2.3.P. DRUG PRODUCT

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2.3.P.1 DESCRIPTION AND COMPOSITION OF THE DRUG PRODUCT

<TERIPARATIDE 20µg/80µL solution for injection> is a clear, colorless solution, free from visible particles, packaged in a glass cartridge (2.4 mL nominal fill volume in 3 mL cartridge) closed with a plunger at one end and with a rubber disc and aluminum cap (combiseal) at the other end. The filled cartridge is assembled into a pen injector intended for multiple injections.

The qualitative and quantitative composition of the drug product is shown in TABLE 1.

TABLE 1. <Teripartide 20µg/80µL Solution for Injection>. Composition

INGREDIENT	QUANTITY (PER DOSE) 80 µL	QUANTITY (PER CARTRIDGE) 2.4 mL	FUNCTION	REFERENCE TO STANDARDS
Teriparatide	µg	mg		Ph Eur* / USP*
Glacial acetic acid	µg	mg		Ph Eur* / USP NF*
Anhydrous sodium acetate	µg	mg		USP NF*
Mannitol	mg	mg		Ph Eur* / USP*
m- Cresol	mg	mg		Ph Eur* / USP*
WFI	µL	mL		Ph Eur* / USP*
Hydrochloric acid 0.1N	q.s. pH	q.s. pH		Ph Eur* / USP NF*
Sodium hydroxide 0.1 N	q.s. pH	q.s. pH		Ph Eur* / USP NF*

* Current edition

2.3.P.2 PHARMACEUTICAL DEVELOPMENT

The objective of the pharmaceutical development studies carried out was to develop a generic pharmaceutical product for *Forsteo 20µg/80µL solution for injection in pre-filled pen* authorized in Europe via the centralized procedure EMEA/H/C/000425 in 2003.

<TERIPARATIDE 20µg/80µL> has the same pharmaceutical form and is essentially similar, in terms of active ingredient and excipient composition, physico-chemical characteristics and bioavailability, to *Forsteo 20µg/80µL solution for injection in pre-filled pen*. It should be noted that the active substance teriparatide in the reference product is a biological product of recombinant origin whereas the active substance in <TERIPARATIDE 20µg/80µL> is chemically synthesized.

2.3.P.2.1. COMPONENTS OF THE DRUG PRODUCT

Drug Substance

Teriparatide is a synthetic polypeptide that consists on the 1-34 amino-acid fragment of human Teriparatide, the biologically active N-terminal region. Physically, the drug substance is a white or off-white amorphous powder with formula $C_{181}H_{291}N_{55}O_{51}S_2$ (as free base), with an average molecular weight of 4117.72 u.m.a. The drug substance is freely soluble in water.

Teriparatide used in drug product manufacture is supplied by Complete information about the drug substance supplied by is included in the Open Part of the DMF included in Section 3.2.S, including complete characterization of the drug substance through state-of-art techniques.

As commented in Section 2.3.S, since there is no monograph on synthetic Teriparatide currently published in any pharmacopoeia, the specifications established by the drug substance manufacturer are based on the Ph Eur and USP current edition monographs on *Teriparatide* produced by recombinant DNA technology. The control specification established contains all relevant attributes for a synthetic peptide. Batch analytical results provided by show consistency from batch to batch and the stability data show that the drug substance is a stable product. There are no outstanding quality issues that would have a negative impact on the quality of the drug product.

The physico-chemical characteristics of teriparatide that could influence the performance of the drug product (solution for injection), and that should be considered in the formulation and

manufacturing development of the drug product are the summarized below. Data is based on the drug substance stress testing data included in the Open Part of the DMF (see summary in Section 2.3.S).

- Oxidation: Teriparatide shows a marked degradation under strong oxidizing conditions. To avoid drug substance oxidation during manufacture, the manufacturing process is conducted under nitrogen atmosphere. Since the product is packaged in airtight pre-filled cartridges with no air chamber in contact with the product, oxidation should not be a concern throughout product shelf-life.

- pH: Teriparatide degrades under strong acidic or alkaline conditions. To ensure that product pH will not have a negative impact on product quality, the target pH for <TERIPARATIDE 20µg/80µL> will be adjusted to that of the reference drug product (pH 4.0 according to the information in the *Forsteo-EPAR-Scientific Discussion (October 2005).*

- Temperature: Teriparatide in solid state shows a marked degradation at 60ºC and 80ºC.

Excipients

Excipients chosen for drug product composition are commonly used in the formulation of injectable products and are the same as those used in the formula of the reference product Forsteo®. All the excipients included in the formula comply with the requirements established in the corresponding monographs of the Ph Eur, USP, USP-NF current edition (see TABLE 1).

Since the excipients used in the developed formula have a well-established history of use in solutions for injection (including the reference product Forsteo®) and comply with the requirements established in the corresponding compendial monographs, no safety concerns should be raised. Moreover, the compatibility of the excipients among them and with the drug substance is demonstrated by their prolonged use in the formulation of the reference product, Forsteo®

2.3.P.2.2. DRUG PRODUCT

Formulation Development

The formula proposed for <TERIPARATIDE 20µg/80µL> is qualitatively and quantitatively the same as that declared for the reference product, as it is shown in TABLE 2. The pH range proposed for the drug product was established based on the pH stated in the *Forsteo-EPAR-Scientific Discussion (October 2005)* and the values observed in the analysis of reference product batch C162547E.

TABLE 2. <Teriparatide 20µg/80µL> *vs* Forsteo. Composition

INGREDIENT	QUANTITY PER mL		FUNCTION
	Teriparatide 20µg/80µL	Forsteo	
Teriparatide	mg*	mg**	
Glacial acetic acid	mg	mg	
Anhydrous sodium acetate	mg	mg	
Mannitol	mg	mg	
m- Cresol	mg	mg	
Hydrochloric acid and/or Sodium Hydroxide	pH	. pH	
WFI	mL	mL	

* Synthetic Origin

** Recombinant Origin

Since the only difference between <TERIPARATIDE 20µg/80µL> and the reference drug product Forsteo® is the origin of the drug substance used in the formulation (chemically synthesized *versus* recombinant, formulation development studies were focused on assessing the potential impact of this difference on product quality and efficacy and safety profile. Specifically, the following studies were conducted:

- Comparison of the structure of the drug substance in the formulations
- Comparison of Purity and assay of formulations
- Pharmacodynamic equivalence assessment and comparison
- Immunogenicity assessment

Structural Comparison between <TERIPARATIDE 20µg/80µL> and the Reference Drug Product Forsteo®

The correct amino acid sequence of synthetic Teriparatide drug substance, has been confirmed by the drug substance manufacturer by a combination of different methods (see Section 3.2.S.3.1 of the Open Part of the DMF). These experiments allow to conclude that Teriparatide manufactured by has a sequence that matches with the expected sequence of Parathyroid Hormone (1-34) Human (PTH (1-34)).

To confirm that the fold of the drug substance (PTH (1-34) molecule) is identical irrespective of the origin of the peptide (either recombinant in Forsteo® or synthetic in <TERIPARATIDE 20µg/80µL>, both formulations were compared using NMR (1D and 2D) spectroscopy. Data for both formulations were acquired under identical experimental settings.

- The 1D H-NMR spectra obtained for Forsteo® and <TERIPARATIDE 20µg/80µL> show identical chemical shift dispersion and ratio when the main components of both preparations are compared. The results obtained also confirm that both formulations have the same qualitative and quantitative composition in terms of excipients.
- The 2D NMR data (TOCSY experiments) of Forsteo® and <TERIPARATIDE 20µg/80µL> formulation shows identical signals for both samples.

The results obtained show that the concentration, sequence and fold of both, recombinant and synthetic Teriparatide molecules (present in <TERIPARATIDE 20µg/80µL> and Forsteo, respectively) are identical under the experimental conditions used for the NMR experiments, which confirms that the two drug substances, as such and in their respective formulations, are identical regardless of its origin (chemical or recombinant).

*Impurity and Degradation Profile. Comparison between <TERIPARATIDE **20µg/80µL> and the** Reference Drug Product*

The purity profile of three batches of <TERIPARATIDE 20µg/80µL> prepared from different batches of the drug substance produced at BCN Peptides by chemical synthesis were compared with one commercial batch of Forsteo® (Batch C453949D) and Forteo® (Batch C470473C). TABLE 3 shows the results obtained for purity and assay analysis of all tested batches.

TABLE 3. <Teriparatide 20µg/80µL> vs Forsteo® / Forteo®. Purity Comparison

Formulation	Batch Number	Purity (%)	Total impurity (%)
<TERIPARATIDE 20µg/80µL>	9941908	97.8	2.2
	9941909	98.3	1.7
	9941913	98.1	1.9
Forsteo	C453949D	96.2	3.8
Forteo	C470473C	97.6	2.4

The results show similar purity values for the three batches of <TERIPARATIDE 20µg/80µL> and the reference drug product in Europe (Forsteo®) and USA (Forteo®).

A detailed comparison of the purity profile of the batches analysed is provided TABLE 4.

TABLE 4. <Teriparatide 20µg/80µL> vs Forsteo® / Forteo®. Purity Comparison (%Area)

r.r.t.	Tentative Identification	9941908	9941909	9941913	Forsteo	Forteo
0.4					0.16	
0.41					0.16	
0.5					0.32	
0.71		0.25	0.17	0.21	0.35	0.32
0.78					0.63	0.49
0.80		0.52	0.32	0.43	0.63	0.60
0.94					0.17	
0.96					0.26	0.19
0.98		0.14	0.13	0.12	0.16	0.15
0.98 -0.99		0.51	0.38	0.41	0.66	0.56
1.00		97.81	98.3	98.13	96.18	97.6
1.02		0.38	0.35	0.45		
1.03					0.10	
1.04					0.10	
1.06		0.13				
1.09		0.26	0.25	0.26		
1.12					0.13	0.10

As it can be observed in TABLE 4, although some differences were found in the impurity profile of Forsteo®/Forteo® and <TERIPARATIDE 20µg/80µL>, global purity profile can be considered similar for all formulations. Forsteo®/Forteo® show some impurities that are not present in <TERIPARATIDE 20µg/80µL> batches (highlighted in green in TABLE 4). On the other hand, three individual impurities are found in <TERIPARATIDE 20µg/80µL> batches that are not detected in Forsteo®/Forteo® (highlighted in yellow in the table). These impurities are in all cases below the identification threshold (>0.5%) defined in the Ph Eur current edition monograph 2034 for peptides obtained by chemical synthesis, and well

below the qualification threshold (>1.0%) stated in the mentioned monograph. Therefore, no concern on the toxicity of these impurities should be raised.

The results obtained confirm that, Forsteo®/Forteo® and <TERIPARATIDE 20µg/80µL>, can be considered equivalent in terms of global purity and assay.

Finally, samples of <TERIPARATIDE 20µg/80µL>, and Forsteo®/Forteo® were analysed at initial time and after 30 days storage at 40±2ºC // 75±5% RH. The results obtained in the study are shown in FIGURE 1, in the following page. It can be observed that all formulations show the same degradation profile, fact that confirms that the origin of the drug substance (either recombinant or chemical synthesis) has no impact at all on the degradation profile of the product.

Biological Activity. Comparison between <TERIPARATIDE 20µg/80µL> and the Reference Drug Product

The PTH1 agonist response of <TERIPARATIDE 20µg/80µL>, and the reference drug product Forsteo®/Forteo®, was assessed in a cellular functional assay, by measuring the concentration of cyclic adenosine monophosphate (cAMP) by Homogeneous Time Resolved Fluorescence (HTRF) in SaOS2 cells expressing the PTH1 receptor. PTHrP(1-34) at 0.1 µM was used as control.

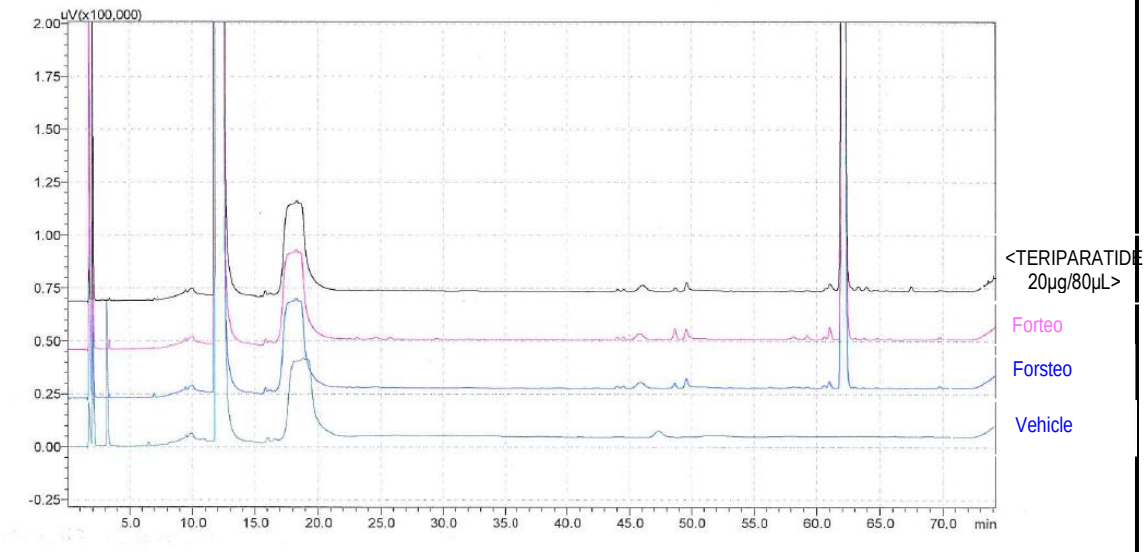
The calculated pEC_{50} values for the different test products are given in TABLE 5. The results of the cell-based *in vitro* pharmacology comparative assay indicate that all studied formulations present a similar agonist response. The small differences observed are within experimental variability.

TABLE 5. <Teriparatide 20µg/80µL> vs Forsteo® / Forteo®. pEC_{50} values

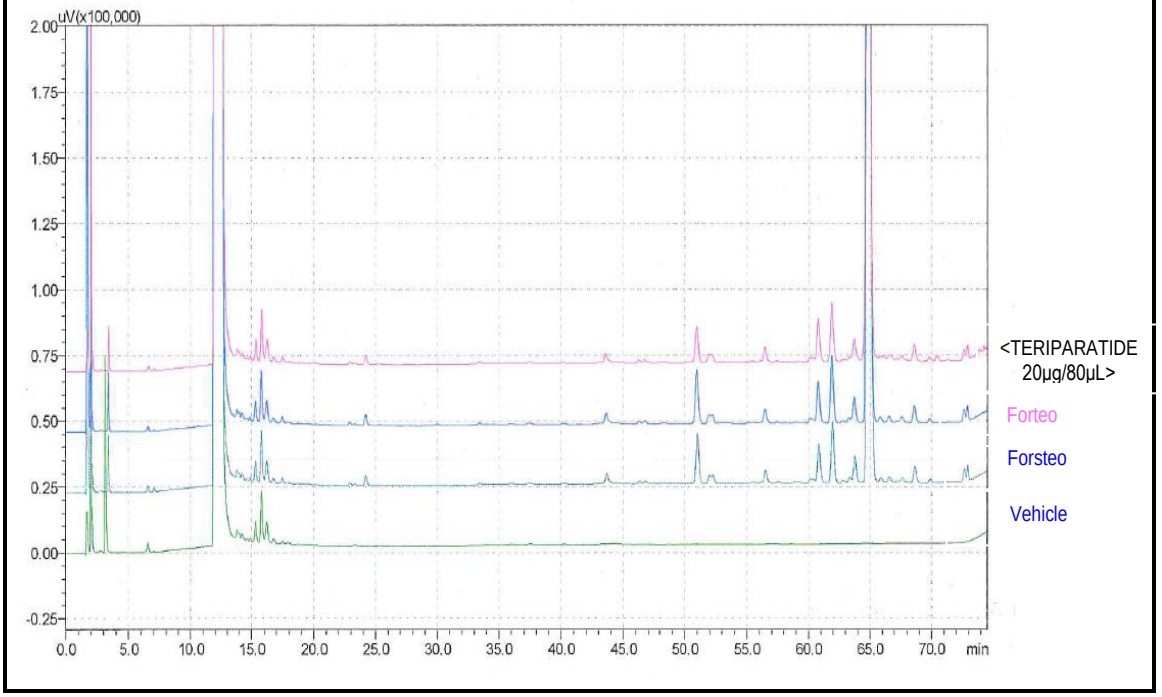
Test Product	Batch	pEC50 [M]
FORTEO	C470473C	6.6
Forsteo	C453949D	6.5
<TERIPARATIDE 20µg/80µL>	9941908	6.7
	9941909	6.8
	9941913	6.6

FIGURE 1. **<TERIPARATIDE 20µg/80µL>** *vs* Forsteo® / Forteo®. Degradation Profile Comparison

INITIAL TIME



30 days storage at 40±2ºC // 75±5% RH



Immunogenicity Aspects: Intrinsic Immunogenicity

As commented previously, the synthetic and recombinant versions of Teriparatide share an identical amino acid sequence, representing the biologically active, N-terminal, 1-34 sequence of human parathyroid hormone (which has 84 amino acids total).

The recombinant version of Teriparatide has been associated with a relatively low level of detectable, treatment-emergent, anti-drug antibodies, as it is recognized in the Public Assessment Reports issued by different Agencies and Scientific sources[1,2,3,4,5]. E.g., *Forsteo-EPAR-Scientific Discussion (October 2005)* states that anti-drug antibodies were detected in only 4% of treated subjects, and these were without any apparent clinical impact, not affecting either the BMD response or serum calcium concentrations.

In addition to the low incidence of drug-induced immunogenicity, there is no evidence that these possible antibodies have a clinical relevance.

The relatively low incidence of detection of antibodies to Forsteo®, allied to slow time-course of antibody formation, implies a low sensitivity to detect possible differences in immunogenicity of different versions of Teriparatide in controlled clinical studies. The absence of any reported clinical correlates of undesirable immunogenicity to Teriparatide could preclude a judgment of clinical relevance of any differences in antibody formation observed. It can be concluded that the intrinsic immunogenicity associated with Teriparatide (synthetic or recombinant) should be considered negligible.

1 www.tga.gov.au/pdf/auspar/auspar-forteo.pdf (Amendment 7 May 2014)
2 NDA 21-318, Forteo, Risk Evaluation and Mitigation Strategy, August 2013, available at http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM173371.pdf
3 NDA 21-318, Forteo, Risk Evaluation and Mitigation Strategy, August 2013, available at http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM173371.pdf
4 Andrews EB *et al*; J Bone & Mineral Res 2012, 27, 12, 2429-2437
5 Bradwell AR & Harvey TC; Lancet 1999, 353, 9150, 370-373

Bioequivalence Studies

Based on the recommendations set forth in the *Note for Guidance on the Investigation of Bioavailability and Bioequivalence* (CPMP/EWP/QWP/1401/98), bioequivalence of <TERIPARATIDE 20µg/80µL> and the reference product (Forsteo®) can be assumed and no bioequivalence study needs to be conducted to proof bioequivalence, based on the following facts:

1. Both formulations have the same qualitative and quantitative composition in terms of active substance. The different origin of the drug substance in <TERIPARATIDE 20µg/80µL> and Forsteo® has no impact on the quality and efficacy/safety profile of the products:

    - The drug substance manufactured by chemical synthesis is a well-controlled peptide fulfilling all the criteria as set forth in the Ph Eur and USP current edition monographs on Teriparatide of recombinant origin.
    - Equivalence has been demonstrated for the identity, amino acid sequence, and structure for the drug substance contained in both formulations (<TERIPARATIDE 20µg/80µL> and Forsteo®).
    - The impurity and degradation profile of both formulations are equivalent.
    - Both products have a comparable biological activity based on the determined pEC_{50} level.
    - The immunogenic potential of <TERIPARATIDE 20µg/80µL>, as the one for Forsteo®, can be considered negligible. It should be noted that <TERIPARATIDE 20µg/80µL> contains chemically synthesized drug substance, and accordingly, there is no concern on immunogenicity because no contaminants from biological origin will be present in the drug product.

2. Both formulations have the same pharmaceutical form and route of administration, i.e., solution of injection in prefilled pen, subcutaneous administration. Consequently, no differences in the performance of the two dosage forms, and in particular, in the release of the drug substance from the dosage form to its target compartment, or its surrogate sampling compartment, the blood circulation and its biological action are expected.

3. Both formulations have the same qualitative and quantitative composition in terms of excipients. Even pH of both products is the same.

2.3.P.2.3. MANUFACTURING PROCESS

The manufacturing process of <TERIPARATIDE 20µg/80µL> solution for injection is a non-standard manufacturing process for the manufacture of sterile solutions. The product is sterilized by filtration through a sterilizing filter of 0.22 µm. The proposed manufacturing process is summarized in FIGURE 2.

The selected manufacturing process is aligned with the process used in the manufacture of the reference drug product Forsteo®, which is also manufactured by sterile filtration and aseptic processing, according to the information included in *the Forsteo-EPAR-Scientific Discussion (October 2005)*.

Since a non-standard sterilization process is being used, the manufacturing process has been validated at industrial scale. The complete validation report is included in Section 3.2.P.3.5. The validation studies conducted allowed the establishment of the parameters of the manufacturing process, including holding times and duration of the critical steps of the process. The results obtained in the validation studies confirm that the manufacturing process established, and the IPC controls set during manufacture lead to a good quality product that consistently complies with the established specifications.

Selection of Drug Product Sterilization Process

Thermal degradation studies conducted by the drug substance manufacturer with the drug substance show a significant degradation at temperatures above 60ºC (see Section 2.3.S). Also, the results obtained in the accelerated stability studies conducted with the drug product at 25±2ºC (see Section 2.3.P.8), show a significant degradation of the drug product along time under these conditions. These observations confirm that a terminal sterilization processes by heating would lead to a marked degradation of the drug product.

Since the formulation can be filtered through a microbial retentive filter, following the decision tree established in the CPMP/QWP/054/98, a combination of aseptic filtration and aseptic processing is proposed for the drug product.

The IPC limit for bioburden prior filtration has been set at ≤ 500 CFU/100 mL. The limit proposed is based on the quantity of the excipient mannitol in batch formula, and on the limit of bioburden allowed for this excipient (nmt 10^2 CFU/g for the excipient to be used in parenteral preparations, according to Ph Eur current edition).

Filter validation studies conducted (enclosed in Section 3.2.P.2), have demonstrated the capability of the two filters used in the manufacturing process of retaining a bioburden of $1 \cdot 10^7$ CFU/cm^2, that is $2 \cdot 10^4$ orders of magnitude above the proposed limit for bioburden.

Based on the above commented facts, the limit proposed for bioburden before filtration is justified, and aligned with the Draft Guideline *Sterilisation of the medicinal product, active substance, excipient and primary container*.

Cartridge Filling Volume

Extractable volume a defined in the label of the reference drug product is 2.4 mL (equivalent to 30 doses of 80 µL).

In order to define the filling volume and plunger start position, and to assure the desired extractable volume and number of doses for <TERIPARATIDE 20µg/80µL>, a characterization of the extractable volume, filled volume, number of doses and death volume of the reference drug product was conducted. The experimental results obtained in the characterization are detailed in Section 3.2.P.2.3 and summarized below:

- Volume per Dose:
- Extractable Volume: mL
- Filled Volume: mL
- Dead Volume: mL

Based on the values observed for the reference drug product, plunger position was set at 54.20 ± 0.5 mm.

Scale - Up

No specific scale-up studies were conducted. Three batches of industrial scale were manufactured in the facilities of the proposed manufacturer, and the manufacturing process was validated (see Section 3.2.P.3.5). In view of the results obtained during the manufacturing validation studies, it was concluded that the formula and manufacturing process proposed lead to a good quality product that consistently complies with the established specifications.

2.3.P.2.4. CONTAINER CLOSURE SYSTEM

The materials in direct contact with the product and the quality standards they comply with are summarized below.

- Cartridge: Siliconized colourless type I glass. It complies with the specifications established in Ph. Eur. current edition monograph *Glass containers for Pharmaceutical Use*.

- Rubber disc: Elastomeric rubber. It complies with the specifications established in the Ph. Eur. current edition monograph on *Rubber Closures for Containers for Aqueous Parenteral Preparations, for Powders and for Freeze-Dried Powders* and with the USP current edition monograph <381> *Elastomeric Closures for Injection.*

- Plunger stopper: Elastomeric rubber. It complies with the specifications established in the Ph. Eur. current edition monograph on *Rubber Closures for Containers for Aqueous Parenteral Preparations, for Powders and for Freeze-Dried Powders* and with the USP current edition monograph <381> *Elastomeric Closures for Injection*.

The proposed container closure system is suitable for drug product since it protects product from microbial contamination (ensuring product sterility along product shelf-life) and, as commented above, it complies with the requirements of the Ph Eur current edition for glass containers and elastomeric closures.

The results obtained up-to-date in the stability studies conducted with the product (see Section 2.3.P.8) confirm the compatibility of the product with the container closure system.

Filled cartridges are assembled into a disposable pen injector, which is a manual device for drug product subcutaneous injection. The device is assembled together with the *Front subassembly*, *Rear subassembly*, and the prefilled cartridge. Before product administration a standard ISO pen needle should also be assembled to the device. Needle is not part of this medicinal product.

Section 3.2.P.7 and Section 3.2.R. include complete information about the container closure system, including the full description of the materials, as well as the specifications these materials comply with.

2.3.P.2.5. MICROBIOLOGICAL ATTRIBUTES

<TERIPARATIDE 20µg/80µL solution for injection> is a sterile product intended to be subcutaneously administered, manufacturing conditions and IPCs have been set to ensure the microbiological quality of the drug product. Moreover, according to the requirements stated in the Ph. Eur. current edition monograph *Parenteral Preparations,* the routine control for batch release will include an analysis for sterility and endotoxins (see Section 2.3.P.5).

On the other hand, since the product is a multidose product intended to be administered as daily doses of 80 µL throughout 28 days, sterility should be guaranteed throughout the product in-use period. For that reason, an antimicrobial preservative is included in the product formula. The antimicrobial preservative selected is qualitatively and quantitatively the same as that used in the formula of the reference drug product Forsteo®/Forteo® (see TABLE 2). Specifications for control of drug product at release and shelf-life include a chemical testing for preservative content.

2.3.P.2.6. COMPATIBILITY

The product is intended to be injected directly to the patient. Therefore, no specific compatibility studies have been conducted. The drug product should not be mixed with other medicinal products.

2.3.P.3 MANUFACTURE

Manufacturers

-

  Functions: Bulk Product Manufacture. Primary packaging. Drug Substance control (Identification and Appearance). Drug Product control (Endotoxins and Sterility).

-

  Functions: Pen assembly. Secondary packaging. Drug Product Control (all tests except for identification, teriparatide and *m*-cresol content, related substances, and endotoxins). Responsible for batch release.

-

  Functions: Drug Substance manufacture. Drug Substance control. Drug Product Control (Identification, Teriparatide Assay, *m*-Cresol content, Related Substances).

Manufacturing Process

The manufacture of <TERIPARATIDE 20µg/80µL> is carried out following Standard Operation Procedures and Good Manufacturing Practices for liquid sterile pharmaceutical forms. The process is performed by a qualified and trained workforce.

The proposed industrial batch size is . The manufacturing formula is shown in TABLE 6.

TABLE 6. <Teripartide 20µg/80µL Solution for Injection>. Manufacturing Batch Formula

COMPONENTS	QUANTITY ()	QUANTITY)	FUNCTION	REFERENCE TO STANDARDS
Active Ingredient:				
Teriparatide**	g	g		Ph Eur* / USP*
Excipients:				
Glacial acetic acid	g	g		Ph Eur* / USP NF*
Sodium acetate anhydrous	g	g		USP NF*
Mannitol	g	g		Ph Eur* / USP*
m-Cresol	g	g		Ph Eur* / USP*
Hydrochloric acid 0.1M	q.s.	q.s. pH		Ph Eur* / USP NF*
Sodium hydroxide 0.1M	q.s.	q.s. pH		Ph Eur* / USP*
Water for Injection	q.s.	q.s.		Ph Eur* / USP*

Density of Solution: 1.012 kg/L

* Current Edition

** The quantity of Teriparatide to be weighed is corrected by net peptide content:

Teriparatide to be weighed = Target amount in the formula / Net Peptide Content x 100

Net Peptide Content = Peptide Content (%) x (100 - Water(%) - Acetic Acid (%)) / 100

Drug product manufacturing process is a straightforward fill finish process comprising the compounding of the drug product solution, sterile filtration and filling into cartridges. The cartridges are then assembled into the secondary packaging, i.e. the single-use pen. Sterile conditions are applied to all material and equipment in contact with the product. The controls set during product manufacture are in accordance with the directions described in the monograph on *Methods of Preparation of Sterile Products* in the Ph. Eur., current edition.

The different steps of product manufacture, as well as the machinery and equipment used during manufacture, are detailed in Section 3.2.P.3.3. FIGURE 2 shows the manufacturing flow chart where the different operations and in-process controls conducted during product manufacture are specified. The critical steps of the process and the in-process parameters established during manufacture are shown in TABLE 7.

FIGURE 2. **<TERIPARATIDE 20µg/80µL>**. Manufacturing Process

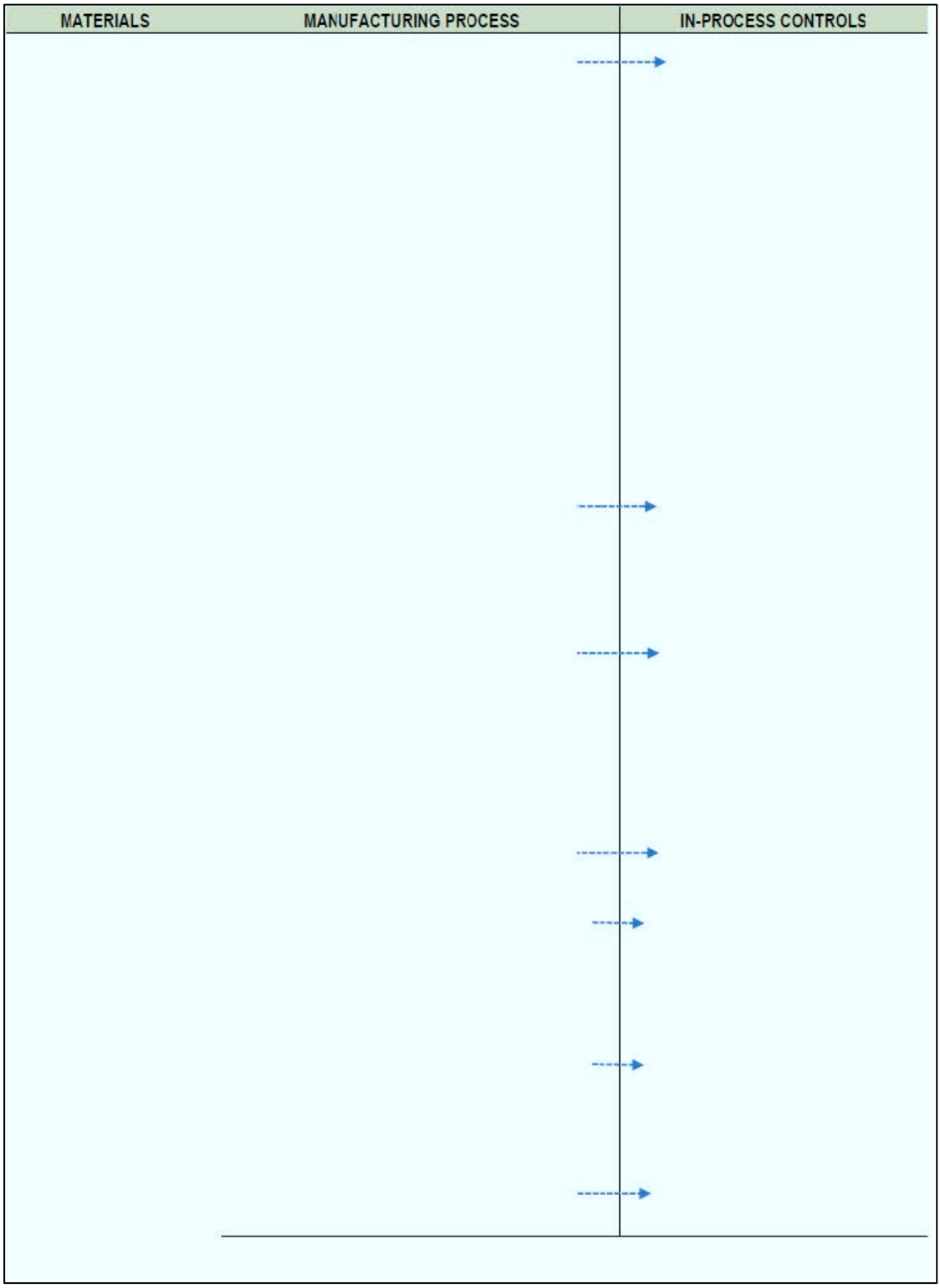


TABLE 7. Teriparatide **20µg/80µL>**. Manufacturing Process. Control of Critical Steps

STEP	PARAMETER	SPECIFICATION	FREQUENCY	METHOD
Step 2				
Step 3				
Step 4				

No intermediates are defined or isolated during the manufacture of the drug product. Control of processing agent nitrogen (including specifications and methods of analysis) is included in Section 3.2.P.3.4.

Three industrial scale batches have been manufactured in the facilities of the proposed manufacturer. The results obtained in the analysis of these batches (see TABLE 8) show that the manufacturing process is reproducible and leads to a product which consistently complies with the specifications established for finished product control.

Moreover, the manufacturing process of industrial batches, at the proposed manufacturing site has been validated. The validation studies conducted (see results enclosed in Section 3.2.P.3.5) confirm the reproducibility of the established manufacturing process and demonstrate its capability to lead to a product consistently fulfilling the quality specifications established both, during product manufacture and final release.

TABLE 8. Teriparatide 20 µg/80µL. Specifications and Batch Analytical Results

PARAMETER	SPECIFICATION	BATCH		
		9941908 Batch size: Manuf. Date: Jun 2016	9941909 Batch size: Manuf. Date: Jun 2016	9941913 Batch size: Manuf. Date: Jun 2016
•				
•				
o				
o				
•				
		mL	mL	mL
		%	%	%
•	%			
•	%	%	%	%
•	%	%	%	%
•	%	%	%	%
		%	%	%

2.3.P.4 EXCIPIENTS

All the excipients used in the manufacturing of the product comply with the specifications stated in the Ph. Eur and/or USP/USP-NF. Tests conducted on each raw material batch follow compendial methods and specifications, fact that ensures the high-quality of these raw materials. As commented in Section 3.2.A. none of the excipients used in the manufacture of the drug product are human or animal origin.

2.3.P.5 CONTROL OF DRUG PRODUCT

The specifications established for the control of finished product (see TABLE 8) have been set based on the requirements stated in the ICH Q6A "*Specifications: Test procedures and acceptance criteria for new substances and new drug products: Chemical Substances"*, *the* Ph. Eur. current edition monograph *Parenteral Preparations* and in the USP current edition monograph *Teriparatide Injection.* Results obtained in the analysis of industrial scale batches are provided in TABLE 8. The corresponding certificates of analysis are provided in Section 3.2.P.5.4. The rationale followed for setting the different control parameters are summarized next.

Appearance: The specification has been set according to the general monograph on Parenteral Preparations of the Ph. Eur. Current edition. Product appearance is the same as that of the Reference drug product.

Clarity and degree of opalescence of liquid: The requirements are those stated in the Ph. Eur. current edition, physical and physicochemical method of analysis 2.2.1. Specification has been set considering the appearance of the Reference drug product.

Degree of Coloration of liquid: The requirements are those stated in the Ph. Eur. current edition, physical and physicochemical method of analysis 2.2.2. Specification has been set considering the appearance of the Reference drug product.

Particulate Contamination: Controls for visible and subvisible particulate contamination have been established, as a general requirement for Parenteral Drug Products (monograph Parenteral Preparations of the Ph. Eur. current edition and ICH Q6A). For subvisible particles, the specification has been set according to the current edition of the Ph. Eur. Monograph on Parenteral Preparations, considering the volume of the product.

Identification: It is performed by HPLC by comparison between the chromatograms of the test and reference solutions.

pH: The test is conducted as required in the ICH Q6A, as a specific requirement for parenteral drug products. The acceptance range has been set according to USP current edition monograph Teriparatide Injection.

Extractable volume: The specification has been set to ensure the quantity of product extracted from the cartridge. The control has been set to ensure the nominal volume declared for one cartridge using the test 2.6.17, of the Ph. Eur. current edition.

Assay: The control has been established following the general requirements established in the ICH Q6A for Parenteral drug products. The limit established at shelf life (90 – 105% of the labelled content) corresponds to the limit established in the USP current edition monograph *Teriparatide Injection*. At release, a stricter limit has been established (95-105%), according to the stability profile observed for the drug product.

The method for assay has been validated. Validation studies cover the following parameters: specificity, linearity, range, accuracy, precision, intermediate precision, robustness and the stability of Test and Reference solutions.

Related Substances: The specifications established at shelf-life are the same as those established in the USP current edition monograph Teriparatide Injection. Stricter limits have been set at release, based on the stability profile observed for the drug product during the stability studies.

Although the method used for related substance determination is the same as that described in the USP current edition monograph Teriparatide Injection, it has been validated to confirm its operability in the facilities of the testing laboratory. Validation studies cover the following parameters: specificity, linearity, range, accuracy, precision, limit of detection, limit of quantitation, intermediate precision, and robustness.

Based on the ICH Q3D, a risk assessment was performed to determine the probability of inclusion of elemental impurities in <TERIPARATIDE 20µg/80µL> and to establish the appropriate controls to ensure the quality of the drug product. The assessment examined the sources of elemental impurities and evaluated their potential to transfer elemental impurities into the drug product. The cumulative effect of the material specifications, in combination with adherence to the overall control strategy for <TERIPARATIDE 20µg/80µL> is sufficient to control elemental impurities in the product within safe levels, i.e. below 30% of the PDE values

described in the *ICH Q3D*" Therefore elemental impurity control has not been included in drug product specifications.

Dose Accuracy: The control has been set as a functionality test of the delivery system, as required in the ICH Q6A for Parenteral Drug Products for parenteral formulations packaged in autoinjector cartridges. The specification has been set in order to ensure the quantity of product administered to the patient, following the requirements of the ISO 11608-1.

m-Cresol Content: The control has been established following the requirements of the ICH Q6A for Parenteral Drug Products needing an antimicrobial preservative.

The method for *m*-cresol content has been validated. Validation studies cover the following parameters: specificity, linearity, range, accuracy, precision, intermediate precision, robustness and the stability of Test and Reference solutions.

Endotoxins: The control has been established as required by the general monograph Parenteral Preparations of the Ph. Eur. current edition and the ICH Q6A for Parenteral Drug Products. The limit established (405 EU/µg of drug substance) correspond to that established in the USP current edition monograph Teriparatide Injection (100 EU/mg of drug product), expressed as EU/ µg of drug substance. The method for endotoxins has been validated showing its suitability for its intended use.

Sterility: The specification has been established as required by the general monograph Parenteral Preparations of the Ph. Eur. current edition and the ICH Q6A for Parenteral Drug Products. The test is conducted following the requirements established in the Ph. Eur. Current edition monograph Sterility (2.6.1). The method for sterility has been validated showing its suitability for its intended use.

Integrity test: The specification has been established as required in the CPMP/ICH/367/96 (ICH Q6A) for parenteral formulations packaged in cartridges.

2.3.P.6 REFERENCE STANDARDS OR MATERIALS

Information about the reference standards of teriparatide and *m*-cresol used for analysis of drug product is provided in Section 3.2.P.6.

2.3.P.7 CONTAINER CLOSURE SYSTEM

Primary packaging consists of a type I glass cartridge (mL extractable volume in mL cartridge) compliant with the Ph. Eur. current edition monograph *Glass for Pharmaceutical Use.* The cartridge is closed with a plunger at one end and with a rubber disc and aluminum cap (combiseal) at the other end. Both plunger and combiseal are compliant with the specifications established in the Ph. Eur. current edition monograph on *Rubber Closures for Containers for Aqueous Parenteral Preparations for Powders and for Freeze-Dried Powders* and with the USP current edition monograph <381> *Elastomeric Closures for Injection.* Section 3.2.P.7 includes detailed information about the technical specifications of the materials.

Filled cartridges are assembled into a pen injector, which is a manual device for drug product subcutaneous injection. The device is assembled together with the *Front subassembly*, *Rear subassembly* and the prefilled cartridge. Before product administration a needle should also be assembled to the device. Materials and specifications of the different pen subassemblies are described in Section 3.2.P.7.

2.3.P.8 STABILITY

With the aim of assessing the product stability, accelerated and long-term stability studies have been conducted with drug product, following the rules stated in the *ICH Q1A (R2) Stability testing of new drug substances and drug products.* Moreover, the stability of the drug product to freezing has also been assessed.

Finally, an in-use stability study has been conducted to confirm the period of time of 28 days during which the multidose product can be used whilst retaining quality within the established specifications once the closure system has been breached. Study has been conducted following the recommendations in the *Note for Guidance on In-use Stability Testing of Human Medicinal Products (*CPMP/QWP/2934/99).

2.3.P.8.1. STANDARD STABILITY PROGRAM

The following stability studies were scheduled:

TABLE 9. Stability Studies Schedule

STABILITY STUDIES	TIME POINTS OF ANALYSIS										
	0	1	2	3	6	9	12	18	24	30	36
Long-term 5ºC ± 3ºC	✓			✓	✓	✓	✓	✓	✓	✓	✓
Accelerated Conditions 25ºC ± 2ºC / 60% ± 5% RH	✓	✓	✓	✓	✓						

The batches included in the stability studies are described in TABLE 10. Batches were manufactured according to the same formula and manufacturing process proposed for commercial batches, and in a container closure system that simulates that proposed for marketing

TABLE 10. Batches included in the Stability Studies

BATCH NO.	MANUFACTURING PLACE	MANUFACTURING DATE	BATCH SIZE	BATCH TYPE	ACTIVE SUBSTANCE MANUFACTURER	ACTIVE SUBSTANCE BATCH
9941908		28/06/2016		Industrial Batch (Validation Batch)		9941819
9941909		29/06/2016				9941820
9941913		30/06/2016				9941819 9941820
9941451		31/03/2016		Industrial Batch (Technical Batch)		9941410

Throughout stability, all stability indicating parameters were controlled. The analytical methods applied during the stability studies are the same as those established for drug product control.

The results obtained up to date in the stability studies are summarized below.

ACCELERATED STABILITY STUDY - 25ºC ± 2ºC / 60% RH ± 5% RH

The stability study has already been finished. The results obtained in the analysis of different parameters at different time points are shown in TABLE 11.

Assay and Related Substances experience a significative variation throughout the stability study, which is more evident from 3 months on. No remarkable variations are observed for the remaining parameters throughout the study.

TABLE 11. Teriparatide 20µg/80µL –25ºC±2ºC / 60%±5% RH

TEST	SPECIFICATIONS	TEST FREQUENCY				
		0	1	2	3	6
Batch: 9941908						
•						
•						
o		part				part
o		part				part
		%	%	%	%	%
•	%		%	%	%	%
•	%	%	%	%	%	%
•	%	%	%	%	%	%
•	%	%	%	%	%	%
	%	%	%	%	%	%
Batch: 9941909						
•						
•						
o		part				part
o		part				part
	%	%	%	%	%	%
•	%		%	%	%	%
•	%	%	%	%	%	%
•	%	%	%	%	%	%
•	%	%	%	%	%	%
	%	%	%	%	%	%
I						

TABLE 11. Teriparatide 20µg/80µL –25ºC±2ºC / 60%±5% RH (*Continuation*)

TEST	SPECIFICATIONS	TEST FREQUENCY				
		0	1	2	3	6
Batch: 9941913						
• • o ≥ o ≥	≤	part part				part part
	%	%	%	%	%	%
• • • •	% % % %	 % % %	% % % %	% % % %	% % % %	% % % %
	%	%	%	%	%	%
	µL	µL				
Batch: 9941451						
• • o ≥ o ≥		part part				part part
x						
	%	%	%	%	%	%
• • • •	% % % %	 % % %	% % % %	% % % %	% % % %	% % % %
	%	%	%	%	%	%
l						

nt: Not tested

LONG TERM STABILITY STUDY – 5ºC ± 3 ºC

The stability study is at 30 months of stability for batch 9941451 and at 24 months of stability for batches 9941908, 9941909 and 9941913. The results obtained in the analysis of different parameters at different time points are shown in TABLE 12.

All the parameters studied remain within specifications throughout the study. Assay values experience a slight decrease throughout the study. Accordingly, a slight increment in related substance values is observed throughout the study. In both cases, results obtained up to date remain within the proposed specification.

2.3.P.8.2. FREEZING STABILITY STUDIES

The innovator drug product (Forsteo) label states that the product should not the frozen. Since the composition of Teriparatide 20µg/80µL is the same as that of the innovator product, it was expected that the product would not be stable after freezing and thawing. To confirm that point, samples of drug product stored at 2-8ºC were kept frozen at -20ºC for 2 days and then thawed at room temperature.

The study was conducted with batch 9941451. After being frozen and thawed, cartridges were visually inspected. A white precipitate was observed at the bottom of the cartridge, on top of the plunger stopper. After shaking the cartridge, the solution obtained was not homogeneous.

The results obtained confirm that the product is not physico-chemically stable to freezing.

TABLE 12. Teriparatide 20µg/80µL –2–8 ºC

TEST	SPECIFICATIONS	TEST FREQUENCY								
		0	3	6	9	12	18	24	30	36
Batch: 9941908										
•										
•										
o	≤									
o	≤									
	%	%	%	%	%	%	%	%		
•	%		%	%	%	%	%	%		
•	%	%	%	%	%	%	%	%		
•	%	%	%	%	%	%	%	%		
•	%	%	%	%	%	%	%	%		
	%	%	%	%	%	%	%	%		
								µL		
Batch: 9941909										
•										
•										
o										
o										
	%	%	%	%	%	%	%	%		
•	%		%	%	%	%	%	%		
•	%	%	%	%	%	%	%	%		
•	%	%	%	%	%	%	%	%		
•	%	%	%	%	%	%	%	%		
	%	%	%	%	%	%	%	%		

TABLE 12. Teriparatide 20µg/80µL –2–8 ºC (*Continuation*)

TEST	SPECIFICATIONS	TEST FREQUENCY								
		0	3	6	9	12	18	24	30	36
Batch: 9941913										
•										
•										
o	≤									
o	≤									
	%	%	%	%	%	%	%	%		
•	%		%	%	%	%	%	%		
•	%	%	%	%	%	%	%	%		
•	%	%	%	%	%	%	%	%		
•	%	%	%	%	%	%	%	%		
	%	%	%	%	%	%	%	%		
	µL									
Batch: 9941451										
•										
•										
o	≥									
o	≥									
	%	%	%	%	%	%	%	%	%	
•	%		%	%	%	%	%	%	%	
•	%	%	%	%	%	%	%	%	%	
•	%	%	%	%	%	%	%	%	%	
•	%	%	%	%	%	%	%	%	%	
	%	%	%	%	%	%	%	%	%	
	µL									

nt: Not tested

2.3.P.8.3. IN USE STABILITY STUDIES

Teriparatide 20µg/80µL is a solution for injection in a pre-filled-pen able to dispense 28 daily doses of 80 µL. An in-use stability study was conducted, following the recommendations in the *Note for Guidance on In-use Stability Testing of Human Medicinal Products (*CPMP/QWP/2934/99), to confirm the period of time of 28 days during which the multidose product can be used whilst retaining quality within the established specifications once the closure system has been breached.

The study was designed to simulate the use of the product in usual practice. To assess the product stability, all stability indicating parameters were be controlled throughout the study. The study was conducted with batch 9941908.

TABLE 13 shows the results obtained in the in-use stability study, along with the specifications established during the study. The analytical methods used were the same as those established for drug product control.

The results obtained support the physicochemical and microbiological stability of the solution after first opening for 28 days if stored at 2-8ºC.

TABLE 13. In Use Stability Results

Batch: 9941908 API Batch: 9941819	Batch size: Manufacturing Date: 28/06/2016	Initial Study Date: 07/11/2018

TEST	SPECIFICATIONS	TEST FREQUENCY (DAY)				
		1	8	14	21	28
• • o µm o µm	≤					
		%		%		%
• • • •	% % % %	% % % %		% % % %		% % % %
	%	%		%		%

2.3.P.8.4. STABILITY CONCLUSIONS

The results obtained in the stability studies show that <TERIPARATIDE 20µg/80µL> is a stable drug product when stored under the conditions set in the Long-Term Stability studies. There is no significant variation in any parameter throughout the studies.

However, under accelerated storage conditions, some of the parameters experience a significant variation throughout stability, failing to meet the acceptance criteria at the end of the study.

Following the ICH Q1A *Guideline on Stability Testing: Stability Testing of New Active Substances and Products (CPMP/ICH/2736/99)*, and the ICH Q1E *Note for Guidance on evaluation of stability data (CPMP/ICH/420/02)*, a shelf life of 36 months is proposed for the drug product when stored in a refrigerator.

Moreover, according to results obtained in the freeze-thaw study, product label should include the following statement: Do not freeze.

Chemical, physical and microbiological in-use stability has been demonstrated for 28 days at 2-8°C. *Once opened, the product may be stored for a maximum of 28 days at 2-8 °C. Other in-use storage times and conditions are the responsibility of the user.*

LIST OF TABLES

LIST OF FIGURES