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Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials

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Introduction (background)

1.1. Objectives of the guideline

The following guideline is to be seen in connection with Regulation (EU) No. 536/2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC, which came into force on June 20, 2014

Since clinical trials can be designed as multi-centre studies potentially involving different Member States, it is the aim of this guideline to define harmonised requirements for the documentation to be submitted throughout the European Union.

Most available guidelines on the quality of biological / biotechnological medicinal products address quality requirements for marketing authorisation applications. Whilst these guidelines may not be fully applicable in the context of a clinical trial application, the principles outlined are applicable and should be taken into consideration during product development. The guidelines on Virus safety evaluation of biotechnological investigational medicinal products (EMEA/CHMP/BWP/398498/05) and Strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products (EMEA/CHMP/SWP/28367/07) should also be consulted.

Assuring the quality of biological medicinal products is challenging, as they often consist of a number of product variants and process related impurities whose safety and efficacy profiles are difficult to predict. However, unlike chemical entities, toxic impurities are generally not an issue, and the safety issues of biological / biotechnological products are more often related to the mechanism of action of the biological product or to immunogenicity.

In the context of an overall development strategy, several clinical trials, using products from different versions of the manufacturing process, may be initiated to generate data to support a Marketing Authorisation Application. The objective of this document is to address the quality requirements of an investigational medicinal product for a given clinical trial and not to provide guidance on a Company's overall development strategy for a medicinal product.

Nevertheless, for all clinical development phases, it is the responsibility of the applicant (sponsor) to ensure protection of the clinical trial subjects using a high quality investigational medicinal product (IMP) that is suitable for its intended purpose, and to appropriately address those quality attributes that may impair patients' safety (e.g. microbiological aspects, viral contamination, dose).

Due to the diversity of products to be used in the different phases of clinical trials, the requirements defined in this guideline can only be taken as illustrative and are not presented as an exhaustive list. IMPs based on innovative and/or complex technologies may require a more detailed data package for assessment.

1.2. Scope

This guideline addresses the specific documentation requirements on the biological, chemical and pharmaceutical quality of IMPs containing biological / biotechnology derived substances.

Moreover, this guideline lists, as regards documentation on the biological, chemical and pharmaceutical quality of the IMP, examples of modifications which are typically considered as 'substantial'.

The guidance outlined in this document applies to proteins and polypeptides, their derivatives, and products of which they are components (e.g. conjugates). These proteins and polypeptides are

produced from recombinant or non-recombinant cell-culture expression systems and can be highly purified and characterised using an appropriate set of analytical procedures. The guideline also applies to Auxiliary Medicinal Products containing these proteins and polypeptides as active substances. The requirements depend on the type of the product (authorised / not authorised / modified / non-modified medicinal product).

The principles may also apply to other product types such as proteins and polypeptides isolated from tissues and body fluids.

Advanced Therapy Medicinal Products are excluded from this guideline.

1.3. General points concerning all IMPs

IMPs should be produced in accordance with the principles and the detailed guidelines of good manufacturing practices for medicinal products (The rules governing medicinal products in the European Community, Volume IV).

1.4. Submission of data

The investigational medicinal product dossier (IMPD) should be provided in a clearly structured format following the CTD format of Module 3 and include the most up-to-date available information relevant to the clinical trial at time of submission of the clinical trial application.

If the active substance used is already authorised in a finished product within the EU/EEA or in one of the ICH regions reference can be made to the valid marketing authorisation. However, depending on the nature of the product additional information might be necessary. A statement should be provided that the active substance has the same quality as in the approved product.

The name of the finished product, the marketing authorisation number or its equivalent, the marketing authorisation holder and the country that granted the marketing authorisation should be given. (Reference is made to Table 1 of Regulation 536/2014)

2. Information on the biological, chemical and pharmaceutical quality concerning biological investigational medicinal products in clinical trials

S Active substance

Reference to an Active Substance Master File or a Certificate of Suitability (CEP) of the European Directorate for the Quality of Medicines is neither acceptable nor applicable for biological / biotechnological active substances.

S.1. General information

S.1.1. Nomenclature

Information concerning the nomenclature of the active substance (e.g. recommended International Non-Proprietary Name (INN), pharmacopoeial name, proprietary name, company code, other names or codes, if any) should be given.

S.1.2. Structure

A brief description of the predicted structure should be provided. Higher order structure, schematic amino acid sequence indicating glycosylation sites or other post-translational modifications and relative molecular mass should be included, as appropriate.

S.1.3. General properties

A list of physico-chemical and other relevant properties of the active substance should be provided including biological activity (i.e. the specific ability or capacity of a product to achieve a defined biological effect). The proposed mechanism of action should be discussed.

S.2. Manufacture

S.2.1. Manufacturer(s)

The name(s) and address(es) and responsibilities of each manufacturer, including contractors, and each proposed production site or facility involved in manufacture, testing and batch release should be provided.

S.2.2. Description of manufacturing process and process controls

The manufacturing process and process controls should be adequately described. The manufacturing process typically starts with one or more vials of the cell bank and includes cell culture, harvest(s), purification, modification reactions and filling. Storage and shipping conditions should be outlined.

A flow chart of all successive steps including relevant process parameters and in-process-testing should be given. The control strategy should focus on safety relevant in-process controls (IPCs) and acceptance criteria for critical steps (e.g. ranges for process parameters of steps involved in virus removal) should be established for manufacture of phase I/II material. These in-process controls (process parameters and in process testing as defined in ICH Q11) should be provided with action limits or preliminary acceptance criteria. For other IPCs, monitoring might be appropriate and acceptance criteria or action limits do not need to be provided. Since early development control limits are normally based on a limited number of development batches, they are inherently preliminary. During development, as additional process knowledge is gained, further details of IPCs should be provided and acceptance criteria reviewed.

Batch(es) and scale should be defined, including information on any pooling of harvests or intermediates.

Any reprocessing during manufacture of the active substance (e.g. filter integrity test failure) should be described and justified. Reprocessing could be considered in exceptional circumstances. For biological products, these situations are usually restricted to certain re-filtration and re-concentration steps upon technical failure of equipment or mechanical breakdown of a chromatography column.

S.2.3. Control of materials

Raw and starting materials

Materials used in the manufacture of the active substance (e.g. raw materials, starting materials, cell culture media, growth factors, column resins, solvents, reagents) should be listed identifying where each material is used in the process. Reference to quality standards (e.g. compendial monographs or manufacturers' in-house specifications) should be made. Information on the quality and control of non-compendial materials should be provided. Information demonstrating that materials (including biologically-sourced materials, e.g. media components, monoclonal antibodies, enzymes) meet standards applicable for their intended use should be provided, as appropriate.

For all raw materials of human or animal origin (including those used in the cell bank generation), the source and the respective stage of the manufacturing process where the material is used should be indicated. Summaries of safety information on adventitious agents for these materials should be provided in Appendix A.2.

Source, history and generation of the cell substrate

A brief description of the source and generation (flow chart of the successive steps) of the cell substrate, analysis of the expression vector used to genetically modify the cells and incorporated in the parental / host cell used to develop the Master Cell Bank (MCB), and the strategy by which the expression of the relevant gene is promoted and controlled in production should be provided, following the principles of ICH Q5D.

Cell bank system, characterisation and testing

A MCB should be established prior to the initiation of phase I trials. It is acknowledged that a Working Cell Bank (WCB) may not always be established.

Information on the generation, qualification and storage of the cell banks is required. The MCB and/or WCB if used should be characterised and results of tests performed should be provided. Clonality of the cell banks should be addressed for mammalian cell lines. The generation and characterisation of the cell banks should be performed in accordance with the principles of ICH Q5D.

Cell banks should be characterised for relevant phenotypic and genotypic markers so that the identity, viability, and purity of cells used for the production are ensured.

The nucleic acid sequence of the expression cassette including sequence of the coding region should be confirmed prior to the initiation of clinical trials.

As for any process change, the introduction of a WCB may potentially impact the quality profile of the active substance and comparability should be considered (see section S.2.6. Manufacturing process development).

The safety assessment for adventitious agents and qualification of the cell banks used for the production of the active substance should be provided in A.2, if appropriate.

Cell substrate stability

Any available data on cell substrate stability should be provided.

S.2.4. Control of critical steps and intermediates

Tests and acceptance criteria for the control of critical steps in the manufacturing process should be provided. Cross reference to section S 2.2 might be acceptable for acceptance criteria or action limits. It is acknowledged that due to limited data at an early stage of development (phase I/II) complete information may not be available. Hold times and storage conditions for process intermediates should be justified and supported by data, if relevant.

S.2.5. Process validation

Process validation data should be collected throughout development, although they are not required to be submitted in the IMPD.

For manufacturing steps intended to remove or inactivate viral contaminants, the relevant information should be provided in the section A2, Adventitious agents safety evaluation.

S.2.6. Manufacturing process development

Process improvement

Manufacturing processes and their control strategies are continuously being improved and optimised, especially during the development phase and early phases of clinical trials. Changes to the manufacturing process and controls should be summarized. This description should allow a clear identification of the process versions used to produce each batch used in non-clinical and clinical studies, in order to establish an appropriate link between pre-change and post-change batches. Comparative flow charts and/or list of process changes may be used to present the process evolution. If process changes are made to steps involved in viral clearance, justification should be provided as to whether a new viral clearance study is required, or whether the previous study is still applicable.

Comparability exercise

Depending on the consequences of the change introduced and the stage of development, a comparability exercise may be necessary to demonstrate that the change would not adversely impact the quality of the active substance. In early phases the main purpose of this exercise is to provide assurance that the post-change product is suitable for the forthcoming clinical trials and that it will not raise any concern regarding safety of the patients included in the clinical trial. In addition, for later phases, it should be assessed if the post-change material could impact the efficacy of the IMP.

This comparability exercise should normally follow a stepwise approach, including comparison of quality attributes of the active substance and relevant intermediates, using suitable analytical methods. Analytical methods usually include routine tests, and may be supplemented by additional characterisation tests (including orthogonal methods), as appropriate. Where the manufacturers' accumulated experience and other relevant information are not sufficient to assess the risk introduced by the change, or if a potential risk to the patients is anticipated, a comparability exercise based only on quality considerations may not be sufficient. During early phases of non-clinical and clinical studies, comparability testing is generally not as extensive as for an approved product. In the case of first in human clinical trials, an IMP representative of the material used in non-clinical studies should be used

(see Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products (EMEA/CHMP/SWP/28367/07)).

S.3. Characterisation

S.3.1. Elucidation of structure and other characteristics

Characterisation of a biotechnological or biological substance (which includes the determination of physico-chemical properties, biological activity, immuno-chemical properties, purity and impurities) by appropriate techniques is necessary to allow a suitable specification to be established. Reference to literature data only is not acceptable, unless otherwise justified by prior knowledge from similar molecules for modifications where there is no safety concern (e.g. C-terminal lysine for monoclonal antibodies). Adequate characterisation should be performed in the development phase prior to phase I and, where necessary, following significant process changes.

All relevant information available on the primary, secondary and higher-order structure including post-translational (e.g. glycoforms) and other modifications of the active substance should be provided. Details should be provided on the biological activity (i.e. the specific ability or capacity of a product to achieve a defined biological effect). Usually, prior to initiation of phase I studies, the biological activity should be determined using an appropriate, reliable and qualified method. Lack of such an assay should be justified. It is recognised that the extent of characterisation data will increase during development.

The rationale for selection of the methods used for characterisation should be provided and their suitability should be justified.

S.3.2. Impurities

Process related impurities (e.g. host cell proteins, host cell DNA, media residues, column leachables) and product related impurities (e.g. precursors, cleaved forms, degradation products, aggregates) should be addressed. Quantitative information on impurities should be provided including maximum amount for the highest clinical dose. For certain process-related impurities (e.g. antifoam agents), an estimation of clearance may be justified.

In case only qualitative data are provided for certain impurities, this should be justified.

S.4. Control of the active substance

When process validation data are incomplete, the quality attributes used to control the active substance are important to demonstrate pharmaceutical quality, product consistency and comparability after process changes. Therefore the quality attributes controlled throughout the development process should not be limited to the tests included in the specification for which preliminary acceptance criteria have been set.

S.4.1. Specification

The specification for the batch(es) of active substance to be used in the clinical trial should define acceptance criteria together with the tests used to exert sufficient control of the quality of the active substance. Tests and defined acceptance criteria are mandatory for quantity, identity and purity and a

limit of 'record' or 'report results' will not be acceptable for these quality attributes. A test for biological activity should be included unless otherwise justified. Upper limits, taking into account safety considerations, should be set for the impurities. Microbiological quality for the active substance should be specified.

As the acceptance criteria are normally based on a limited number of development batches and batches used in non-clinical and clinical studies, they are by their nature inherently preliminary and may need to be reviewed and adjusted during further development.

Product characteristics that are not completely defined at a certain stage of development (e.g. glycosylation, charge heterogeneity) or for which the available data is too limited to establish relevant acceptance criteria, should also be recorded. As a consequence, such product characteristics could be included in the specification, without pre-defined acceptance limits. In such cases, a limit of 'record' or 'report results' is acceptable. The results should be reported in the Batch Analyses section (S.4.4).

Additional information for phase III clinical trials

As knowledge and experience increases, the addition or removal of parameters and modification of analytical methods may be necessary. Specifications and acceptance criteria set for previous trials should be reviewed and, where appropriate, adjusted to the current stage of development.

S.4.2. Analytical procedures

The analytical methods used for all tests included in the active substance specification (e.g. chromatographic methods, biological assay, etc.) should be listed including those tests reported without acceptance limits. A brief description of all non-compendial analytical procedures, i.e. the way of performing the analysis, should be provided, highlighting controls used in the analysis.

For methods which comply with a monograph of the European Pharmacopoeia (Ph. Eur.), the pharmacopoeia of an EU Member State, the United States Pharmacopoeia (USP) or the Japanese Pharmacopoeia (JP), reference to the relevant monograph will be acceptable.

S.4.3. Validation of analytical procedures

Validation of analytical procedures during clinical development is seen as an evolving process.

Analytical procedures, which are either described in Ph. Eur., the pharmacopoeia of a Member State, USP or JP, or are linked to a product specific monograph, are normally considered as validated. Proposed modifications or alternatives to compendial methods must be validated

For phase I and II clinical trials, the suitability of the analytical methods used should be confirmed. The acceptance limits (e.g. acceptance limits for the determination of the content of impurities, where relevant) and the parameters (specificity, linearity, range, accuracy, precision, quantification and detection limit, as appropriate) for performing validation of the analytical methods should be presented in a tabulated form. If validation studies have been undertaken for early phase trials, a tabulated summary of the results of analytical method validation studies could be provided for further assurance.

Information for phase III clinical trials

Validation of the analytical methods used for release and stability testing should be provided. A tabulated summary of the results of the validation carried out should be submitted (e.g. results or values found for specificity, linearity, range, accuracy, precision, quantification and detection limit, as

appropriate). By the end of phase III full method validation must be completed, including confirmation of robustness. It is not necessary to provide a full validation report.

S.4.4. Batch analyses

As the specification may initially be very wide, actual batch data are important for quality assessment. For quantitative parameters, actual numerical values should be presented.

The focus of this section is to demonstrate the quality of the batches (conformance to established preliminary specification) to be used in the clinical trial. For early phase clinical trials where only a limited number of batches of active substance have been manufactured, test results from relevant clinical and non-clinical batches should be provided, including those to be used in the clinical trial supported by the IMPD. For active substances with a longer production history, it could be acceptable to provide results for only a number of representative batches, if appropriately justified.

Batch number, batch size, manufacturing site, manufacturing date, control methods, acceptance criteria and the test results should be listed together with the use of the batches. The manufacturing process used for each batch and any differences in these processes should be identified.

A statement should be included whether the batch analyses data presented are from the batches that will be used in the clinical trial, or whether additional batches not yet manufactured at time of submission of the IMPD might be used.

S.4.5. Justification of specification

A justification for the quality attributes included in the specification and the acceptance criteria for purity, impurities, biological activity and any other quality attributes which may be relevant to the performance of the medicinal product should be provided. The justification should be based on relevant development data, the batches used in non-clinical and/or clinical studies and data from stability studies, taking into account the methods used for their control. It is acknowledged that during clinical development, the acceptance criteria may be wider and may not reflect process capability. However, for those quality attributes that may impact patient safety, the limits should be carefully considered taking into account available knowledge (e.g. process capability, product type, dose, duration of dosing etc.). The relevance of the selected potency assay and its proposed acceptance limits should be justified.

Changes to a previously applied specification (e.g. addition or removal of parameters, widening of acceptance criteria) should be indicated and justified.

S.5. Reference standards or materials

Due to the nature of biologically / biotechnology derived active substances, a well characterised reference material is essential to ensure consistency between different batches but also to ensure the comparability of the product to be marketed with that used in clinical studies and to provide a link between process development and commercial manufacturing. The characterisation of the reference material should be performed with reliable state-of-the-art analytical methods, which should be adequately described. Information regarding the manufacturing process used to establish the reference material should be provided.

If more than one reference standard has been used during the clinical development, a qualification history should be provided describing how the relationship between the different standards was maintained.

If available, an international or Ph. Eur. standard should be used as primary reference material. Each in-house working standard should be qualified against this primary reference material. However, it should be noted that the use of an international or Ph. Eur. standard might be limited to certain defined test methods, e.g. biological activity. If an international or Ph. Eur. standard is not available, an in-house standard should be established during development as primary reference material. The stability of the reference material should be monitored. This can be handled within the quality system of the company

S.6. Container closure system

The immediate packaging material used for the active substance should be stated. Possible interactions between the active substance and the immediate packaging should be considered.

S.7. Stability

Stability summary and conclusions (protocol / material and method)

A stability protocol covering the proposed storage period of the active substance should be provided, including specification, analytical methods and test intervals. The testing interval should normally follow the guidance given in ICH Q5C.

The quality of the batches of the active substance placed into the stability program should be representative of the quality of the material to be used in the planned clinical trial.

The active substance entered into the stability program should be stored in a container closure system of the same type and made from the same materials as that used to store active substance batches to be used in the clinical trial. Containers of reduced size are usually acceptable for the active substance stability testing.

Studies should evaluate the active substance stability under the proposed storage conditions. Accelerated and stress condition studies are recommended as they may help understanding the degradation profile of the product and support an extension of the shelf-life.

The methods used for analysing the stability-indicating properties of the active substance should be discussed, or cross-reference to S.4.3 made to provide assurance that changes in the purity / impurity profile and potency of the active substance would be detected. A potency assay should be included in the protocol, unless otherwise justified.

A re-test period (as defined in ICH Q1A guideline) is not applicable to biological / biotechnology derived active substances.

Stability data / results

Stability data should be presented for at least one batch made by a process representative of that used to manufacture material for use in the clinical trial. In addition, supportive stability data on relevant development batches or batches manufactured using previous manufacturing processes should be provided, if available. Such batch data may be used in the assignment of shelf life for the active substance provided an appropriate justification of the representative quality for the clinical trial material is given.

The relevant stability data should be summarised in tabular format, specifying the batches tested, date of manufacture, process version, composition, storage conditions, time-points, test methods, acceptance criteria and results.

For quantitative parameters, actual numerical values should be presented. Any observed data trends should be discussed.

Progressive requirements will need to be applied to reflect the amount of available data and emerging knowledge about the stability of the active substance during the different phases of clinical development. By phase III the applicant should have a comprehensive understanding of the stability profile of the active substance.

Shelf-life determination

The claimed shelf-life of the active substance under the proposed storage conditions should be stated and accompanied by an evaluation of the available data. Any observed trends should be discussed.

The requested storage period should be based on long term, real time and real temperature stability studies, as described in ICH Q5C. However, extension of the shelf-life beyond the period covered by real-time stability data may be acceptable, if supported by relevant data, including accelerated stability studies and/or relevant stability data generated with representative material.

The maximum shelf-life after the extension should not be more than double, or more than twelve months longer than the period covered by real time stability data obtained with representative batch(es). However, extension of the shelf life beyond the intended duration of the long term stability studies is not acceptable.

Where extensions of the shelf-life are planned, the applicant should commit to perform the proposed stability program according to the presented protocol, and, in the event of unexpected issues, to inform Competent Authorities of the situation, and propose corrective actions.

Prior knowledge including platform technologies could be taken into consideration when designing a stability protocol. However, on its own this data is not considered sufficient to justify the shelf-life of the actual active substance.

For shelf-life extension by way of substantial modification, see section 6.

P Investigational medicinal product under test

P.1. Description and composition of the investigational medicinal product

The qualitative and quantitative composition of the IMP should be stated. The information provided should include:

- a short statement or a tabulation of the dosage form
- composition, i.e. list of all components of the dosage form and their amount on a per-unit basis (including overages, if any), the function of the components, and a reference to their quality standards (e.g. compendial monographs or manufacturer's specifications)
- description of accompanying diluents(s)

- an outline of the type of container and closure used for the dosage form and for any accompanying reconstitution diluent and devices, if applicable. A complete description should be provided in section P.7.

P.2. Pharmaceutical development

For early development there may be only limited information to include in this section.

A short description of formulation development, including justification of any new pharmaceutical form or excipient, should be provided.

For products requiring additional preparation (e.g. reconstitution, dilution, mixing), compatibility with the used materials (e.g. solvents, diluents, matrix) should be demonstrated and the method of preparation should be summarised (reference may be made to a full description in the clinical protocol).

It should be documented that the combination of intended formulation and packaging material does not impair correct dosing, ensuring for example that the product is not adsorbed to the wall of the container or infusion system. This is particularly relevant for low dose and highly diluted presentations. Where applicable, the reliable administration of very small doses in first-in-human studies should be addressed as laid down in the Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products (EMEA/CHMP/SWP/28367/07).

Manufacturing process development

Changes in the manufacturing process including changes in formulation and dosage form compared to previous clinical trials should be described. An appropriate comparability exercise should support significant changes, e.g. formulation changes. In this regard, expectations are similar to those described in S.2.6. This data should be sufficiently detailed to allow an appropriate understanding of the changes and assessment of possible consequences to the safety of the patient.

Any changes in the formulation during the clinical phases should be documented and justified with respect to their impact on quality, safety, clinical properties, dosing and stability of the medicinal product.

P.3. Manufacture

P.3.1. Manufacturer(s)

The name(s), address(es) and responsibilities of all manufacturer(s) and each proposed production site involved in manufacture, testing and batch release should be provided. In case multiple manufacturers contribute to the manufacture of the IMP, their respective responsibilities should be clearly stated.

P.3.2. Batch formula

The batch formula for the batch(es) to be used for the clinical trial should be presented. This should include a list of all components. The batch sizes or range of batch sizes should be given.

P.3.3. Description of manufacturing process and process controls

A flow chart showing all steps of the manufacturing process, including relevant IPCs (process parameters and in-process-tests), should be provided accompanied by a brief process description. The IPCs may be recorded as action limits or reported as preliminary acceptance criteria and the focus should be on safety relevant attributes. For other IPCs, monitoring might be appropriate and acceptance criteria and action limits do not need to be reported. During development, as additional process knowledge is gained, further details of IPCs should be provided and acceptance criteria reviewed.

Most products containing recombinant proteins and monoclonal antibodies are manufactured by an aseptic process, which is considered to be non-standard. Non-standard manufacturing processes or new technologies and new packaging processes should be described in sufficient detail (see the Guideline on process validation for finished products - information and data to be provided in regulatory submissions, EMA/CHMP/CVMP/QWP/BWP/70278/2012).

Reprocessing may be acceptable for particular manufacturing steps (e.g. re-filtration) only if the steps are adequately described and appropriately justified.

P.3.4. Control of critical steps and intermediates

Tests and acceptance criteria for the control of critical steps in the manufacturing process should be provided. It is acknowledged that due to limited data at an early stage of development (phase I/II) complete information may not be available.

If holding times are foreseen for process intermediates, duration and storage conditions should be provided and justified by data in terms of physicochemical, biological and microbiological properties.

For sterilisation by filtration the maximum acceptable bioburden prior to the filtration must be stated in the application. In most situations NMT 10 CFU/100 ml will be acceptable. Test volumes of less than 100 ml may be used if justified.

P.3.5. Process validation

The state of validation of aseptic processing and lyophilisation should be briefly described, if applicable. Taking into account EudraLex Vol. 4, Annex 13, the validation of sterilising processes should be of the same standard as for product authorised for marketing. The dossier should particularly include information directly relating to the product safety, i.e. on bioburden and media fill runs.

P.4. Control of excipients

P.4.1. Specification

References to Ph. Eur., the pharmacopoeia of an EU Member State, USP or JP may be made. For excipients not covered by any of the aforementioned standards, an in-house specification should be provided.

P.4.2. Analytical procedures

In cases where reference to a pharmacopoeial monograph listed under P.4.1 cannot be made, the analytical methods used should be indicated.

P.4.3. Validation of the analytical procedures

Not applicable.

P.4.4. Justification of specification

For non-compendial excipients as listed above in P.4.1, the in-house specification should be justified.

P.4.5. Excipients of human or animal origin

For excipients of human or animal origin, information should be provided regarding adventitious agents safety evaluation (e.g. sources, specifications, description of the testing performed) and viral safety data according to the Guideline on virus safety evaluation of biotechnological investigational medicinal products (EMEA/CHMP/BWP/398498/05) in Appendix A.2. Furthermore, compliance with the note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01) should be documented in section A.2.

If human albumin or any other plasma derived medicinal product is used as an excipient, information regarding adventitious agents safety evaluation should follow the relevant chapters of the Guideline on plasma-derived medicinal products (CPMP/BWP/706271/2010). If the plasma derived component has already been used in a product with a Marketing Authorisation then reference to this can be made.

P.4.6. Novel excipients

For excipients used for the first time in a medicinal product or by a new route of administration, full details of manufacture, characterisation and controls, with cross references to supporting safety data (non-clinical and/or clinical), should be provided according to the active substance format (details in A.3).

P.5. Control of the investigational medicinal product

P.5.1. Specification

The same principles as described for setting the active substance specification should be applied to the medicinal product. In the specification, the tests used as well as their acceptance criteria should be defined for the batch(es) of the product to be used in the clinical trial to enable sufficient control of quality of the product. Tests for content, identity and purity are mandatory. Tests for sterility and endotoxins are mandatory for sterile products. A test for biological activity should be included unless otherwise justified. Upper limits, taking safety considerations into account, should be set for impurities. They may need to be reviewed and adjusted during further development.

Acceptance criteria for IMP quality attributes should take into account safety considerations and the stage of development. Since the acceptance criteria are normally based on a limited number of

development batches and batches used in non-clinical and clinical studies, their nature is inherently preliminary. They may need to be reviewed and adjusted during further development.

The analytical methods and the limits for content and bioactivity should ensure a correct dosing.

For the impurities not covered by the active substance specification, upper limits should be set, taking into account safety considerations.

Additional information for Phase III clinical trials

As knowledge and experience increases the addition or removal of parameters and modification of analytical methods may be necessary. The specification and acceptance criteria set for previous trials should be reviewed for phase III clinical trials and, where appropriate, adjusted to the current stage of development.

P.5.2. Analytical procedures

The analytical methods for all tests included in the specification should be described. For some proteins and complex or innovative pharmaceutical forms, a higher level of detail may be required.

For further requirements refer to S.4.2.

P.5.3. Validation of analytical procedures

For requirements refer to S.4.3.

P.5.4. Batch analysis

As specifications may initially be very wide, actual batch data are important for quality assessment. For quantitative parameters, actual numerical values should be presented.

The focus of this section is to demonstrate the quality of the batches (conformance to established preliminary specification) to be used in the clinical trial. For early phase clinical trials where only a limited number of batches have been manufactured, test results from relevant clinical and non-clinical batches should be provided, including those to be used in the clinical trial supported by the IMPD. For products with a longer production history, it could be acceptable to provide results for only a number of representative batches, if appropriately justified.

Batch number, batch size, manufacturing site, manufacturing date, control methods, acceptance criteria and the test results should be listed together with the use of the batches. The manufacturing process used for each batch should be identified.

A statement should be included whether the batch analyses data presented are from the batches that will be used in the clinical trial, or whether additional batches not yet manufactured at time of submission of the IMPD might be used.

P.5.5. Characterisation of impurities

Additional impurities and degradation products observed in the IMP, but not covered by section S.3.2, should be identified and quantified as necessary.

P.5.6. Justification of specification

A justification for the quality attributes included in the product specification should be provided mainly based on the active substance specification. Stability indicating quality attributes should be considered. The proposed acceptance criteria should be justified.

P.6. Reference standards or materials

The parameters for characterisation of the reference standard should be submitted, where applicable.

Section S.5 may be referred to, where applicable.

P.7. Container closure system

The intended primary packaging to be used for the IMP in the clinical trial should be described. Where appropriate, reference should be made to the relevant pharmacopoeial monograph. If the product is packed in a non-standard administration device, or if non-compendial materials are used, description and specifications should be provided.

If a medical device is to be used for administration its regulatory status should be explicitly stated (e.g. whether it is CE marked for its intended purpose or not). In the absence of certification for its intended purpose, a statement of compliance of the medical device with relevant legal requirements for safety and performance is required. Where a medicinal product is combined with an integral medical device and the principal mechanism of action is that of the medicinal product, the combined product is governed by the medicines legislation and a CE mark is not required during development. However, at the time of MAA the requirements of article 117 of Regulation (EU) 2017/745 should be taken into account.

For products intended for parenteral use where there is potential for interaction between product and container closure system, more details may be needed (e.g. extractable/leachable for phase III studies).

P.8. Stability

The same requirements as for the active substance are applied to the medicinal product, including the stability protocol, stability results, shelf-life determination, including extension of shelf-life beyond the period covered by real-time stability data, stability commitment and post-approval extension. Stability studies should provide sufficient assurance that the IMP will be stable during its intended storage period. The presented data should justify the proposed shelf life of the product from its release to its administration to patients. The stability protocol for the IMP should take into account the knowledge acquired on the stability profile of the active substance.

Bracketing and matrixing approaches may be acceptable, where justified.

In-use stability data should be presented for preparations intended for use after reconstitution, dilution, mixing or for multidose presentations. These studies are not required if the preparation is to be used immediately after opening or reconstitution.

Appendices

A.1. Facilities and equipment

Not applicable.

A.2. Adventitious agents safety evaluation

All materials of human or animal origin used in the manufacturing process of both the active substance and the medicinal product, or such materials coming into contact with active substance or medicinal product during the manufacturing process, should be identified. Information assessing the risk with respect to potential contamination with adventitious agents of human or animal origin should be provided in this section.

TSE agents

Detailed information should be provided on the avoidance and control of transmissible spongiform encephalopathy agents. This information can include, for example, certification and control of the production process, as appropriate for the material, process and agent.

The note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMEA/410/01) in its current version is to be applied.

Viral safety

Where applicable, an assessment of the risk with respect to potential viral contamination should be provided in this section. The documentation should comply with the requirements outlined in the guideline on virus safety evaluation of biotechnological investigational medicinal products (EMEA/CHMP/BWP/398498/05).

Other adventitious agents

Detailed information regarding other adventitious agents, such as bacteria, mycoplasma, and fungi should be provided in appropriate sections within the core dossier.

A.3. Excipients

For novel excipients, information as indicated in section S should be provided in line with the respective clinical phase.

A.4. Solvents for reconstitution and diluents

For solvents for reconstitution and diluents, the relevant information as indicated in section P should be provided.

3. Information on the quality of authorised, non-modified biological test and comparator products in clinical trials

Information on the authorised, non-modified test/comparator product provided in the IMPD should meet the requirements as outlined in section 3 of the Guideline on the requirements to the chemical

and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials (EMA/CHMP/QWP/834816/2015).

In the case when only repackaging is performed without changing the primary packaging, the following information should be included in the simplified IMPD in addition to the requirements listed in section 3 of EMA/CHMP/QWP/834816/2015:

- Information that will satisfy the requirement to ensure that the investigational medicinal product will have the proper identity, strength, quality and purity (e.g. cross-reference to the Summary of Product Characteristics for the EU marketed product).
- Details on the site of repackaging/relabeling operations.

4. Information on the quality of modified authorised biological comparator products in clinical trials

Information on the modified authorised test/comparator product provided in the IMPD should meet the requirements as outlined in this guideline.

Sections not impacted by the modification may cross-refer to the authorised product.

5. Information on the chemical and pharmaceutical quality concerning placebo products in clinical trials

Information on the placebo product to be provided in the IMPD should meet the requirements as outlined in section 6 of the Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials (EMA/CHMP/QWP/834816/2015).

6. Changes to the investigational medicinal product and auxiliary medicinal product with a need to request a substantial modification to the IMPD

In accordance with Good Manufacturing Practice, a Product Specification File should be maintained for each IMP/auxiliary medicinal product at the respective site and be continually updated as the development of the product proceeds, ensuring appropriate traceability to the previous versions.

In compliance with the Clinical Trials Regulation (CTR), a change to IMP/auxiliary medicinal product quality data is either:

- a substantial modification (Art. 2.2.13);
- a change relevant to the supervision of the trial (Art. 81.9);
- a non-substantial modification (changes outside the scope of substantial modifications and changes irrelevant to the supervision of the trial).

Substantial modification means any change which is likely to have a substantial impact on the safety and rights of the subjects or on the reliability and robustness of the data generated in the clinical trial. Assessment of an IMPD should be focussed on patient safety. Therefore, any modification involving a potential new risk has to be considered a substantial modification. This may be especially the case for

changes in impurities profile, microbial contamination, viral safety, or the risk of TSE contamination or in some particular cases to stability when degradation products of concern may be generated.

Non-substantial modifications relevant to the supervision of the trial (Art 81.9 change) are concepts introduced under the CTR, which aims to update certain, specified information in the EU database (CTIS) without the need for a substantial modification application, when this information is necessary for oversight but does not have a substantial impact on patients safety and rights and/or data robustness. Art 81.9 states "The sponsor shall permanently update in the EU database information on any changes to the clinical trials which are not substantial modifications but are relevant for the supervision of the clinical trial by the Member States concerned". Art 81.9 changes can be submitted only if the change does not trigger additional changes, which are expected to be submitted as a substantial modification application.

For non-substantial modifications, documentation should not be proactively submitted, but the relevant internal and study documentation supporting the change should be recorded within the company and if appropriate, at investigator site. At the time of an overall IMPD update or submission of a substantial modification the non-substantial changes should be incorporated into the updated documentation. However, when submitting a modified IMPD, the sponsor should clearly identify which modifications are substantial and which are not.

When a modification will become effective with the start of a new clinical trial (e.g. change of name of the IMP, new manufacturing process), the notification will take place with the application for the new trial. Submissions of substantial modifications are only necessary for changes to ongoing clinical trials (i.e. after time of approval).

In the following table, examples are given for changes in IMPs containing biological active substances, and their classification. This list does not claim to be exhaustive. The sponsor should decide on a case by case basis how to classify the change.

Changes to IMPD	Substantial Modification (SM)	Art. 81.9 Non-substantial Modification (NSM)	Non-substantial Modification (NSM)
Manufacturer of the active substance	• Any addition to section S2.1/P3.1 Addition or replacement of manufacturer, manufacturing site or QC testing site, (including sites at a different location within a company) • Deletion of manufacturing, or QC testing site (for quality/safety reason or GMP non-compliance).		• Deletion of manufacturing, or QC testing site (for reasons not impacting quality/safety of the IMP, or GMP compliance) • Name change of manufacturer
Manufacturing process of the active substance	Changes such as: • new expression cell line • new master cell bank • introduction of a working cell bank if prepared from an approved MCB • change of a raw material of biological origin • changes to the viral safety tests performed on cell banks or unprocessed bulk batches, • change in scale of the production bioreactor (upstream process), • changes to the cell culture conditions potentially impacting on quality attributes • changes in the purification process (downstream): addition or removal		• Addition or tightening of IPC if not due to safety reasons • Modification of the process parameters (same process, analogous raw materials) where no effect on product quality is demonstrated. • reprocessing if adequately described and accepted in the initial submission • minor changes in the manufacturing process which do not require a comparability exercise • changes to the controls of non-critical raw materials

Changes to IMPD	Substantial Modification (SM)	Art. 81.9 Non-substantial Modification (NSM)	Non-substantial Modification (NSM)
	of a purification step • changes in the process conditions of any steps that have been identified as contributing to virus removal/inactivation, or that require new virus validation studies (viral clearance studies) • any reprocessing not described in the IMPD • changes leading to the occurrence of new impurities and product related substances		
Specifications (release and shelf life) of the active substance	• Change in the specification, if acceptance criteria are widened or deleted • Addition of specification or acceptance criteria for safety/quality reasons		• Tightening acceptance criteria or adding acceptance criteria for no safety/quality reasons • Addition, deletion or replacement of a specification parameter due to compendial change
Analytical methods for control of the active substance	• Introduction of a new test method • Change to a test method that impacts the current method performance parameters		• Improvement of the same analytical method (e.g., greater sensitivity, precision, accuracy) provided 1) the acceptance criteria are similar or tighter 2) the improved method is suitable for use or validated according to the stage of development, and lead to comparable

Changes to IMPD	Substantial Modification (SM)	Art. 81.9 Non-substantial Modification (NSM)	Non-substantial Modification (NSM)
			or better validation results • Minor changes of the test method already covered by the IMPD which does not impact the current method performance parameters • Update of the test method to comply with revised Ph.Eur., USP, or JP monograph
Batch analysis of the active substance			• Additional batch data manufactured using the same process described in the IMPD unless it is requested otherwise
Reference standard	▪ Introduction of a new reference standard for biological active substance		▪ New RS for biological DS if it was manufactured according to the same manufacturing process as the current RS and the new RS has been qualified following the approved qualification protocol. ▪ New RS for a chemical compound provided that equivalence has been established to the previous RS
Container closure system for active substance	▪ Change to the container closure system that may impact the stability of drug substance (e.g., contact material, surface/volume ratio)		▪ Change of supplier of packaging components if the material is identical and equivalent quality (e.g. the same compendial quality)

Changes to IMPD	Substantial Modification (SM)	Art. 81.9 Non-substantial Modification (NSM)	Non-substantial Modification (NSM)
Stability of the active substance	• changes in the approved storage conditions • Change in the agreed stability protocol • any extension of the shelf-life outside the agreed stability protocol or without prior commitment • Reduction in shelf life due to safety or quality related issues		• Additional intermediate stability time point but which is not yet covered (e.g., additional pull point at 42months) without changing the conditions for the extrapolation, leading to corresponding interim shelf life extension • Reduction in Shelf-Life if not safety or quality related Shelf-life extension if: • each additional extension of the shelf-life is not more than double and is not more than 12 months longer than available real time data and does not go beyond the duration as outlined in the agreed stability protocol • the extension is covered and in compliance with the approved stability protocol • no OOS results or significant trends which may lead to an OOS result during the approved shelf life have been detected in ongoing stability studies at the designated storage temperature

Changes to IMPD	Substantial Modification (SM)	Art. 81.9 Non-substantial Modification (NSM)	Non-substantial Modification (NSM)
Composition of the investigational medicinal product	• change to the qualitative and quantitative composition of the formulation including changes in the active substance concentration and excipient composition		
Manufacturer of the investigational medicinal product	• Addition or replacement of manufacturing, packaging or QC testing sites • Deletion of manufacturing, packaging or testing site (for quality/safety reason, GMP non-compliance). • Addition or replacement of batch release certification site (QP certification)		• Deletion of manufacturing, packaging or testing site (no quality/safety reason) • Name change of manufacturer • Addition or replacement of an importation site that is not a QP certification site, with a valid GMP status
Manufacturing process of the investigational medicinal product	• Significant changes to the manufacturing process and critical process controls (e.g. bioburden limit)		• Modifications of process parameters (same process) where no effect on product quality is demonstrated. • Scale-Up of filling process if supported by appropriate media fills.
Specifications (release and shelf life) of the investigational medicinal	▪ Change in the specification, if acceptance criteria are widened or deleted		• Tightening acceptance criteria for no safety/quality reasons • Addition of specification parameter for

Changes to IMPD	Substantial Modification (SM)	Art. 81.9 Non-substantial Modification (NSM)	Non-substantial Modification (NSM)
product	▪ Addition of specification or acceptance criteria for safety/quality concerns		no safety/quality reasons
Analytical methods for control of the investigational medicinal product	▪ Introduction of a new test method ▪ Change to a test method that impacts the current method performance parameters		• Improvement of the same analytical method (e.g., greater sensitivity, precision, accuracy) provided 1) the acceptance criteria are similar or tighter 2) the improved method is suitable for use or validated according to the stage of development, and lead to comparable or better validation results • Minor changes of the test method already covered by the IMPD which does not impact the current method performance parameters • Update of the test method to comply with revised PhEur, USP, or JP monograph
Batch analysis of the investigational medicinal product			• Additional batch data manufactured using the same process described in the IMPD unless it is requested otherwise

Changes to IMPD	Substantial Modification (SM)	Art. 81.9 Non-substantial Modification (NSM)	Non-substantial Modification (NSM)
Container closure system of the investigational medicinal product	• changes to primary packaging		• Changes to secondary packaging • Change of supplier (deletion, replacement or addition) of primary packaging components if the material is identical and specifications are at least equivalent.
Medical devices	• Addition of, changes to, or replacement of, a medical device in the IMPD that potentially impacts the quality, safety and/or efficacy.		• Changes to, or replacement of, a medical device in the IMPD which is not considered to impact the quality, safety and/or efficacy.
Stability of the investigational medicinal product	• Changes in the agreed stability protocol • changes in the approved in-use stability recommendations • any extension of the shelf-life outside the agreed stability protocol or without prior commitment • Reduction in shelf life due to safety or quality related issues		• Additional intermediate stability timepoint but which is not yet covered (e.g., add. pull point at 42m) without changing the conditions for the extrapolation, leading to corresponding interim shelf life extension • Reduction in Shelf-Life if not safety or quality related Shelf-life extension if: • each additional extension of the shelf-life is not more than double and is not more than 12 months longer than available real time data and does not go beyond the duration as outlined in the agreed

Changes to IMPD	Substantial Modification (SM)	Art. 81.9 Non-substantial Modification (NSM)	Non-substantial Modification (NSM)
			stability protocol • the extension is covered and in compliance with the approved stability protocol • no OOS results or significant trends which may lead to an OOS result during the approved shelf life have been detected in ongoing stability studies at the designated storage temperature

IND 012757

MEETING MINUTES

Genzyme Corporation
Attention: Vanessa Davidson
Director, Global Regulatory Affairs
55 Corporate Drive, Mailstop: 55C-300
Bridgewater, NJ 08807

Dear Ms. Davidson:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for GZ402665.

We also refer to the teleconference between representatives of your firm and the FDA on March 24, 2021. The purpose of the meeting was to discuss your proposed plan for a Biologics License Application (BLA) submission for GZ402665 as (b) (4) treatment of non-central nervous system manifestations of acid sphingomyelinase deficiency (ASMD) in pediatric and adult patients.

A copy of the official minutes of the meeting/telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Jenny Doan, Regulatory Project Manager, at (301) 796-1023.

Sincerely,

{See appended electronic signature page}

Kathleen M Donohue, MD, MSc
Director
Division of Rare Diseases and Medical Genetics
Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes

U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-BLA

Meeting Date and Time: March 24, 2021; 11:15AM – 12:15PM EST
Meeting Location: Teleconference

Application Number: 012757
Product Name: GZ402665
Indication: Enzyme replacement therapy for (b) (4) treatment of non-central nervous system (CNS) manifestations of acid sphingomyelinase deficiency (ASMD) in pediatric and adult patients.

Sponsor Name: Genzyme Corporation
Regulatory Pathway: 351(a) of the Public Health Service Act

Meeting Chair: Anita Zaidi, MD, Clinical Team Leader
Meeting Recorder: Jenny Doan, Regulatory Project Manager

FDA ATTENDEES

Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine (ORPURM)
Hylton Joffe, MD, MMSc, Director
Janet Maynard, MD, Deputy Director

Division of Rare Diseases and Medical Genetics (DRDMG)
Kathleen Donohue, MD, Director
Anita Zaidi, MD, Clinical Team Leader
Christine Hon, PharmD, Clinical Analyst

Division of Pharm/Tox of Rare Diseases, Pediatric, Urologic and Reproductive Medicine
Mukesh Summan, PhD, Director
Mary Ellen McNerney, PhD, Reviewer

Division of Regulatory Operations for Rare Diseases and Medical Genetics
Pam Lucarelli, Director, Project Management Staff
Michael White, PhD, Chief, Project Management Staff
Jenny Doan, MSN, BSN, Regulatory Health Project Manger

Office of Clinical Pharmacology/Division of Translational and Precision Medicine (DTPM)
Jie (Jack) Wang, PhD, Clinical Pharmacology Team Leader
Xiaohui (Michelle) Li, PhD, Clinical Pharmacology Reviewer

Lian Ma, PhD, Pharmacometrics Team Leader
Yuching, PhD, PBPK Lead

Office of Biostatistics/ Division of Biometrics IV
Yan Wang, PhD, Biostatistics Team Leader
Yared Gurmu, PhD, Biostatistics Reviewer

Office of Biotechnology Products (OBP)
Ram Sihag, PhD, CMC Team Leader
Maria Gutierrez-Hoffman, PhD, Team Leader

Office of Pharmaceutical Manufacturing Assessment (OPMA)
Maria Gutierrez-Hoffman, PhD, Reviewer
Virginia Carroll, PhD, Team Leader

Office of Biostatistics/ Division of Biometrics III/ Patient-Focused Statistical Support (PFSS)
Lili Garrard, PhD, PFSS Team Leader (Acting)
Marian Strazzeri, MS, PFSS Reviewer

Division of Clinical Outcome Assessment (DCOA)
Christopher St. Clair, PharmD, COA Reviewer
Elektra Papadopoulos, MD, MPH, Deputy Director (Acting)

Office of Surveillance and Epidemiology (OSE)
Laura Zendel, PharmD, BCPS, Team Leader, Division of Risk Management (DRM)
Theresa Ng, PharmD, BCPS, CDE, Risk Management Analyst, DRM
Sarah Vee, PharmD, Safety Evaluator, Division of Medication Errors Prevention and Analysis (DMEPA)
Idalia Rychlik, PharmD, Team Leader, DMEPA
Su-Lin Sun, RPh, PharmD, GWCPM, Safety Regulatory Project Manager
Aleksander Winiarski, PharmD, RPh, Team Leader

SPONSOR ATTENDEES
Colleen Costello, PhD, Associate Vice President, Global Regulatory Affairs – US
Vanessa Davidson, Director, Global Regulatory Affairs – US
Sandy Furey, MD, PhD, Therapeutic Area Strategy Lead Rare Diseases, Specialty PV
Don Gieseker, PharmD , AVP of US Regulatory Affairs
(b) (4) External Consultant, Clinical Outcomes Assessment
Ruth Pulikottil Jacob, PhD, Health Economics and Value Assessment Business Partner
Andreas Jessel, MD, Vice President, Global Project Head, Rare Disease Development
Barbara Kittner, MD, Therapeutic Area Head Rare Diseases, Specialty PV
Karin Knobe, MD, PhD, Vice President, Therapeutic Area Head, Development Rare Diseases and Rare Blood Disorders
Monica Kumar, MD, MPH, Senior Director, Clinical Research

Priti Lad, Senior Director, Global Regulatory Affairs – US
Jing Li, Associate Director, PK PD Modeling
Sreeraj Macha, Senior Director, PK PD modeling
Amanda Meisel, PharmD, Post-Doctoral Fellow, Global Regulatory Affairs – US
Susan Richards, PhD, FAAPS, Vice President, Translational Medicine and Early Development
Joyce Tay, PhD, Manager, Global Regulatory Affairs – CMC Biologics
Susana Zaph, PhD, Head Translational Disease Modeling- Rare
Qi Zhang, PhD, Director, Biostatistics

1.0 BACKGROUND

FDA Regulatory Background

The sponsor, Genzyme Corporation (Genzyme), is developing GZ402665, also referred to as olipudase alfa, an enzyme replacement therapy for the treatment of non-central nervous system manifestations of acid sphingomyelinase deficiency (ASMD) in pediatric and adult patients. Olipudase alfa is a recombinant human acid sphingomyelinase (rhASM), produced by mammalian cell culture technology using a Chinese hamster ovary cell line. The product is intended to be supplied as a lyophilized powder, to be reconstituted for intravenous infusion, and administered (b) (4) according to body weight.

Olipudase alfa was granted orphan drug designation for the treatment of ASMD (Niemann-Pick disease) on August 3, 2000. The IND was submitted to the FDA on October 26, 2005, granted Fast Track designation on April 23, 2007, and Breakthrough Therapy designation on May 26, 2015, both for the treatment of non-neurological manifestations of ASMD.

The olipudase alfa clinical development program had multiple changes in the manufacturing process during the course of the drug development, including a switch from Process A to Process B and Process C (b) (4) eventually to Process C (b) (4) as to-be marketed drug substance and drug product process. Highlights of the FDA interactions related to the manufacture processes for olipudase are outlined in the table below.

October 4, 2011	Type C meeting to discuss proposed clinical and manufacturing development plans for olipudase alfa. To support phase 2 and future clinical development programs for olipudase alfa, the sponsor intended to implement (b) (4) (b) (4) (b) (4) (Process B) to replace (b) (4) (Process A). Meeting minutes issued on November 4, 2011.
April 7, 2015	Type C meeting to discuss Genzyme's plan to change the manufacturing process from Process B to Process C, which is (b) (4) for the ongoing phase 2/3 and proposed pediatric clinical trials. The FDA

	requested Genzyme provide additional information to support the comparability between the two processes and raised concerns on the timing of introducing new material to the ongoing clinical studies. Meeting minutes issued on April 13, 2015.
January 25, 2017	Type B meeting to discuss FDA's concerns regarding the comparability issues, particularly due to changes in specific activity between Process B and Process C. The FDA also recommended additional clinical data would be needed to evaluate and characterize the impact of these changes. Meeting minutes issued on January 31, 2017. Additional comments were provided in an advice letter on March 3, 2017.
July 26, 2017	Type C meeting to discuss the pediatric extrapolation plan for olipudase alfa. The FDA indicated (b) (4) (b) (4) challenges for the extrapolation for safety and efficacy. Genzyme proposed to enroll at least 8 additional pediatric patients (age < 12 years) into the open-label DFI13803 trial to be initiated with Process C product. Meeting minutes issued on July 31, 2017.
July 27, 2018	FDA issued a WRO in response to a CMC-only meeting request to discuss Genzyme's additional change to the drug substance manufacturing, which includes transitioning from a (b) (4) (Process C (b) (4) to a (b) (4) (Process C (b) (4). The FDA commented on the proposed comparability assessment plan between Process C (b) (4) and Process C (b) (4). Additional FDA feedback was provided on incorporating Process C (b) (4) into the ongoing clinical studies in an advice letter on October 5, 2018.
August 28, 2019	Type B meeting to discuss Genzyme's proposed data package for a rolling review BLA for olipudase alfa. The FDA stated its concerns regarding the format and content of the BLA submission, the proposed datasets, and the timeline given the various manufacturing processes. Meeting minutes issued on September 8, 2019.
October 18, 2019	FDA issued a WRO to comment on Genzyme's clarifications for their rolling BLA submission strategy.
January 31, 2020	FDA issued an advice letter in response to the CMC amendment submitted September 20, 2019, which contains a biochemical comparability assessment between Process C (b) (4) and to-be-market Process C (b) (4) The FDA concurred that the materials from these two processes are analytically comparable.

Genzyme plans to submit a BLA rolling review with the following schedule:

BLA Submission Wave	Proposed Submission Date	Content
Wave 1	June 14, 2021	Non-clinical modules
Wave 2	September 30, 2021	CMC and Clinical modules

On January 21, 2021, Genzyme submitted a meeting request to discuss the BLA data package for olipudase. On January 27, 2021, the FDA granted a type B pre-BLA teleconference, which is scheduled to take place on March 24, 2021. The meeting briefing package was received on February 22, 2021. FDA sent preliminary comments to Genzyme on March 17, 2021. The meeting took place as scheduled.

FDA Clinical Background

Acid spingomyelinase deficiency (ASMD) is an autosomal recessive disease caused by genetic mutations in the *SMPD1* gene leading to a deficiency in the lysosomal enzyme acid sphingomyelinase (ASM), which catalyzes the degradation of sphingomyelin. ASMD has traditionally been broken down into two subgroups. Type A generally causes severe neurodegenerative disease during infancy, whereas type B is generally not considered to be a neurologic disease. There is also an intermediate phenotype known as A/B form.[1]

ASMD type B is a milder later onset form of ASMD and can develop symptoms from infancy to adulthood. It is associated with systemic disease that can vary widely in severity and extent. Patients may have hepatosplenomegaly, deterioration in lung function, liver disease, growth delays and low weight, osteopenia, and dyslipidemia. Patients with ASMD type B usually do not develop neurological symptoms but may develop mild symptoms. Some affected children and adolescents may develop nystagmus and cerebellar signs, which includes unsteady manner of walking and clumsiness. Intellectual disability and psychiatric disorders, abnormalities of the retina, and peripheral neuropathy may occur.[2]

2.0 DISCUSSION

FDA Introductory Comment

Your proposed BLA submission for adults consists of one adequate and well-controlled trial (DFI12712). In that trial, the primary endpoint that uses a patient reported outcome, the splenomegaly-related score (SRS), appears to have shown no difference between the treated and placebo arms. Therefore, your pivotal trial fails to meet the primary endpoint on a clinically meaningful outcome. As such, it is unclear how the other primary endpoints (DLco, spleen volume) directly measure how a patient feels, functions or survives. In order to receive traditional approval, you need to provide

[1] GeneReviews. Acid sphingomyelinase deficiency. Accessed March 4, 2021. https://www.ncbi.nlm.nih.gov/books/NBK1370/
[2] National Organization for Rare Disorders' Rare Disease Database. Acid sphingomyelinase deficiency. Accessed March 4, 2021. https://rarediseases.org/rare-diseases/acid-sphingomyelinase-deficiency/

justification and evidence that the other primary endpoints (DLco, spleen volume) are expected to have a clinically meaningful benefit or have been shown to predict a specific clinical benefit to patients.

Also, in order to establish substantial evidence of effectiveness, you must accompany your adequate and well-controlled trial with confirmatory evidence of treatment effect. This evidence should be specifically described in your BLA submission. We refer you to the FDA draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019)[3,4] for examples of how a single trial together with confirmatory evidence can establish effectiveness.

You also do not have a well-controlled trial for the pediatric population that you propose to treat. Therefore, you will need to justify your lack of a well-controlled trial and provide all evidence that would intend to establish substantial evidence of effectiveness in the pediatric population.

Meeting Discussion: ***Refer to attached Sponsor's response to FDA Preliminary Comments (Section 5.0).***

Although the Sponsor's overall proposal appears reasonable, the Agency reiterated that the adequacy of the data package will be determined at filing after the BLA is submitted. The Sponsor's overall approach to using partial extrapolation also appears reasonable. Whether the study data and results support the partial extrapolation of efficacy from adult to pediatrics will be determined during the BLA review.

The Agency stated that detailed information is needed in the BLA to demonstrate a clinically meaningful benefit to the patients. The Sponsor should specify a clinically meaningful threshold for the selected endpoints in the target population and provide adequate justification for such thresholds. The degree of change in the biomarker should be clinically meaningful for the targeted population. Information on the correlation of the biomarker with clinical outcomes from clinical trials and/or literature should be provided. Refer to the Post-Meeting Comments below regarding how the available evidence and literature can be used to justify the use of a surrogate endpoint as a clinically meaningful endpoint.

The Sponsor also stated, when asked by the Agency, that the lack of difference in SRS in DFI12712 was due to an unexpected placebo effect. The Agency stated that the BLA should include a detailed argument summarizing the Sponsor's point of view regarding why the changes in the biomarker endpoints are clinically meaningful despite the lack of improvement seen on the PRO endpoint.

[3] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[4] https://www.fda.gov/media/133660/download

Post-Meeting Comments: ***DLCO, FVC, spleen size, and platelets etc. are biomarker measures that do not directly measure how patients feel, function, and survive. To support traditional approval using these biomarkers as surrogate endpoints in ASMD, summarize the available evidence (published literature or proprietary data, in vitro, in vivo, or clinical) linking the underlying pathophysiology of the disease (e.g. sphingomyelin accumulation) with the biomarker endpoints and the clinical relevance of those changes for ASMD patients.***

1. ***Sphingomyelin is tissue toxic when it accumulates***
2. ***Sphingomyelin accumulates in all tissues where the disease causes structural damage and functional loss***
3. ***Degree of sphingomyelin accumulation is correlated with degree of tissue damage***
4. ***Reduction in sphingomyelin is associated with normalization of structure and function in surrogate endpoints (e.g. DLCO, FVC, spleen size, platelets).***
5. ***The magnitude of this reduction is clinically meaningful in the target patient population***
6. ***Drug removes sphingomyelin from disease target tissues***

Organize the evidence for each of the above six points in a table like the following:

Senior author or protocol number (w/ hyperlink)	***Year study completed or published (in ascending order)***	***Population number & type (patients, healthy volunteers, animal models, cell lines)***	***Study design***	***Intervention (e.g. dose) vs. control (e.g. placebo)***	***Results (treatment difference, 95%CI, p-value)***

Question 1: Does the Agency agree that the proposed clinical data package is sufficient to support the filing and review of the BLA for the proposed indication?

FDA Response to Question 1: The adequacy of the data package for filing will be determined during the filing review of the BLA. Refer to the Introductory Comment and the comments below.

We remind you to submit the following for study DFI12712 (ASCEND) under Section 5.3.5.3 of the eCTD[5]:

- An exact copy (e.g., screenshot) of each COA used to evaluate efficacy, safety, measurement properties, and/or meaningful change in study DFI12712 *as administered* in the trial;
- A detailed scoring algorithm for each administered COA that includes how scores were computed in the presence of missing item responses;
- A clear description of how each COA-based endpoint was constructed from COA scores;
- A final Psychometric Analysis Plan (PAP); and
- A COA Evidence Dossier compiling and synthesizing all psychometric and meaningful change results.

The evaluation of the measurement properties of the COAs (e.g., the SRS, BFI Item 3, BPI-SF Item 3, and FACIT-Dyspnea) and the interpretation of COA-based endpoints intended for labeling in study DFI12712 (ASCEND) will be review issues. If you intend to conduct patient exit interviews and include these data in the BLA, we strongly recommend submitting the interview protocol and interviewer guide(s) to the Agency for review and comment as soon as possible. We recommend that the interviews include open-ended concept elicitation regarding symptoms and impacts of ASMD and cognitive debriefing of the SRS. We refer you to the FDA Patient-Focused Drug Development guidance series[6] (particularly the Guidance 4 discussion document[7]) regarding use of qualitative data to support interpretation of meaningful change.

For safety assessment, you need to submit the narratives for deaths, serious adverse events, adverse events of special interests, and withdrawal due to adverse event for all the studies.

We recommend that you perform exploratory analyses evaluating the impact of *SMPD1* genotype on PK, PD, safety, and efficacy.

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[5] Per the FDA guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims* (December 2009); accessible at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-reported-outcome-measures-use-medical-product-development-support-labeling-claims).

[6] https://www.fda.gov/drugs/development-approval-process-drugs/fda-patient-focused-drug-development-guidance-series-enhancing-incorporation-patients-voice-medical

[7] https://www.fda.gov/media/132505/download

Meeting Discussions: ***Refer to attached Sponsor's response to FDA Preliminary Comments (Section 5.0)***

The Sponsor should submit to the BLA a dossier containing all justification and evidence related to the COAs. Rationale for the selection/development of the COAs (including but not limited to SRS) should be included (relevant literature, clinical expert input, etc.). The results of psychometric analyses should also be included. It is acceptable not to include the interview protocol and interviewer guide.

The Sponsor's proposed exploratory analyses evaluating the impact of SMPD1 genotype appears reasonable. The Agency may have additional comments during the BLA review.

Post Meeting Comment: The Sponsor should also perform exploratory analyses assessing the correlation of baseline residual acid sphingomyelinase activity with PK, PD, safety, and efficacy.

Question 2: Does the Agency agree with Sanofi Genzyme's proposed plan to include clinical data and analyses related to manufacturing Processes B, C (b) (4) and C (b) (4) in the clinical study reports, Integrated Summary of Safety, Integrated Summary of Efficacy, and Integrated Summary of Immunogenicity in the BLA?

FDA Response to Question 2: Your overall proposed plan to include clinical data and analyses related to different manufacturing process drug products in the clinical study reports, ISS, ISE, and ISI appears reasonable. We have the following comments regarding some of the planned analyses. We may also have additional comments during the BLA review.

- The safety assessment of TEAEs between drug products manufactured with Process B and C (b) (4) in DFI13803 ASCEND-Peds CSR should include the evaluation of treatment emergent SAEs, hypersensitivity IARs, and anaphylaxis reactions IARs.
- For efficacy assessment between Process B and Process C (b) (4) drug products in the DFI12712 ASCEND CSR, LTS13632 CSR, and ISE, include evaluations of other efficacy/PD measurements such as DLco, liver volume, ALT, HDL, LDL, and lyso sphingomyelin, etc. in addition to the currently proposed endpoints.

Meeting Discussion: ***No further discussion occurred.***

Question 3: Does the Agency agree that the clinical data provided address the concerns from the Agency regarding comparability between Process B and Process C (b) (4)?

FDA Response to Question 3: The clinical comparability between Process B and Process C (b) (4) drug products will be a review issue and determined during the review of the BLA. Please also refer to the response to Question 2.

Meeting Discussion: ***No further discussion occurred.***

Question 4: Does the Agency agree Sanofi Genzyme's proposal to include the following data from patients treated with Process C (b) (4) in the initial BLA and in the 120 day safety update?

FDA Response to Question 4:
Your proposal appears reasonable.

Meeting Discussion: ***No further discussion occurred.***

Question 5: Does the Division agree with Sanofi Genzyme's plan to present descriptive statistics and to not include "minimum detectable difference calculations" in the analyses comparing the different manufacturing processes as requested by the Division?

FDA Response to Question 5:
Your proposed analysis plan for comparing the different manufacturing processes appears reasonable.

Meeting Discussion: ***No further discussion occurred.***

Question 6: Does the Agency agree with the planned content of Module 2.7.2 of the BLA, including modeling (population PK, exposure-response, population PK/PD and quantitative system pharmacology) analyses?

FDA Response to Question 6: The proposed content of Module 2.7.2 appears sufficient to support the review of clinical pharmacology components of your BLA.

We have the following additional clinical pharmacology comments.

- For the evaluation of the impact of anti-drug antibodies (ADA) on pharmacokinetic (PK), we recommend that you include between-subject comparison (i.e., between ADA positive subjects and ADA negative subjects) as well as within-subject comparison (i.e., before ADA positive and after ADA positive) of PK data.
- We acknowledge that you plan to conduct population PK analysis to support PK and dose selection. We encourage you to include subject's ADA status as a covariate in the population PK analysis on an exploratory basis to evaluate the impact of ADA on PK. In the population PK analysis, further explore the necessity of treating the subject ADA status as a time-varying variable for ADA positive subjects with or without the ADA titer data.

- Submit bioanalytical method performance summary tables for all the bioanalytical methods used for the PK and PD assessment in your clinical studies. Use the format of summary tables as in FDA guidance for industry *Bioanalytical Methods Templates*.[8] Include the method performance summary for each of the supported clinical studies. Do not delete any rows from the tables. State "not applicable" if certain rows of columns are not applicable. Include any other additional bioanalytical information in a separate table that might be relevant for your BLA review.
- We recommend the content and format of information in the Clinical Pharmacology section (Section 12) of labeling be consistent with FDA guidance for industry *Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format*.[9]

Meeting Discussion: ***No further discussion occurred.***

Question 7: Does the Agency agree with the content, layout, and location of the proposed patient visualization profiles?

FDA Response to Question 7: We agree with the eCTD location of the proposed patient visualization profiles. We have the following comments for the content and the layout of these patient profiles.

- We noted that you have included in the patient profiles the upper and lower reference limits (as depicted by green dotted lines) for some but not all laboratory tests. We recommend that you include the upper and lower reference values for all laboratory tests in the patient profiles.
- As shown in Appendix B, the current layout of the patient profiles is one graph for one variable/profile per page. To facilitate the review of these patient profiles and the relationship of one profile to another, we recommend that you group relevant patient profiles and plot them together in one page. Below are some example layouts of the patient profiles.
    - Dose and duration, ADA, AEs, and concomitant medications
    - Dose and duration, ceramide levels, lyso sphingomyelin CRP, IL-6, and IL-8
    - Dose and duration, iron, ferritin, and platelet count
    - Dose and duration, bilirubin, alkaline phosphate, AST, and ALT
    - Spleen and liver volumes, DLCO, FVC, FEV, and TLC
    - High resolution CT and chest X-ray evaluations
- When plotting individual profiles over time for the key outcome variables (as shown in Appendix B), use different colors to indicate the data associated with each manufacturing process.

[8] https://www.fda.gov/media/131425/download
[9] https://www.fda.gov/media/74346/download

Meeting Discussion: ***No further discussion occurred.***

Question 8: Does the Division agree with the proposed analyses related to the COVID-19 pandemic that will be included in the clinical study reports for LTS13632 and DFI12712 (ASCEND), Integrated Summary of Safety, Integrated Summary of Efficacy, and Integrated Summary of Immunogenicity?

FDA Response to Question 8: The overall approach of analyzing the clinical data to evaluate the impact of COVID-19 appears reasonable. In addition to TEAEs, we recommend that you evaluate the impact of COVID-19 on treatment emergent SAEs, hypersensitivity IARs, and anaphylaxis reactions IARs.

Meeting Discussion: ***No further discussion occurred.***

Question 9: Does the Agency agree with Sanofi Genzyme's plan to submit the DFI12712 ASCEND clinical study report and dataset?

FDA Response to Question 9: Your plan to submit the DFI12712 ASCEND clinical study report and dataset appears reasonable. You should include treatment emergent SAEs, hypersensitivity IARs, and anaphylaxis reactions IARs in the comparison report summarizing the changes to the PAP data in the DFI12712 ASCEND interim CSR version 1 vs. version 2.

Your efficacy datasets should include a flag variable indicating the manufacturing processes. Provide this flag variable for efficacy datasets from trials DFI13412, DFI13803 ASCEND Peds, LTS13632, DFI12712 ASCEND and the extension study.

Meeting Discussion: ***No further discussion occurred.***

Question 10: Does the Division agree with the proposed Study Data Standardization Plan?

FDA Response to Question 10: The overall proposed Study Data Standardization Plan appears reasonable.

Your overall plan to submit the datasets and computer program codes to support the psychometric evaluation of COAs implemented in study DFI12712 (ASCEND) appears reasonable. However, we remind you that computer program (e.g., SAS, R) code used to conduct all (not just for construct validity) scoring, psychometric analyses, meaningful change analyses should be submitted.

Meeting Discussion: ***No further discussion occurred.***

Question 11: Does the Agency agree that the safety profile as summarized in section 12.1 supports Sanofi Genzyme's position that a risk evaluation and mitigation strategy

(REMS) should not be required and that labeling would be adequate to inform health care professionals and patients about the appropriate use of olipudase alfa?

FDA Response to Question 11: We have insufficient information at this time to determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks, and if it is necessary, what the required elements will be. We will determine the need for a REMS during the review of your application.

Meeting Discussion: ***No further discussion occurred.***

Question 12: Does the Agency agree that the electronic Common Technical Document (eCTD) Table of Content (TOC) is acceptable for the submission?

FDA Response to Question 12: The overall eCTD TOC appears acceptable for the BLA submission. We have the following additional comments.

- Clarify the eCTD location in which the standalone report describing the clinical comparison between olipudase alfa manufactured with Process B versus Process C (b) (4) will be submitted. We recommend that you submit the data analysis datasets that were used for analyzing and comparing the two drug products manufactured with Process B and Process C (b) (4) under this section of eCTD or provide in the study report the specific eCTD locations in which such datasets are submitted.
- If referencing Drug Master Files, include letters of authorization in section 1.4 References.
- Refer to "The Comprehensive Table of Contents Headings and Hierarchy"[10] for more specific headings that may be used for the BLA.
- We note reproductive and developmental toxicology studies are listed in eCTD module 4.2.3.5. Kindly confirm that these study reports will be submitted in the June 2021 nonclinical submission.
- Refer to Additional Comments from CMC and Microbiology.

Meeting Discussion: ***No further discussion occurred.***

Question 13: Does the Agency agree with the proposed rolling submission schedule?

FDA Response to Question 13: Your proposed rolling review submission appears reasonable. Refer to the guidance for industry *Expedited Programs for Serious Conditions – Drugs and Biologics*[11] for the formal rolling review request.

[10] https://www.fda.gov/media/76444/download
[11] https://www.fda.gov/media/86377/download

Meeting Discussion: ***No further discussion occurred.***

Question 14: Does the FDA agree with Sanofi Genzyme's proposal to use data cut off dates for the olipudase alfa ongoing trials LTS13632 and DFI12712 approximately 6 months prior to the submission date of the last wave of the rolling BLA submission?

FDA Response to Question 14: No, we do not agree. Your proposed data cutoff dates for the ongoing trials LTS13632 and DFI12712 are more than 6 months from the proposed submission date of the last wave of the rolling BLA submission (i.e., September 30, 2021). The data cutoff dates for the two trials should be as close as possible to but no sooner than 6 months (i.e., April 1, 2021) from the submission date of the last wave of the rolling BLA submission (i.e., September 30, 2021). Otherwise, provide adequate justification for your proposed cutoff dates.

In addition, clarify the data cutoff dates for the ongoing trials LTS13632 and DFI12712 in Appendix A. Under Module 5.3.3.2 of Appendix A, the data cut-off date for DFI12712 Interim CSR Version 2 is missing. The data cut-off date for LTS13632 is (b) (4) (b) (4) different from the proposed data cut-off date of March 1, 2021, as described in the current meeting package.

Meeting Discussion: ***Refer to attached Sponsor's response to FDA Preliminary Comments (Section 5.0).***

The Sponsor provided justification for the proposed data cut-off dates of March 1, 2021, for LTS13632 and March 15, 2021, for DFI12712. The FDA stated that the proposed data cut-off dates for the two studies appear reasonable.

Question 15: Does the FDA agree with Sanofi Genzyme's proposal to use the submission date of the last wave of the rolling BLA as the data cut-off date for the 120 day safety update report and to submit the 120 day safety update report to the FDA within 120 calendar days after the last wave of the rolling BLA is submitted to the FDA?

FDA Response to Question 15: That appears reasonable. However, we remind you to submit the updated efficacy and safety data analysis datasets in the 120-day safety update submission.

Meeting Discussion: ***No further discussion occurred.***

Question 16: Sanofi Genzyme requests guidance on whether the BLA may be designated for Priority Review and if the Agency plans to conduct an expedited review.

FDA Response to Question 16: The determination on the priority and expedited review designation will be made during the filing review of your application.

Meeting Discussion: ***No further discussion occurred.***

Question 17a: Does the Agency agree that olipudase alfa may qualify as a rare pediatric disease product application?

FDA Response to Question 17a: Whether an application qualifies for a Rare Pediatric Disease Priority Review Voucher is a matter of review. FDA would need to evaluate the application to determine whether the BLA is eligible for a priority review voucher. Please consult the draft guidance for industry *Rare Pediatric Disease Priority Review Vouchers,*[12] for instructions on how to submit a Rare Pediatric Disease Priority Review Voucher request and the eligibility criteria.

Meeting Discussion: ***No further discussion occurred.***

Question 17b: Does the Division have any additional feedback regarding Sanofi Genzyme's justification and the potential for the olipudase alfa BLA to receive a Priority Review Voucher?

FDA Response to Question 17b: If an applicant seeks approval in both adults and pediatric patients with the rare disease for the same indication, it will not affect voucher eligibility, as described in the guidance. However, we remind applicants seeking a voucher that – whether or not they seek approval for use in an adult population – we expect them to submit data adequate for labeling the drug for use by the affected pediatric patients.

Meeting Discussion: ***No further discussion occurred.***

Question 18: Does the FDA agree that, based upon the data shared to date that an Advisory Committee is unlikely?

FDA Response to Question 18: The determination on the Advisory Committee will be made during your application review.

Meeting Discussion: ***No further discussion occurred.***

3.0 ADDITIONAL FDA COMMENTS

Human Factors

We understand that you are planning to use olipudase alfa as enzyme replacement therapy for (b) (4) treatment of non-central nervous system (CNS) manifestations of acid sphingomyelinase deficiency (ASMD) in pediatric and adult patients. However, you have not submitted a comprehensive risk analysis. It is unclear from your submission who are the intended users or the anticipated use environment. If you intend to have

[12] http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM423325.pdf

non healthcare providers (e.g., caregivers) prepare and administer your proposed product in a home setting, we are concerned that medication errors may occur.

Thus, we recommend you conduct a comprehensive use-related risk analysis if you have not already completed one. The comprehensive use-related risk analysis should include a comprehensive and systematic evaluation of all the steps involved in using your product (e.g., based on a task analysis) the errors that users might commit or the tasks they might fail to perform and the potential negative clinical consequences of use errors and task failures.

Your risk analysis should also discuss risk-mitigation strategies you employed to reduce risks you have identified and the methods you intend to use for validating the risk-mitigation strategies. This information is needed to ensure that all potential risks involved in using your product have been considered and adequately mitigated and the residual risks are acceptable.

Based on this risk analysis, you will need to determine whether you need to submit the results of a human factors (HF) validation study conducted under simulated use conditions with representative users performing necessary tasks to demonstrate safe and effective use of the product.

If you determine that you do need to submit a HF validation study for your product, the risk analysis can be used to inform the design of a human factors validation study protocol for your product. We recommend you submit your study protocol for feedback from the Agency before commencing your study. Please note we will need 60 days to review and provide comments on the HF validation study protocol. Plan your development program timeline accordingly. Note that submission of a protocol for review is not a requirement. If you decide not to submit a protocol, this approach carries some risk to you because prospective Agency review is not possible, but this is a decision for your company.

Please refer to our draft guidance *Contents of a Complete Submission for Threshold Analyses and Human Factors Submissions to Drug and Biologic Applications* for the content of a human factors validation study protocol submission.

The requested information should be submitted to the IND. Place the requested information in eCTD Section 5.3.5.4 – Other Study reports and related information.

Guidance on human factors procedures to follow can be found in the following guidance documents:

Applying Human Factors and Usability Engineering to Medical Devices

Guidance on Safety Considerations for Product Design to Minimize Medication Errors

Note that we recently published three draft guidance documents that, while not yet finalized, might also be useful in understanding our current thinking and our approach to human factors for combination products, product design, and labeling:

Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development

Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors

Contents of a Complete Submission for Threshold Analyses and Human Factors Submissions to Drug and Biologic Applications

CMC

To facilitate the Agency's review of the drug substance (DS) and drug product (DP) manufacturing processes for olipudase alfa, in your BLA application provide the information for process parameters and in-process control, as applicable, in the following tabular format. Please provide a separate table for each unit operation. The tables should summarize information from module 3 and may be submitted either to module 1 or module 3R.

Process Parameter/ Operating Parameter/ In-Process Control	Proven Acceptable Range/ Control Limits/Targets[1] for Commercial Manufacturing Process	Criticality Classification[2]	Characterized Range/ Control Limits/Targets[1] tested in Process Development Studies	Manufactured Range/ Control Limits/ Targets[1] used for Pivotal Study Lots	Manufactured Range/ Control Limits/ Targets[1] used in Process Validation	Justification of the Proposed Commercial Acceptable Range[3]	Comment[4]

[1] As applicable
[2] For example, critical process parameter, key process parameter, non-critical process parameter, as described in module 3.
[3] This could be a brief verbal description or links to the appropriate section of the eCTD.
[4] Optional.

To facilitate the Agency's review of the control strategy for olipudase alfa, in your BLA application provide information for quality attributes and process and product related impurities for the DS and DP in the following tabular format. The tables should summarize information from module 3 and may be submitted either to module 1 or module 3R.

Quality Attributes and Process and Product Related Impurities for CI, DS and DP	Criticality Classification[1]	Impact[2]	Source[3]	Analytical Method [4]	Proposed Control Strategy[6]	Justification of the Proposed Control Strategy[6]	Comment[7]

[1] For example, critical quality attribute or non-critical quality attribute.
[2] What is the impact of the attribute, e.g. contributes to potency, immunogenicity, safety, efficacy.
[3] What is the source of the attribute or impurity, e.g. intrinsic to the molecule, fermentation, protein A column.
[4] List all the methods used to test an attribute in-process, at release, and on stability. For example, if two methods are used to test identity then list both methods for that attribute.
[5] List all the ways the attribute is controlled, for example, in-process testing, validated removal, release testing, stability testing.
[6] This could be a brief verbal description or links to the appropriate section of the eCTD.
[7] Optional.

Microbiology:

The FDA is providing additional product quality microbiology comments for you to consider during development of your commercial manufacturing process and preparation of your 351(a) BLA submission.

All facilities should be registered with the FDA at the time of the 351(a) BLA submission and ready for inspection in accordance with 21 CFR 600.21 and 601.20(b)(2). Include in the BLA submission a complete list of the manufacturing and testing sites with their corresponding FEI numbers. A preliminary manufacturing schedule for the drug substance and drug product should be provided in the BLA submission to facilitate the planning of pre-license inspections during the review cycle. Manufacturing facilities should be in operation and manufacturing the product under review during the inspection.

Information and data for CMC product quality microbiology should be submitted in the specified sections indicated below.

The CMC Drug Substance section of the 351(a) BLA (Section 3.2.S) should contain information and data summaries for microbial and endotoxin control of the drug substance. The information should include, but not be limited to the following:

- Bioburden and endotoxin levels at critical manufacturing steps should be monitored using qualified bioburden and endotoxin tests. Bioburden sampling

should occur prior to any 0.2 µm filtration step. The pre-established bioburden and endotoxin limits should be provided (3.2.S.2.4).

- Bioburden and endotoxin data obtained during manufacture of three process qualification (PPQ) lots (3.2.S.2.5).
- Microbial data from three successful product intermediate hold time validation runs at manufacturing scale. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided (3.2.S.2.5).
- Chromatography resin and UF/DF membrane lifetime study protocols and acceptance criteria for bioburden and endotoxin samples. During the lifetime studies, bioburden and endotoxin samples should be taken at the end of storage prior to sanitization (3.2.S.2.5).
- Information and summary results from the shipping validation studies (3.2.S.2.5).
- Drug substance bioburden and endotoxin release specifications (3.2.S.4).
- Summary reports and results from bioburden and endotoxin test method qualification studies performed for in-process intermediates and the drug substance. If compendial test methods are used, brief descriptions of the methods should be provided in addition to the compendial reference numbers (3.2.S.4).

The CMC Drug Product section of the 351(a) BLA (Section 3.2.P) should contain validation data summaries to support the aseptic processing operations. For guidance on the type of data and information that should be submitted, refer to the FDA guidance for industry *Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products.*[13]

The following information should be provided in Sections 3.2.P.3.3 and/or 3.2.P.3.4, as appropriate.

- Identification of the manufacturing areas and type of fill line (e.g. open, RABS, isolator), including area classifications.

[13] http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072171.pdf

- Description of the sterilizing filter (supplier, size, membrane material, membrane surface area, etc.); sterilizing filtration parameters (pressure and/or flow rate), as validated by the microbial retention study; wetting agent used for post-use integrity testing of the sterilizing filter and post-use integrity test acceptance criteria.
- Parameters for filling and capping for the vials.
- A list of all equipment and components that contact the sterile drug product (i.e. the sterile-fluid pathway) with the corresponding method(s) of sterilization and depyrogenation, including process parameters. The list should include single-use equipment.
- Processing and hold time limits, including the time limit for sterilizing filtration and aseptic filling.
- Sampling points and in-process limits for bioburden and endotoxin. Bioburden samples should be taken at the end of the hold time prior to the subsequent filtration step. Pre-sterile filtration bioburden limits should not exceed 10 CFU/100 mL.

The following study protocols and validation data summaries should be included in Section 3.2.P.3.5, as appropriate:

- Bacterial filter retention study for the sterilizing filter. Include a comparison of validation test parameters with routine sterile filtration parameters.
- Sterilization and depyrogenation of equipment and components that contact the sterile drug product. Provide summary data for the three validation studies and describe the equipment and component revalidation program.
- In-process microbial controls and hold times. Three successful product intermediate hold time validation runs should be performed at manufacturing scale, unless an alternative approach can be scientifically justified. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided.
- Isolator decontamination summary data and information, if applicable.
- Three successful consecutive media fill runs, including summary environmental monitoring data obtained during the runs. Describe the environmental and personnel monitoring procedures followed during media fills and compare them to the procedures followed during routine production.

- Information and summary results from shipping validation studies.
- Validation of capping parameters, using a container closure integrity test.
- Lyophilizer sterilization validation summary data and information.

The following product testing and method validation information should be provided in the appropriate sections of Module 3.2.P:

- Container closure integrity testing. System integrity should be demonstrated initially and during stability. Container closure integrity method validation should demonstrate that the assay is sensitive enough to detect breaches that could allow microbial ingress (≤ 20 microns). Container closure integrity testing should be performed *in lieu* of sterility testing for stability samples every 12 months (annually) until expiry.
- Summary report and results for qualification of the bioburden, sterility, and endotoxin test methods performed for in-process intermediates (if applicable) and the finished drug product, as appropriate. If compendial test methods are used, brief descriptions of the methods should be provided in addition to the compendial reference numbers. Provide full descriptions and validation of non-compendial rapid microbial methods.
- Summary report and results of the Rabbit Pyrogen Test conducted on three batches of drug product in accordance with 21 CFR610.13(b).
- Low endotoxin recovery studies. Certain product formulations have been reported to mask the detectability of endotoxin in the USP <85> *Bacterial Endotoxin Test* (BET). The effect of hold time on endotoxin detection should be assessed by spiking a known amount of standard endotoxin (RSE or purified CSE) into undiluted drug product and then testing for recoverable endotoxin over time.
- Microbiological studies in support of the post-reconstitution and post-dilution storage conditions. Describe the test methods and results that employ a minimum countable inoculum (10-100 CFU) to simulate potential microbial contamination that may occur during dilution. The test should be run at the label's recommended storage conditions, be conducted for twice the recommended storage period, bracket the drug product concentrations that would be administered to patients, and use the label-recommended reconstitution solutions and diluents. Periodic intermediate sample times are recommended. Challenge organisms may include strains described in USP <51> *Antimicrobial Effectiveness Testing*, plus typical skin flora or species associated with hospital-

borne infections. *In lieu* of this data, the product labeling should recommend that the post-reconstitution and post-dilution storage period is not more than 4 hours.

***Meeting Discussion:* No further discussion occurred.**

4.0 OTHER IMPORTANT INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[14] and Pregnancy and Lactation Labeling Final Rule[15] websites, which

[14] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[15] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.

- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.

- Regulations and related guidance documents.

- A sample tool illustrating the format for Highlights and Contents, and

- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be

pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.

- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).

- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).

- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission "**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**" in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and

DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
(1)				
(2)				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
(1)				
(2)				

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[16] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[17]. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions,* and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications,* be provided to facilitate

[16] https://www.fda.gov/media/84223/download
[17] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and

development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[18]

NONPROPRIETARY NAME

On January 13, 2017, FDA issued a final guidance for industry *Nonproprietary Naming of Biological Products*, stating that, for certain biological products, the Agency intends to designate a proper name that includes a four-letter distinguishing suffix that is devoid of meaning.

Please note that certain provisions of this guidance describe a collection of information and are under review by the Office of Management and Budget under the Paperwork Reduction Act of 1995 (PRA). These provisions of the guidance describe the submission of proposed suffixes to the FDA, and a sponsor's related analysis of proposed suffixes, which are considered a "collection of information" under the PRA. FDA is not currently implementing provisions of the guidance that describe this collection of information.

However, provisions of the final guidance that do not describe the collection of information should be considered final and represent FDA's current thinking on the nonproprietary naming of biological products. These include, generally, the description of the naming convention (including its format for originator, related, and biosimilar biological products) and the considerations that support the convention.

To the extent that your proposed 351(a) BLA is within the scope of this guidance, FDA will assign a four-letter suffix for inclusion in the proper name designated in the license at such time as FDA approves the BLA.

5.0 ATTACHMENTS AND HANDOUTS

On March 22, 2021, Genzyme sent via email a response to the FDA preliminary comments as read-ahead materials for the teleconference.

[18] https://www.fda.gov/media/85061/download

22 Pages have been Withheld in Full as B4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JENNY N DOAN
03/26/2021 04:09:17 PM
Signed on behalf of Dr. Donohue.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 112952

MEETING MINUTES

River Vision Development Corporation
Attention: Liz Lucini, Pharm.D.
U.S. Regulatory Agent
One Rockefeller Plaza
Suite 1204
New York, NY 10020

Dear Dr. Lucini:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for RV001 (teprotumumab for injection).

We also refer to the meeting between representatives of your firm and the FDA on August 19, 2016. The purpose of the meeting was to discuss with the Agency the data generated in Study TED01RV and potential for this study to support a BLA filing.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Lois Almoza, M.S., Regulatory Health Project Manager at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, MD
Deputy Division Director
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: End of Phase 2

Meeting Date and Time: August 19, 2016 from 9:30AM – 10:30AM (EST)
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1309
Silver Spring, Maryland 20903

Application Number: 112952
Product Name: RV001 (teprotumumab for injection)
Indication: treatment of moderate to severe thyroid eye disease (TED)
Sponsor/Applicant Name: River Vision Development Corporation

Meeting Chair: Wiley A. Chambers, MD
Meeting Recorder: Lois Almoza, MS

FDA ATTENDEES

Renata Albrecht, MD	Director, Division of Transplant and Ophthalmology Products (DTOP)
Wiley A. Chambers, MD	Deputy Division Director, DTOP
William Boyd, M.	Clinical Team Leader, DTOP
Sonal Wadhwa, MD	Clinical Reviewer, DTOP
Martin Nevitt, MD	Clinical Reviewer, DTOP
Sunita Shukla, MPH, PhD	Associate Director for Regulatory Science, Office of Antimicrobial Products (OAP)
Philip Colangelo, PharmD, PhD	Clinical Pharmacology Team Leader, Office of Clinical Pharmacology (OCP)/Division of Clinical Pharmacology IV (DCPIV)
Abhay Joshi, PhD	Clinical Pharmacology Reviewer, OCP/DCPIV
Lori Kotch, PhD	Pharmacology/Toxicology Team Leader, DTOP
Maria Rivera, PhD	Pharmacology/Toxicology Reviewer, DTOP
Jee Chung, PhD	Product Quality Team Leader, Office of Biotechnology Products (OBP)/Division of Biotechnology Review and Research I (DBRRI)
Subramanian Muthukkumar, PhD	Product Quality Reviewer, OBP/DBRRI
Yan Wang, PhD	Statistical Team Leader, Office of Biometrics (OB)/ Division of Biometrics IV (DBIV)

Yunfan Deng, PhD	Statistical Reviewer, OB/DBIV
Lois Almoza, MS	Regulatory Health Project Manager, DTOP

SPONSOR ATTENDEES

Kathleen Gabriel, RN, MFT	Director, Clinical Operations
Guido Magni, MD, PhD	Chief Medical Officer
David Madden, MBA	Chief Executive Officer
Richard Woodward, PhD	Chief Scientific Officer
(b) (4)	Regulatory Consultant
	CMC Consultant
Liz Lucini, PharmD	Regulatory Consultant
(b) (4)	CMC consultant
Anne Rentz	Clinical consultant
Bent Hygum	VP Quality, CMC Biologics

BACKGROUND

A June 22, 2016, submission, from River Vision Development Corporation (River) requested a meeting for IND 112952 to discuss with the Agency the data generated in Study TED01RV and potential for this study to support a BLA filing for treatment of moderate to severe thyroid eye disease (TED).

A Meeting Request Granted letter issued on, July 5, 2016. The July 15, 2016, Meeting Package was received on July 15, 2016. Meeting Preliminary Comments were sent to River via e-mail on August 16, 2016.

River forwarded talking points and a graphic via e-mail on August 18, 2016. The talking points have been incorporated throughout the meeting minutes in bold italic font and the graphic is attached(see attachment 1) A question pertaining to the meeting was e-mailed from River on August 24, 2016, and the Division responded via e-mail on August 25, 2016(see attachment 2).

DISCUSSION

Following, in **bold font**, are the questions in the July 15, 2016, Meeting Package. The FDA responses to these questions are in *italic* font. Talking points from the Sponsor sent via e-mail on, August 18, 2016, are in ***bold, italic*** font. Discussions that took place during the August 19, 2016, teleconference are in regular font.

Clinical Questions:

1. **Does the Agency agree with the Sponsor's efficacy conclusions from study TED01RV; specifically,**
    a. **Does the Agency agree that the statistically significant results for the primary outcome measure of reduction ≥ 2 in the clinical activity score (CAS) and reduction ≥ 2 mm in proptosis in the study eye, without a similar degree of**

deterioration in CAS or proptosis in the non-study eye demonstrate the efficacy of teprotumumab in the treatment of moderate to severe active TED?

FDA Response: The results appear favorable; however, decisions regarding acceptability of the efficacy results for approval can only be made once the complete BLA package is reviewed.

Sponsor Comments: To address the points raised in the responses to questions 1 and 2, we will submit the CSR for Study TED01RV as soon as it is ready, which we currently anticipate to be in about 2 months as we are still waiting for the PK data. Would the Division find it helpful to receive datasets as well?

Meeting Discussion: Yes. The Division would find it helpful to receive datasets as well.

b. Does the Agency agree that the statistically significant results for the secondary endpoints of Graves' Ophthalmopathy quality of life scale (GO-QOL), proptosis, and CAS provide further evidence of the efficacy of teprotumumab in the treatment of moderate to severe active TED?

FDA Response: While the results appear favorable, we would need to see the data supporting the validation of the GO-QOL before commenting on its interpretation. See also response to Question #1.

Sponsor Comments: We would like to clarify this point further. Our plan would be to provide information on the psychometric properties of the GO-QOL to show that the reliability and validity information is sufficient. Would this approach be acceptable to the Division? Can you please also confirm that the intent is to validate vs. qualify this instrument, as we recognize the terms mean different things and we'd like clarification on the guidance to follow.

As GO-QOL is a secondary endpoint, is validation of the endpoint a requirement for labeling or for another purpose?

Meeting Discussion:

The Sponsor asked for confirmation that the intent is to validate versus qualify this instrument, as they recognize the terms mean different things. They plan to provide information from the published literature on the psychometric properties of the GO-QOL to show that its reliability and validity are sufficient.

The Division recommended that the Patient-Reported Outcomes(PRO) Guidance be followed and the Sponsor noted that if their intent is to include results of the GO-QOL in the USPI, they would validate the GO-QOL in accordance with the 2009 Guidance document "Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims" and submit a PRO dossier for this scale. The Division noted that without validation, single questions are more likely to be accepted for the USPI than results from a multiple component endpoint.

2. **Based on the safety data from Study TED01RV, the Sponsor has identified hyperglycemia as an AE of Special Interest.**

    a. **Does FDA have any comments on the proposed risk mitigation for this event?**

FDA Response: No, not at this time; we may have additional comments once we see a final CSR (Clinical study report).

Meeting Discussion: None

    b. **Does FDA have any other comments regarding the safety profile of teprotumumab observed in Study TED01RV?**

FDA Response: No, not at this time; we may have additional comments once we see a final CSR (Clinical study report).

Meeting Discussion: None

3. **Does the Agency agree with the proposed safety database for teprotumumab, including utilizing the solid tumor safety data from the oncology program as supportive safety information?**

FDA Response: Potentially, provided the safety database for teprotumumab utilized the same product dosing or greater product dosing than that proposed for TED.

Sponsor Comment: The dosing in the oncology indication was similar or greater than the dosing proposed for TED. Most of the patients in the oncology studies received 9 mg/kg/week.

Meeting Discussion: None

4. **Does the Agency agree that the statistically significant and clinically meaningful results from study TED01RV and the safety profile of teprotumumab support proceeding with a BLA filing for teprotumumab for the unmet medical need of moderate to severe active TED?**

FDA Response: No. The Agency expects at least two adequate and well-controlled trials to support the safety and efficacy of a product. In addition, at least one of these trials should have used the-to-be marketed final formulation.

Sponsor Comments: We would like to clarify this point further.

Meeting Discussion:

The Agency advised that while the Sponsor could file a BLA based on the single trial, this approach is not recommended as it would be unlikely to support an approval. The Agency clarified that the intent of a second study would be to both provide corroborative evidence of efficacy as well as provide clinical exposure with the proposed commercial product. The Agency

agreed that a new trial could begin with the currently available [redacted] (b) (4) product and switch to use of the new process [redacted] (b) (4) product when available.

The Sponsor noted several challenges it would anticipate in conducting an additional placebo-controlled trial, including the reluctance of investigators to participate given the efficacy seen in the TED01RV trial and the likelihood that placebo subjects would be withdrawn early from the study for lack of efficacy. The Sponsor stated that a potential new trial would likely not be the same as the TED01RV trial in either design or size. The Agency acknowledged that a second trial may differ in design (number of subjects, duration, etc.) and expressed willingness to review and discuss the acceptability of any proposed new study.

The Agency suggested that the Sponsor consider submitting the new protocol under a Special Protocol Assessment (SPA); however, the Sponsor stated that they did not feel this would be necessary.

Additional Comments:
In any future TED trials, randomization should include stratification for baseline factors which can significantly impact the outcome (ie. level of TED at onset of trial).

Meeting Discussion: None

Clinical Pharmacology Question

5. **Does the Agency agree that the clinical pharmacology data generated to date with teprotumumab are adequate to support registration for the treatment of moderate to severe active TED, with respect to the following elements?**
    a. **ADME profile**
    b. **Drug-drug interaction potential**
    c. **TQT potential**
    d. **Renal and hepatic impairment**

FDA Response: Yes, we agree for item d. However, with regard to items a, b and c, only brief summaries are provided without the teprotumumab pharmacokinetic data in TED patients. Once the complete study report for Study TED01RV is submitted, adequacy of the Clinical Pharmacology data will be reassessed.

Sponsor Comment: We have no points for further discussion on this question.

We will also look into conducting the PK and PK/PD analyses noted in additional points 2 and 3 but note we do have limited PK data.

Meeting Discussion: None

Nonclinical Questions

6. **Does the Agency agree that further fertility studies are not necessary for teprotumumab?**

FDA Response: We agree that fertility studies might not be warranted. However, based on mechanism of action and literature information, an effect on fertility cannot be excluded. The BLA should include an integrated summary and a copy of all published literature used to support a role of IGF/IGF-1R in fertility and any adverse effects related to IGF/IGF-1R inhibition, and a formal waiver should be submitted, as noted under Question 7.

Sponsor Comment: We have no points for further discussion on the nonclinical questions and will plan to submit waivers for fertility and carcinogenicity studies to the IND.

Meeting Discussion: None

7. **Does the Agency agree that the overall nonclinical program conducted to date with teprotumumab is sufficient to support registration for the treatment of moderate to severe active TED?**

FDA Response: The overall nonclinical program conducted to date appears adequate to support registration, with the following recommendations:

a. *Please submit formal waiver requests to the Division to omit fertility and peri-postnatal studies. They should include your rationale, a summary of all safety data to support your rationale, and a copy of all literature referenced in the summaries.*
b. *If you believe that carcinogenicity studies are not needed, you should also submit a formal waiver to the Division for review providing your rationale to omit the studies.*

A final decision as to the adequacy of the data to support registration will be determined upon review of the waiver requests and the BLA.

In addition, based on the manufacturing changes, additional nonclinical studies may be required if biological comparability is not demonstrated for the drug substance and/or the drug product.

Meeting Discussion: None

Pediatrics Question

8. **Does the Agency agree with River Vision's rationale that a waiver of pediatric requirements would apply for teprotumumab?**

FDA Response: If teprotumumab has been granted orphan designation for the treatment of active TED, PREA would not apply to this orphan-designated indication.

Sponsor Comment: We have no points for further discussion on this question.

Meeting Discussion: None

CMC Questions

Given the breakthrough status recently granted to teprotumumab, we strongly encourage you to request a CMC only meeting to discuss product development, including product characterization, process development, analytical methods development, and stability studies. The current meeting package is incomplete and contains substantial errors, e.g., mislabeled, incomplete, and inaccurate figures and tables, an unclear description of the bioassay bridging strategy, etc. (see specific responses to your questions below). To enable effective meetings with meaningful discussions and efficient receipt of substantially informative advice, please ensure that subsequent meeting packages contain complete and accurate information (with appropriate data) to describe and support the questions posed.

Sponsor Comments: Considering the recently granted breakthrough status, the Sponsor does intend to request a CMC meeting to discuss and achieve concurrence in aspects of product development, including product characterization, process development, analytical methods development, and stability studies related to the program. What additional briefing materials would be needed by the Agency in order to make this meeting as productive as possible?

The Sponsor acknowledges and apologizes for the incomplete nature of the current meeting package.

Meeting Discussion: See Meeting Discussion for Question 9.

9. The manufacturing of teprotumumab is being changed (site transfer and process adaptions) for both the drug substance and drug product. Does the Agency agree that the proposed program to demonstrate biological comparability is adequate and sufficient to support a BLA filing?

FDA Response: No; insufficient information was provided to support the proposed comparability program. A number of potential issues with the proposed program have been identified.

While it is appropriate to implement many of the previous FDA CMC recommendations for the current comparability program, the expectations regarding comparability change over the course of product development; protocols and data determined to be acceptable during early stages of product development are often not sufficient to support comparability during or after completion of pivotal clinical studies. Ultimately, the determination of comparability will be a BLA review issue.

Meeting Discussion:

The Sponsor provided an overview of the planned CMC activities and intent to meet with FDA in the future to discuss the comparability protocol. The Agency recommended having a meeting

to review the comparability protocol, lots to be compared, and the bridging strategy for the bioassay. The Agency recommended requesting the meeting before the comparability data are available after the Sponsor stated their comparability data would not be available until the beginning of 2017.

The Agency noted the importance of using testing results from material used in the clinic when setting acceptance criteria. Sponsor clarified the plan to generate acceptance criteria by using the (b) (4) material, both of which were used in the TED01RV trial. The Agency requested that the future meeting briefing packages include information on which lots were used in the TED01RV trial.

The Sponsor stated its intent to make a future side-by-side comparison using the (b) (4) material for comparison to the new material. The Sponsor noted that to start a new study using the new material, use of 2 (b) (4) produced lots to establish comparability rather than 3 would be preferable from a timing perspective.

Sponsor Comments: The Sponsor acknowledges the Agency's comments and intends to seek concurrence on the comparability protocol for the drug substance and drug product manufactured (b) (4) respectively.

Regarding the proposed comparability study, we have the following comments:

a. *The changes to both the drug substance (DS) (b) (4) and the drug product (DP) manufacturing process are significant. It is not clear why only one lot of DS manufactured (b) (4) at the new site (b) (4) (b) (4) will be compared to the current DS lots, rather than performing testing side-by-side all three DS lots manufactured (b) (4). In order to evaluate and understand any potential differences in DS quality, more than a single lot should be used in the comparability study.*

Sponsor Comment: The Sponsor intends to demonstrate comparability of the drug substance manufactured (b) (4) using multiple lots derived from the new manufacturing process.

b. *The comparability study states that only DS lots will be used to conduct stressed stability studies for comparison of the rate and pathways of degradation of the materials. Because changes are also proposed for the DP manufacturing process, the comparability study should also include stressed stability studies for the DP batches from previous and current manufacturing process if the (b) (4) DP stability data are intended to provide any support for the (b) (4) process and expiry period.*

Sponsor Comment: The Sponsor intends to perform stressed stability studies under accelerated conditions to compare the rates and degradation pathways associated with the drug product manufactured (b) (4).

c. *You indicated on page 9 of Appendix 1 that the old bioassay is not reliable and that side-by-side testing using this assay will not be performed. To identify potential product*

differences due to the manufacturing changes, samples should be tested in a side-by-side manner to minimize variability due to issues with the old bioassay. In addition, there is insufficient support for not performing side-by-side testing using the new bioassay. The use of combined historical and current data can lead to the inability to interpret the data, for example, if different early development reference standards are used or if there are instabilities in the reference standard(s).

Sponsor Comments: The current (old) bioassay is currently performed by (b) (4) on behalf of the Sponsor. (b) (4) has reported that the current assay repeatedly fails to meet the system suitability criteria associated with the test method resulting in repeated assay failures. The Sponsor, together with (b) (4), has developed a new bioassay based on an AlphaLISA assay format. This assay is currently being validated at (b) (4) (b) (4) and is intended to be used for the release of drug substance and products. The bioassay test method, validation protocol, and validation report will be submitted to the Agency for review in the BLA.

See also response to Question 11.

d. *Acceptance criteria should not be based on Roche data and small-scale studies. The key comparisons should be to the pivotal clinical study material (b) (4) (b) (4). The product quality attributes of the manufacturing-scale materials should be characterized and an evaluation of critical quality attributes should be used to inform the comparability acceptance criteria.*

Sponsor Comments: The Sponsor acknowledges the Agency's guidance. Acceptance criteria established to date have been based on the Roche (b) (4) material, two lots of which were used in the TEDRV01 study. The data from the (b) (4) process will be incorporated together with the Roche (b) (4) data to establish acceptance criteria. For clarity, no small-scale data was used in the development of the criteria presented in the briefing document. Considering that there were only two batches of the (b) (4) material produced, it would be difficult to create acceptance criteria on the basis of only those two batches.

e. *Where new methods are being implemented to replace the current methods due to issues with the current methods, the new methods should be an integral part of the comparability study, with acceptance criteria more informative than "report results."*

Sponsor Comment: The Sponsor acknowledges the Agency's guidance and will incorporate any new methods into the comparability protocol and implement numerical limits as part of the acceptance criteria associated with these methods.

f. *"Report results" is generally not an acceptable acceptance criterion for a comparability study. Similarly, for methods such as oligosaccharide mapping, "chromatogram comparable to reference," is not a sufficient acceptance criterion. Although teprotumumab glycosylation might not significantly impact in vitro potency, the*

oligosaccharide profile can impact PK and immunogenicity and should be assessed with appropriate consideration of these potential impacts.

Sponsor Comments: The Sponsor acknowledges the Agency's guidance. Where applicable, numerical limits will be applied to test methods.

g. *Small-scale model data will not support comparability evaluations. Small-scale models of DS* (b) (4) *manufacturing are typically not fully representative of the manufacturing-scale process and product.*

Sponsor Comments: The Sponsor provided small-scale data in the briefing document solely for information purposes and as an indication of what might be expected in evaluating comparability between the drug substance derived from the (b) (4) ***processes once completed. The Sponsor intends to establish comparability using multiple lots manufactured at scale using the*** (b) (4) ***process***.

h. *The data presented in figures 8-15 are not clear. In future submissions, text should not cover the data, full-scale and enlarged images should be provided, and overlays of chromatograms, electropherograms, peptide maps, etc. should be provided where appropriate.*

Sponsor Comments: The Sponsor acknowledges the Agency's request and apologizes for the technical issues in reproducing chromatograms and will provide full-scale and enlarged images, overlays of chromatograms, electropherograms, peptide maps, etc. in future submissions.

Meeting Discussion: None

10. Does the Agency agree to the control strategy proposed for both drug substance and drug product?

FDA Response: No. We do not agree. The proposed control strategy for the DS and DP shown in Appendix 2 appears to include only one aspect of product control strategy, (b) (4) (b) (4) *. The control strategy for your DS and DP should include consideration and understanding of* (b) (4) (b) (4) *how these factors contribute to the overall product quality.*

Sponsor Comment: The Sponsor acknowledges the Agency's guidance and will provide a description of the entire control strategy for the drug substance and product at future meetings.

Regarding the testing aspect of your control strategy, limited specific advice can be provided at this time because the commercial specifications tables, Table 14 and Table 15, appear to be mislabeled; they are incomplete and inconsistent with the Appendix. In addition, the

specifications need to be evaluated in the context of the complete historical clinical lot data and product characterization data and information. The BLA should include justifications and supporting data for not including testing of excluded product quality attributes as part of lot release and stability specifications. It is not clear that the proposed potency assay is fully representative of the teprotumumab mechanism of action; detailed information and data to demonstrate that the surrogate endpoint is appropriate to use to control potency should be included in the BLA. Container closure integrity testing should be performed in lieu of sterility testing for DP stability.

Sponsor Comments: The Sponsor apologizes for mislabeling of the referenced tables. The Sponsor acknowledges the Agency's guidance regarding the justification of quality attributes with respect to lot release and stability specifications in light of historical data. In addition, a justification of the potency assay will be provided. Container closure integrity will be employed in lieu of sterility testing.

Meeting Discussion: None

11. Does the Agency agree with the Bioassay bridging strategy?

FDA Response: No. It appears that the only information included is the "sponsor rationale," and based only on this comment, the strategy for bridging the bioassays is not clear. Although the samples to be used in the new assay are not clear, it appears that it would not be acceptable to only compare historical values derived from the existing assay to results generated by the new assay. The most appropriate bridging strategy is a direct side-by-side comparison of existing (b) (4) *samples,* (b) (4) (b) (4) *, and all available proposed commercial product material, using both current and new methods. The strategy used should be able to attribute any differences observed in the results to differences between the methods and not to differences in product quality. With respect to the use of any historical data, the reference standard(s) used and the stability of these materials should be considered.*

Sponsor Comments: See response provided to Question 9c. The Sponsor intends to compare the results of the current bioassay with the new bioassay. Unfortunately, given issues currently experienced with the assay, this may not be possible due to the failed system suitability criteria. The Sponsor will provide all data produced in this comparison to the Agency for its review.

Meeting Discussion:

The Sponsor explained the issues that have been experienced in using the old bioassay, leading to assay failures and therefore a new assay has been developed. The Agency expressed that they would like to see the old assay and the new assay tested side-by-side with the same samples. The Sponsor noted that it may no longer be possible to get valid results from the old assay. The Agency recommended providing the details of their issues with the old bioassay with data to support alternative approaches in a future meeting package. Sponsor clarified that they will use (b) (4) samples from (b) (4) lots to establish comparability and for bridging the new bioassay with the

current bioassay. The Agency also stated that if only the new bioassay is used to test retain samples, then the stability of the old (b) (4) samples should be addressed in the bridging study proposal.

12. Does the Agency agree that the proposed strategy to qualify commercially available assay reagents for HCP quantitation is acceptable and the generation of (b) (4) specific reagents is not necessary?

FDA Response: It is unclear from the rationale provided in the meeting package how the commercial kit coverage of HCPs will be demonstrated. However, if sufficient coverage is demonstrated using the commercially available reagents, then (b) (4) specific reagents will not be necessary. (b) (4) (b) (4) (b) (4) *. These data should be used to determine the approximate percent of potential HCP impurities that are recognized by the HCP antiserum.* (b) (4) (b) (4)

Sponsor Comments: The Sponsor intends to seek concurrence with the Agency on the HCP assay reagent qualification protocol prior to its execution. If sufficient coverage is achieved using the commercial kit, then the assay will be used as part of the control strategy for the commercial drug substance manufactured by (b) (4) for the Sponsor.

Meeting Discussion: None

13. Does the Agency agree with the proposed outline for the process validation strategy for both drug substance and drug product?

FDA Response: An outline of the proposed process validation strategy was not provided.

The proposal to base the process validation approach on the FDA and ICH guidance documents sited as background to this question is appropriate. However, the adequacy of your process validation studies will depend on the data generated and will be a BLA review issue.

Sponsor Comments: The Sponsor apologizes for this error in the briefing document. The Sponsor intends to provide the Agency with validation protocols and a more detailed planning of the process validation strategy for concurrence at future meetings.

Meeting Discussion: None

Additional Comments:
We are providing additional product quality microbiology comments for you to consider for the preparation of your BLA 351(a) submission.

All facilities should be registered with FDA at the time of the BLA submission and ready for inspection in accordance with 21 CFR 600.21 and 601.20(b)(2). The facility should be in operation and manufacturing the product during the inspection. A preliminary manufacturing schedule for both the drug substance and drug product should be provided in the Module 1 of the BLA to facilitate the planning of the pre-license inspections during the review cycle. Please include in the BLA submission a complete list of the manufacturing and testing sites with their corresponding FEI numbers.

The CMC Drug Substance section of the BLA (Section 3.2.S) should contain information and data summaries for microbial and endotoxin control. The provided information should include, but not be limited to the following:

a. *Bioburden and endotoxin levels at critical manufacturing steps should be monitored using qualified bioburden and endotoxin tests. The pre-established bioburden and endotoxin limits should be provided (3.2.S.2.4).*
b. *Three successful consecutive product* (b) (4) *validation runs at manufacturing scale. Bioburden and endotoxin levels* (b) (4) (b) (4) *should be monitored and bioburden and endotoxin limits provided (3.2.S.2.5).*
c. *Provide* (b) (4) *study protocols and acceptance criteria. During the* (b) (4) *studies, bioburden and endotoxin samples should be taken* (b) (4) *(3.2.S.2.5).*
d. *Bioburden and endotoxin data obtained during manufacture of at least three performance qualification lots (3.2.S.2.5).*
e. *Information and summary results from the shipping validation studies (3.2.S.2.5).*
f. *Drug substance bioburden and endotoxin release specifications (3.2.S.4).*
g. *Summary report and results from bioburden and endotoxin test methods qualification performed for* (b) (4) *the drug substance. If compendial test methods are used, brief descriptions of the methods should be provided in addition to the compendial reference numbers (3.2.S.4).*
h. *Certain formulations have been reported to interfere with endotoxin recoverability in the USP LAL test methods over time. The effect* (b) (4) *on endotoxin recovery should be assessed* (b) (4) (b) (4) *(3.2.S.4).*

The CMC Drug Product section of the BLA (Section 3.2.P) should contain validation data summaries to support (b) (4)*. For guidance on the type of data and information that should be submitted, refer to the 1994 "FDA Guidance for Industry, Submission Documentation* (b) (4) (b) (4)

The following information should be provided in sections 3.2.P.3.3 and/or 3.2.P.3.4, as appropriate.

(b) (4)

The following study protocols and validation data summaries should be included in Section 3.2.P.3.5:

a.

b. (b) (4)

c. (b) (4) *Three successful product* (b) (4) (b) (4) *validation runs should be performed at manufacturing scale. Bioburden and endotoxin levels* (b) (4) *should be monitored and bioburden and endotoxin limits provided.*

d. (b) (4)

e.

f. (b) (4) *validation demonstrating maintenance of container closure integrity.*

The following product testing and method validation information should be provided in the appropriate sections of Module 3.2.P:

a. Container closure integrity testing. System integrity (b) (4) (b) (4) *should be demonstrated initially and during stability. Container*

closure integrity method validation should demonstrate that the assay is sensitive enough to detect breaches that could allow microbial ingress (≤ (b) (4) microns). Container closure integrity testing should be performed (b) (4) for stability samples (b) (4) (b) (4).

b. *Summary report and results for qualification of the bioburden, sterility and endotoxin test methods performed for (b) (4) the drug product, as appropriate. If compendial test methods are used, brief descriptions of the methods should be provided in addition to the compendial reference numbers.*
c. *Summary report and results of the Rabbit Pyrogen Test conducted on three batches of drug product in accordance with 21 CFR 610.13(b).*
d. *Certain formulations have been reported to interfere with endotoxin recoverability in the USP LAL test methods over time. The effect (b) (4) on endotoxin recovery should be assessed (b) (4)*

(b) (4)

Sponsor Comment: The Sponsor acknowledges the Agency's guidance in these additional comments and in each case will provide the relevant data and reports to the BLA.

Meeting Discussion: None

14. The first batches of the 500 mg/vial drug product strength manufactured (b) (4) (b) (4) are expected to be available in Q1/2017. These will be put on stability according to ICH Q1A(R2). Data evaluation/extrapolation in line with ICH Q1E is planned to be used to determine an initial shelf life for the marketed drug. As additional data will become available, shelf life of the drug is planned to be extended upon submission of these data. Does the Agency agree with this approach for defining an initial shelf life for teprotumumab?

FDA Response: No. The shelf-life for the DP should be based on real time stability data from DP batches manufactured using a process that is fully representative of the intended commercial

process, (b) (4) (b) (4) (b) (4). The DS and DP stability programs should include stress stability studies performed under appropriate conditions to assist in elucidating the potential degradation pathways and identifying stability-indicating test methods. Please refer to ICH Q5C "Stability Testing of Biotechnological/Biological Products" for additional guidance.

Sponsor Comment: The Sponsor acknowledges to Agency's guidance regarding the definition of a shelf-life for the drug product and the need for the stability programs to include stress conditions.

It is not clear why DS manufactured using the (b) (4) process was not placed into a stability program. The stability data derived from the Roche product will not provide support for the commercial expiry. In addition, the (b) (4) DP data will provide limited support for the (b) (4) (b) (4) DP expiry period.

The expiry period can be (b) (4) (b) (4)

Sponsor Comments: The drug substance manufactured by (b) (4) was not placed on a formal stability program, since at the time of manufacture, the Sponsor planned to convert the entire batch to the drug product to provide sufficient clinical trial material for the TED study.

The Sponsor acknowledges the Agency's guidance with respect to the value of the (b) (4) drug product stability data in support of the definition of a commercial expiration date.

Meeting Discussion: None

Additional Comments:

1. *We note that the dosing rationale is based on the results that >90% IGF receptor occupancy is expected at 20 µg/mL, which was estimated with the SP2/0 material. If available, please provide the information on the IGF receptor occupancy comparison between SP2/0 and CHO material.*

Sponsor Comment: We will provide a response in the future to address this point.

2. *We note that PK analysis is pending for Study TED01RV and you had also planned for biomarker assessment(s). Upon completion of the planned analyses, we recommend that you attempt to develop an integrated population PK model utilizing the PK data from all studies (including oncology studies). We also recommend that you attempt to characterize the effects of major covariates (e.g., disease presence, weight, immunogenicity), relevant intrinsic and extrinsic factors (e.g., concomitant drugs, hepatic and/or renal impairment) on the PK of teprotumumab.*

3. *In addition, upon completion of the planned analysis in Comment 2 above, we also recommend that you characterize the exposure response relationships (e.g., dose-response, concentration-response) for safety. You may also consider including the safety data from other indications (e.g., oncology; DME) in determining the exposure/dose-response relationships for safety risk(s) (e.g., hyperglycemia).*

Sponsor Comment: Points 2 and 3 addressed in clinical pharmacology above.

Meeting Discussion: None

ATTACHMENTS AND HANDOUTS

Attachment 1 – CMC Timelines and Milestones graphic from Sponsor sent via e-mail on, August 18, 2016

Attachment 2 – August 24, 2016, e-mail from Sponsor containing post-meeting related question, and the August 25, 2016, response from Division.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WILEY A CHAMBERS
09/13/2016