaluate the environmental impacts of the proposed actions to determine whether they will have a significant impact on the environment. So even for CMC supplements, you must submit either an environmental assessment or a claim of categorical exclusion. Typically, CMC supplements will qualify for a categorical exclusion under 21 CFR 25.33(a) because the action will not increase the use of the drug. You would fill check the "claim of categorical exclusion" and "21 CFR 25.33(a)" boxes on this page. If you think that the effect of the supplement does not qualify under 21 CFR 25.33(a), you could still qualify for a different categorical exclusion that is listed in the regulations, and you could enter that citation on this page here. But you can contact us before you submit your application if you have any questions.

Also, when you submit a categorical exclusion, you are required to certify that to the best of your knowledge, no extraordinary circumstances exist that may significantly impact the quality of the human environment for the proposed action. This requirement is also in the regulations, so you must check this box in order to complete your submission. Failure to certify, by checking the box, will prevent the completion of the submission.

On screen 5, you can include any additional comments if you have. This will complete your comparability protocol submission. For additional information regarding the information to be filled for each question in this template, you can refer to Guidance for industry #156.

This concludes the demonstration of the post-approval submissions templates. 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.