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Assessment report

Review under Article 5(3) of Regulation (EC) No 726/2004

Teicoplanin

Procedure no: EMEA/H/A-5(3)/1315

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Background information on the procedure

1.1. Request for CHMP opinion by France

Teicoplanin was first approved for marketing in Italy as Targocid, with an International Birth Date (IBD) of 30 July 1987. Targocid (hereafter also referred to as the reference product) is a complex antibiotic, consisting of six closely related glycopeptide subcomponents (A2-1 to A2-5 and A3) as defined in the current European Pharmacopoeia (Ph. Eur.) monograph for teicoplanin.

The first application for a generic of the reference product was submitted in 2005 by Hospira through the decentralised procedure (DCP). During the assessment of Teicoplanin Hospira it was noted that the compositional profile of glycopeptide subcomponents present in the generic version differed significantly in comparison to Targocid. As agreement could not be reached in the DCP the matter was referred to the Committee for Medicinal Products for Human Use (CHMP) in 2008. Due to these differences the safety and efficacy of the generic product could not be assured. A marketing authorisation was not granted to Teicoplanin Hospira[1].

Since the Teicoplanin Hospira procedure, other decentralised and national procedures have been initiated for Teicoplanin as generic or hybrid applications. The majority of these procedures are pending finalisation further to obtaining clarification on this issue.

The half-lives of the A2 components correlate to their lipophilicity. For generics which would have a lower proportional content of subcomponents with a longer half-life and a higher proportion with a shorter half-life, the overall elimination of total teicoplanin would be faster, and the resulting area under the curve (AUC) would be lower compared to the originator.

Experience with teicoplanin-containing generic products has raised concerns about the data on the qualitative and quantitative composition of the active substance submitted for generic applications. Compliance with the Ph. Eur. (monograph available since January 2009) alone has not been considered sufficient to fulfil the primary condition for a generic application (i.e. having the same qualitative and quantitative composition in the active substance as compared to the reference product), and therefore, issues have been raised to address the need for therapeutic equivalence of these teicoplanin-containing generic products.

Therefore, in order to address the disharmony across the EU in terms of the requirements for generics of teicoplanin, a procedure according to Article 5(3) of Regulation EC (No) 726/2004 was triggered by France on 22 September 2011. The aim of this procedure was to achieve a consensual view on the requirements to be fulfilled to show equivalence between the generics and the reference product of this antibiotic.

The CHMP has been asked:

- to comment on the assay limits described in the Ph. Eur. monograph for teicoplanin (for both minimum and maximum content of each of the subcomponents of the active substance)
- to discuss the need to require additional (non-) clinical data with the purpose of demonstrating therapeutic equivalence between generics/hybrids and the reference product (Targocid)

[1] For more information on the referral procedure, please consult the following link on the Agency's website at http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Teicoplanin_Hospira_29/WC500014116.pdf .

2. Scientific discussion

2.1. Introduction

Teicoplanin is a glycopeptide antibiotic that has bactericidal activity against Gram positive aerobic and anaerobic bacteria. It inhibits the growth of susceptible organisms by interfering with the biosynthesis of the cell-wall at a site different from that affected by beta-lactam antibiotics. Teicoplanin is a true fermentation product produced by *Actinoplanes teichomyceticus* strains.

Teicoplanin is a mixture of glycopeptide components which, on the basis of high performance liquid chromatography (HPLC) separation, are currently classified into six main subcomponents (as individual or as a group) according to their alkyl side chain and therefore by their polarity in elution in the referenced chromatographic system:

- Group A3: one principle component A3-1, corresponding to the most polar component,
- Group A2: five principle subcomponents as individual or as a group; A2-1 group, A2-2, A2-3 group, A2-4, and A2-5 group, where the polarity decreases; A2-5 being the most lipophilic in protein binding.

All teicoplanin components are glycopeptide analogs, which have the same core glycopeptide structure composed of a linear heptapeptide aglycone, an α-D-mannose and an acetyl–β-D-glucosamine.

The A3-1 component is the core glycopeptide that is common to all teicoplanin like components that have been identified; the five components of the A2-group contain an additional N-acyl-β-D-glucosamine and differ only in the length and nature of this acyl-aliphatic side chain.

A Ph. Eur. monograph for teicoplanin has been available since January 2009. The limits adopted by the monograph for content of each subcomponent are quite wide as shown below:

teicoplanin A2 group:	NLT 80%
teicoplanin A2-2:	35 to 55%
teicoplanin A2-1:	NMT 20%
teicoplanin A2-3:	NMT 20%
teicoplanin A2-4:	NMT 20%
teicoplanin A2-5:	NMT 20%
teicoplanin A3:	NMT 15%

As the composition of the teicoplanin subcomponents is dependent upon the strain of microorganism and the fermentation conditions used, these may give rise to significant differences in the composition between the generic and reference product[2].

Based on data obtained from several manufacturers of teicoplanin, it became apparent that a revision of the current Ph. Eur. monograph along with some additional measures mentioned below in this report needed to be taken in order to ensure therapeutic equivalence of teicoplanin from different active substance sources with the reference product and address variability among themselves.

[2] Borghi A., Edwards D., Franco Zerilli L., Factors affecting the normal and branched-chain acyl moieties of teicoplanin components produced by actinoplanes teichomyceticus. Journal of general microbiology. 1991; 137. 587-592

The following regulatory strategy was considered:

- CHMP to make proposals for the revision of the Ph. Eur. monograph in the context of this Art 5(3) procedure and forward these proposals to EDQM.
- An acceptable finished product range for A2 and A3 groups at shelf life should be published.
- A generic product of teicoplanin powder for solution for injection may be considered equivalent to the reference finished product without the need for clinical or non-clinical studies, if the composition of the active substance in subcomponents remains within the established variability of that of the reference product.
- Based on the data provided, CHMP to make clear recommendations, to support generic equivalence, on quality grounds alone, without the need for additional clinical studies.

The CHMP approached the MAH for the reference product Targocid and generic/hybrid manufacturers of teicoplanin with a request to provide data on the active substance composition with respect to its individual subcomponents and to share their proposals for the revision of the Ph. Eur. monograph limits, that would allow a better reflection of the composition of teicoplanin subcomponents available on the market. The potency of the active substance as determined by microbiological assay and declared in International Units (IU) was also addressed by the teicoplanin manufacturers.

2.2. Discussion

2.2.1 Quality aspects

The quality discussion was mainly aimed at the need to update the Ph. Eur. monograph, in order to limit variability among different sources of teicoplanin active substance within a specified range considered suitable to ensure satisfactory quality and therapeutic equivalence. Stability and finished product specifications were also extensively discussed during the course of this procedure.

A number of manufacturers of generic teicoplanin shared their experience with production of teicoplanin. It appeared that teicoplanin from all these manufacturers complied with the Ph. Eur. requirements; however, the contents of individual subcomponents varied considerably in comparison to those of the reference product and between different manufacturers of generic teicoplanin.

Generic manufacturers generally agreed on the need to have tighter specifications for teicoplanin subcomponents in line with those of the reference product Targocid, which has been on the EU market for many years, in order to satisfactorily fulfil the requirements for a generic application, and that this may be achieved by appropriate refinement of the teicoplanin fermentation process, if necessary. Some of these manufacturers have already successfully initiated efforts to produce an active substance with limits of subcomponents closer to that of Targocid.

The MAH of the reference product shared a very extensive package of data on the active substance manufacturing process, in-house specifications, batch results, analytical methodology and stability. Some aspects of the finished product, especially the parameters related to the composition of the active substance, were also analysed.

Analysis of active substance data

Batch-to-batch variability based on batch data

Based on data provided by the MAH of the reference product on active substance batches, it may be noted that:

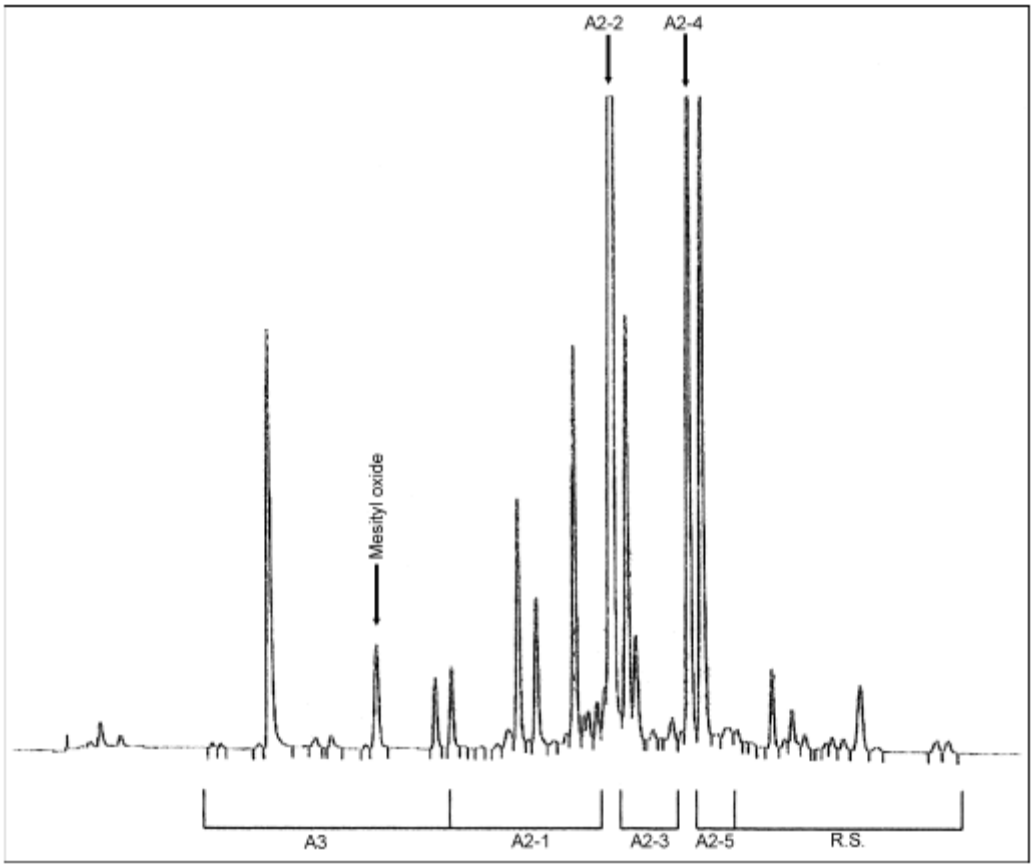
- All batches met the current Ph. Eur. monograph specifications at release

- The overall results were within expected variability for fermentation processes
- For all components of teicoplanin, the current Ph. Eur. monograph specifications appear excessively wide when compared to historical batch data presented by the MAH for the reference product; therefore, their tightening appears possible and desirable with respect to manufacturing capability

Throughout the discussion with the MAH of the reference product, it has been confirmed that there is no change in the chromatographic profile of teicoplanin. A comparison between the chromatographic profile of teicoplanin batches representative of the current production and that of an old batch manufactured in 1987 shows that HPLC chromatographic profiles are equivalent with respect to the composition of components and subcomponents, thus demonstrating batch to batch consistency over time.

Analysis of teicoplanin chromatogram available (EDQM web site)

The following chromatogram is available at the EDQM website, knowledge database:



Originally, according to the Ph. Eur. monograph and the chromatogram available for teicoplanin, it was apparent that all peaks with a relative retention time of ≤ 1.25 may be considered as components of teicoplanin active substance and that all peaks with a relative retention time of > 1.25 may be considered related substances (except for Impurity A mesityl oxide and disregarding all peaks ≤ 0.25%).

However in light of the discussion with the MAH for the reference product and based on an extensive amount of data submitted, the following conclusions were drawn:

- Concerning the teicoplanin A-3 group, it was confirmed that the defined chromatographic window includes the principal single peak due to A3-1, but may also include other minor peaks due to teicoplanin A2 components with only short aliphatic side chains (see chromatogram).
- It was confirmed that any peaks with a relative retention > 0.70 and < 1.25 present a teicoplanin-like structure (glycopeptide analogs, which have the same core glycopeptide structure composed of a linear heptapeptide aglycone, an α-D-mannose and an acetyl–β-D-glucosamine).
- Furthermore, it was confirmed that all peaks, even outside the RRT 0.70-1.25 range, participate in the activity of teicoplanin and in its therapeutic profile. Indeed it was confirmed that all the peaks (except mesityl oxide) present in the reference active substance chromatogram are characterised by the same glycopeptide core structure and that any sub-components having a teicoplanin core structure will contribute to the antimicrobial activity. As a consequence, the teicoplanin like structure applies to the whole product and cannot be restricted to its "historical" part, i.e. RRT 0.70 – 1.25 range only. Hence the so called related substances RS1, RS2 and the peak at RRT 1.38 should also be considered teicoplanin like in structure.
- To avoid confusion, new terminology should be applied to teicoplanin like structures currently defined as RS1, RS2, RS3, and RS4 and the peak at about 1.38.
- Any other peak in the chromatogram should be identified and confirmed to have a teicoplanin-like structure. The MAH of the reference product considers that identification and monitoring down to 0.5% is feasible, but that the complexity of the product prevents routine monitoring of components at lower content.

Additional limits and tests proposed for the active substance subcomponents, based on the batch results and proposal for the Ph. Eur. monograph revision

In view of the above discussion and bearing in mind that the composition of individual subcomponents can be impacted by modification of the fermentation conditions, new limits and tests, in addition to those required by the current Ph. Eur. monograph, are proposed to address all teicoplanin like structure peaks. These new tests and limits are given below and these should be forwarded to EDQM for inclusion in the Ph. Eur. monograph.

Teicoplanin A3 group	**4.0 - 12.0 %**
Teicoplanin A2 group	**84.0 - 93.0 %**
Teicoplanin A2-1 group	**10.0 - 19.0 %**
RRT about 0.85 (RS3):	0.5-5.5%
RRT about 0.88 (RS4)	0.5-4.0%
RRT about 0.93 (A2-1)	2.0-7.0%
Teicoplanin A2-2	**37.0 % - 50.0 %**
Teicoplanin A2-3 group	**5.0 - 11.0 %**
RRT about 1.03 (A2-3)	4.0-8.5%
Teicoplanin A2-4	**7.0 - 15.0 %**
Teicoplanin A2-5 group	**7.0 - 17.0 %**
RRT about 1.15(A2-5)	7.0-15.0%
Related substances	**NMT 5.0 %**

RRT about 1.25 (RS1):	NMT 1.5%
RRT about 1.30 (RS2)	NMT 1.5%
RRT about 1.38	NMT 2.5%
Any non-teicoplanin like impurity	**NMT 0.5%**

A limit for total of non-teicoplanin-like impurities should also be considered and would also need to be included in the monograph.

Analysis of finished product data

Batch-to–batch variability based on batch data

The MAH of the reference product provided batch data of finished product batches for each strength 200mg and 400mg. It may be noted that:

- The composition of the finished product batches, expressed as ratio of subcomponents, differs slightly from the active substance batches.

Stability and degradation of teicoplanin finished product

The degradation pattern occurring during finished product manufacturing and storage is well understood: it consists in degradation of A2 group of subcomponents to A3. The overall conversion of A2 into A3 is estimated to be around 5%. Due to this degradation, the material in the finished product would not necessarily comply with the revised Ph. Eur. monograph at release and shelf life.

It is understood that

- the content of each subcomponent is determined in the active substance,
- the relationship between active substance and finished product composition is well known,
- the degradation pattern occurring during finished product manufacturing and storage is well understood,
- if the active substance used in the manufacture of the finished product complies with the revised Ph. Eur. as proposed above - it is considered that only the A2 and A3 subcomponent groups need to be controlled in the finished product.

In view of the above statements and in line with stability batch results available for the reference product marketed, it is concluded that setting individual subgroup specifications in the finished product would not be necessary. The following specifications for A2 and A3 groups are proposed at the end of shelf-life:

A3	NMT 17%
A2	NLT 78%

It is considered that specifications at release for these two subcomponent groups are process dependent and should be assessed on a case by case basis.

Declaration of finished product strength

The strengths of teicoplanin finished product are conventionally declared and prescribed in terms of mass (e.g. 200mg and 400mg), but given the variability of the active substance, it is the potency of the finished product, as determined by microbiological assay and declared in IU (e.g. 200,000IU or 400,000IU), that determines the quantitative amount of active substance in the finished product.

The potency of the active substance may vary and the Ph. Eur. monograph specifies a minimum potency 900IU/mg. However, the convention of declaring the strength of the finished product in terms of mass (mg) is based on a nominal fixed potency of 1000IU/mg for the active substance. There were concerns that this convention could lead to inconsistencies between finished products in terms of formulation and declaration of strength, if generic products were to be marketed.

This was addressed during the procedure by a series of questions to the reference product and generic companies.

It was confirmed that during product manufacture, the required quantity of the active substance per vial is formulated by taking into consideration the actual microbiological potency (IU/mg) of the active substance, to achieve the target activity of 200,000IU or 400,000IU per vial.

The product information should therefore declare the qualitative and quantitative details of the active substance in terms of mass and IU, for example:

200mg finished product

Each vial contains 200mg teicoplanin equivalent to 200,000 IU

400mg finished product

Each vial contains 400mg teicoplanin equivalent to 400,000 IU

Other strengths should follow this convention.

The product name should remain consistent with prescribing convention as follows:

Teicoplanin 200mg or 400mg Powder for Solution for Injection

With respect to finished product limits for potency, it was confirmed that these may need to be wider than those usually specified to ensure satisfactory recovery before use.

The Ph. Eur. monograph for teicoplanin includes a requirement for the microbiological assay of antibiotics according to the Ph. Eur. monograph 2.7.2. With respect to the assay of the active substance in the finished product, it is again necessary to apply the same Ph. Eur. monograph to determine the potency, using appropriate statistical methods. Consequently, the potency declaration is based on lower and upper fiducial limits.

It should be noted that in line with best practice, the precision of the assay should be such that the fiducial limits of error are not less than 95% and not more than 105% of the estimated potency.

The release assay limits should be specified so that it can be unequivocally confirmed that the finished product complies with the stated label claim (IU).

The shelf life assay limits should be specified so that it can be unequivocally confirmed when the finished product is not in compliance with the stated label claim (IU).

The following release and shelf life limits for potency would be considered acceptable:

For a 200mg finished product:

Release:	lower fiducial limit 95% (NLT 190,000 UI/vial)
	upper fiducial limit 115% (NMT 230,000 UI/vial)
Shelf-life:	lower fiducial limit: 115% (NMT 230,000 UI/vial)
	upper fiducial limit 95% (NLT 190,000 UI/vial)

For a 400mg finished product:

Release:	lower fiducial limit 95% (NLT 380,000 UI/vial)
	upper fiducial limit 115% (NMT 460,000 UI/vial)
Shelf-life:	lower fiducial limit: 115% (NMT 460,000 UI/vial)
	upper fiducial limit 95% (NLT 380,000 UI/vial)

3. Overall conclusion

The aim of this Scientific Opinion procedure was to achieve a scientific view on the requirements to be fulfilled to show equivalence between teicoplanin generics and the reference product Targocid.

The CHMP conclusions on the following points are as follows:

- to comment on the assay limits described in the Ph. Eur. monograph of teicoplanin (for both minimum and maximum content of each of the subcomponents of the active substance).

From the data provided, it is concluded that the current Ph. Eur. monograph is not sufficient to characterise the active substance within the established variability of that of the reference product. In addition, the current monograph does not satisfactorily address the control of non-teicoplanin-like substances.

To ensure that generic active substance may be sufficiently characterised, new tests and limits are proposed, in addition to those currently specified in the monograph. These proposed new tests and limits will be forwarded to the EDQM, with the recommendation that the monograph is revised accordingly.

- to discuss the need to require additional (non-) clinical data with the purpose of demonstrating therapeutic equivalence between generics/hybrids and the reference product (Targocid).

From the data provided, it is concluded that equivalence between teicoplanin generics and the reference products may be based on quality grounds alone, but this should be established not only upon compliance with material and product specifications but also based on impact of the manufacturing processes on the stability of the finished product.

Additional (non)-clinical data with the purpose of demonstrating therapeutic equivalence between generics/hybrids and the reference product are not considered necessary, if the generic products comply with the following recommendations given in this report in the recommendations section.

Recommendation for setting equivalence between teicoplanin generics and reference products

Given the known degradation of A2 subcomponents to A3, the active substance in the finished product at the end of the finished product's shelf life may no longer fully comply with the active substance specification. This is accepted, and considered qualified. If the active substance used in the manufacture of the finished product complies with the above-recommended additional limits and tests, then it is considered that only the A2 and A3 subcomponent groups need to be controlled in the finished product at release and end of shelf-life. Specifications at release for these two subcomponents are process dependent and should be assessed on a case by case basis; however, shelf life specifications for the A2 and A3 subcomponents, which are in line with stability batch results available for the reference product marketed, are proposed.

With respect to finished product limits for potency, it was confirmed that these may need to be wider than those usually specified to ensure satisfactory recovery before use.

The convention of declaring the strength of the finished product in terms of mass (mg) is based on a nominal fixed potency of 1000IU/mg for the active substance. There were concerns that this convention could lead to inconsistencies between products in terms of formulation and declaration of strength, if generic products were to be marketed. Guidance on the declaration of strength is therefore also provided.

Because teicoplanin is a critical antibiotic used for the treatment of potentially severe infections, it is also strongly recommended that the potential sources of variability of the fermentation process are minimised and the recommended approach for setting equivalence is followed, with the goal of maximising the similarity between generic and reference product.

Recommendations for the active substance and finished product

Active Substance

New limits and tests proposed for the active substance subcomponents, to amend the current Ph. Eur. monograph

Teicoplanin A3 group	**4.0 - 12.0%**
Teicoplanin A2 group	**84.0 - 93.0%**
Teicoplanin A2-1 group	**10.0 - 19.0%**
RRT about 0.85 (RS3):	0.5-5.5%
RRT about 0.88 (RS4)	0.5-4.0%
RRT about 0.93 (A2-1)	2.0-7.0%
Teicoplanin A2-2	**37.0% - 50.0%**
Teicoplanin A2-3 group	**5.0 - 11.0%**
RRT about 1.03 (A2-3)	4.0-8.5%
Teicoplanin A2-4	**7.0 - 15.0%**
Teicoplanin A2-5 group	**7.0 - 17.0%**
RRT about 1.15(A2-5)	7.0-15.0%
Related substances	**NMT 5.0%**
RRT about 1.25 (RS1):	NMT 1.5%
RRT about 1.30 (RS2)	NMT 1.5%
RRT about 1.38	NMT 2.5%
Any non-teicoplanin like impurity	**NMT 0.5%**

A limit for total of non-teicoplanin-like impurities should also be considered and would also need to be included in the monograph.

These proposed new tests and limits will be forwarded to the EDQM, with the recommendation that the monograph is revised accordingly.

Finished Product

Only the A2 and A3 subcomponent groups, and not individual subcomponents, need be controlled in the finished product.

To account for the known degradation of teicoplanin A2 subcomponents to A3, these should be specified at shelf life as follows:

A3 NMT 17%

A2 NLT 78%

Specifications at release for these two subcomponent groups are process dependent and should be assessed on a case by case basis.

Comparative chromatographic profiling with the reference product should be undertaken to provide an assurance that there are no new unqualified impurities in the finished product.

The product information should declare the qualitative and quantitative details of the active substance in terms of mass and IU, for example:

200mg finished product

Each vial contains 200mg teicoplanin equivalent to 200,000 IU

400mg finished product

Each vial contains 400mg teicoplanin equivalent to 400,000 IU

Other strengths should follow this convention.

The product name should remain consistent with prescribing convention as follows:

Teicoplanin 200mg or 400mg Powder for Solution for Injection

The manufacturing process should clearly specify the steps taken to achieve the declared qualitative and quantitative composition, in terms of IU.

The Ph. Eur. monograph for teicoplanin includes a requirement for the microbiological assay of antibiotics according to Ph. Eur. monograph 2.7.2. With respect to the assay of the active substance in the finished product, it is again necessary to apply the same Ph. Eur. monograph to determine the potency, using appropriate statistical methods. Consequently, the potency declaration is based on lower and upper fiducial limits.

The precision of the assay should be such that the fiducial limits of error are not less than 95% and not more than 105% of the estimated potency.

The release assay limits should be specified so that it can be unequivocally confirmed that the finished product complies with the declaration of strength of the finished product (IU).

The shelf life assay limits should be specified so that it can be unequivocally confirmed when the finished product is not in compliance with the declaration of strength of the finished product (IU).

The following release and shelf life limits for potency would be considered acceptable:

For a 200mg finished product:

Release: lower fiducial limit 95% (NLT 190,000 UI/vial)

upper fiducial limit 115% (NMT 230,000 UI/vial)

Shelf-life: lower fiducial limit: 115% (NMT 230,000 UI/vial)

upper fiducial limit 95% (NLT 190,000 UI/vial)

For a 400mg finished product:

Release: lower fiducial limit 95% (NLT 380,000 UI/vial)

upper fiducial limit 115% (NMT 460,000 UI/vial)

Shelf-life: lower fiducial limit: 115% (NMT 460,000 UI/vial)

upper fiducial limit 95% (NLT 380,000 UI/vial)