Table 1.2-6. Comparative Drug Product Manufacturing Sites, Epirubicin Hydrochloride Injection 2 mg/mL

DA
Section 3.2.P.3.1 Manufacturer(s)

Table 3.1.P.3.1-1. Site and Responsibilities for Epirubicin Hydrochloride RTU Solution for Injection 2 mg/mL

Site	Responsibility
Actavis Italy S.p.A. Nerviano Plant Viale Pasteur 10 20014 Nerviano (Milan) Italy	Manufacturing Packaging Labelling QC Testing Release Stability testing

A
Section 3.2.P.3.1 Manufacturer(s)

Table 3.2.P.3.1-1 Sites and Responsibilities for Epirubicin Hydrochloride Injection 2mg/mL in Polypropylene Vials

	Name	**Address**
Manufacturing Site of Drug Product	**Pfizer (Perth) Pty Limited**	**15 Brodie Hall Drive** **Technology Park Bentley WA 6102** **AUSTRALIA**
Testing Site		
Packaging Site		
Release Site		
EU Release Site	Pfizer Service Company bvba	Hoge Wei, 10 B-1930 Zaventem BELGIUM

Tipo IA_{IN} B.II.b.1.a). Sostituzione o aggiunta di un sito di fabbricazione per una parte o per la totalità del procedimento di fabbricazione del prodotto finito - Sito di confezionamento secondario

Table 1.2-7. Comparative Drug Product Manufacturing Sites, Epirubicin Hydrochloride Injection 2 mg/mL

DA
Section 3.2.P.3.1 Manufacturer(s)

Table 3.1.P.3.1-1. Site and Responsibilities for Epirubicin Hydrochloride RTU Solution for Injection 2 mg/mL

Site	Responsibility
Actavis Italy S.p.A. Nerviano Plant Viale Pasteur 10 20014 Nerviano (Milan) Italy	Manufacturing Packaging Labelling QC Testing Release Stability testing

A
Section 3.2.P.3.1 Manufacturer(s)

Table 3.2.P.3.1-1 Sites and Responsibilities for Epirubicin Hydrochloride Injection 2mg/mL in Polypropylene Vials

	Name	**Address**
Manufacturing Site of Drug Product	Pfizer (Perth) Pty Limited	**15 Brodie Hall Drive** **Technology Park Bentley WA 6102** **AUSTRALIA**
Testing Site		
Packaging Site		
Release Site		
EU Release Site	Pfizer Service Company bvba	Hoge Wei, 10 B-1930 Zaventem BELGIUM

Tipo IA B.II.b.2.a) Modifiche a livello di importatore, di modalità di rilascio dei lotti e di prove di controllo qualitativo del prodotto finito - Sostituzione o aggiunta di un sito in cui si effettuano il controllo dei lotti/le prove

Table 1.2-8. Comparative Drug Product Manufacturing Sites, Epirubicin Hydrochloride Injection 2 mg/mL

DA
Section 3.2.P.3.1 Manufacturer(s)

Table 3.1.P.3.1-1. Site and Responsibilities for Epirubicin Hydrochloride RTU Solution for Injection 2 mg/mL

Site	Responsibility
Actavis Italy S.p.A. Nerviano Plant Viale Pasteur 10 20014 Nerviano (Milan) Italy	Manufacturing Packaging Labelling QC Testing Release Stability testing

A
Section 3.2.P.3.1 Manufacturer(s)

Table 3.2.P.3.1-1 Sites and Responsibilities for Epirubicin Hydrochloride Injection 2mg/mL in Polypropylene Vials

	Name	**Address**
Manufacturing Site of Drug Product	**Pfizer (Perth) Pty Limited**	**15 Brodie Hall Drive** **Technology Park Bentley WA 6102** **AUSTRALIA**
Testing Site		
Packaging Site		
Release Site		
EU Release Site	Pfizer Service Company bvba	Hoge Wei, 10 B-1930 Zaventem BELGIUM

Tipo IA_{IN} B.II.b.2.c.1. Modifiche a livello di importatore, di modalità di rilascio dei lotti e di prove di controllo qualitativo del prodotto finito - Sostituzione o aggiunta di un fabbricante responsabile dell'importazione e/o del rilascio dei lotti - Esclusi il controllo dei lotti/le prove

Table 1.2-9. Comparative Drug Product Manufacturing Sites, Epirubicin Hydrochloride Injection 2 mg/mL

DA
Section 3.2.P.3.1 Manufacturer(s)

Table 3.1.P.3.1-1. Site and Responsibilities for Epirubicin Hydrochloride RTU Solution for Injection 2 mg/mL

Site	Responsibility
Actavis Italy S.p.A. Nerviano Plant Viale Pasteur 10 20014 Nerviano (Milan) Italy	Manufacturing Packaging Labelling QC Testing Release Stability testing

A
Section 3.2.P.3.1 Manufacturer(s)

Table 3.2.P.3.1-1 Sites and Responsibilities for Epirubicin Hydrochloride Injection 2mg/mL in Polypropylene Vials

	Name	**Address**
Manufacturing Site of Drug Product	Pfizer (Perth) Pty Limited	15 Brodie Hall Drive Technology Park Bentley WA 6102 AUSTRALIA
Testing Site		
Packaging Site		
Release Site		
EU Release Site	**Pfizer Service Company bvba**	**Hoge Wei, 10** **B-1930 Zaventem** **BELGIUM**

Tipo II B.II.b.4.d Modifica della dimensione del lotto (comprese le categorie di dimensione del lotto) del prodotto finito -La modifica riguarda tutte le altre forme farmaceutiche fabbricate secondo procedimenti di fabbricazione complessi

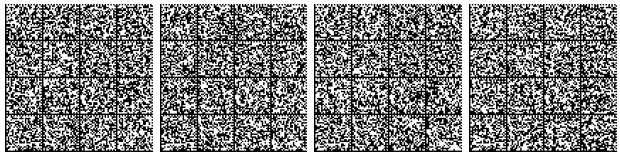
Table 1.2-10. Comparative Batch Sizes, Epirubicin Hydrochloride Injection 2 mg/mL

Current **Section 3.2.P.3.2 Batch Formula**	**Proposed** **Section 3.2.P.3.2 Batch Formula**
The current commercial batch sizes for Epirubicin Hydrochloride RTU solution for injection 2 mg/mL are: • 130 L of solution are equivalent to 130.650 Kg (relative density: 1.005 g/mL) and correspond to 25,000 theoretical vials for Epirubicin Hydrochloride RTU solution for injection 10 mg. 5.20 mL are equivalent to 5.226 g. …. • 200 L of solution are equivalent to 201.0 Kg (relative density: 1.005 g/mL) and correspond to 7,843 theoretical vials for Epirubicin Hydrochloride RTU solution for injection 50 mg. 25.50 mL are equivalent to 25.628 g.	**Minimum (60 L) and maximum (650 L)** batch sizes for commercial production of Epirubicin Hydrochloride Injection 2 mg/mL in polypropylene vials are presented in Table 3.2.P.3.2-1., with an original development stability batch size (50 L) included for reference. As Epirubicin Hydrochloride Injection 2 mg/mL is formulated as a simple aqueous solution, commercial batch sizes may vary within the stated range (**60 L – 650 L**) following appropriate validation studies conducted as per the process validation protocol described in Section 3.2.R.1. …

Tipo IB unforeseen B.II.b.3.z) Modifica nel procedimento di fabbricazione del prodotto finito, compreso un prodotto intermedio utilizzato per la fabbricazione del prodotto finito - Altra variazione

Tipo IA B.II.b.5.b Modifica delle prove in corso di fabbricazione o dei limiti applicati durante la fabbricazione del prodotto finito - Aggiunta di nuove prove e di nuovi limiti

	A **Section 3.2.P.3.4 Controls of Critical Steps and Intermediates**
	Assay
	A **Section 3.2.P.3.4 Controls of Critical Steps and Intermediates**
	Assay of epirubicin hydrochloride in the bulk solution prior to filtration is to be performed by an ultraviolet (UV) absorption spectrophotometric test method. A copy of the UV absorption spectrophotometric test method is provided in Section 3.2.P.3.4.1. **The acceptance criterion of 2.00 – 2.20 mg/mL for epirubicin hydrochloride (100.0 – 110.0% label claim) is identical to the acceptance criterion for assay of epirubicin hydrochloride in the time-of-manufacture (release) specification for the drug product.** ***Chloride*** **The chloride content of the bulk solution prior to filtration is determined by a potentiometric autotitration test method, a copy of which is provided in Section 3.2.P.3.4.1. The acceptance criterion of 145 – 165 mmol/L confirms the required tonicity for the drug product.**



Tipo IA B.II.b.5.c Modifica delle prove in corso di fabbricazione o dei limiti applicati durante la fabbricazione del prodotto finito -Soppressione di una prova in corso di fabbricazione non significativa: Appearance

Tipo IB unforeseen B.II.b.5.z) Modifica delle prove in corso di fabbricazione o dei limiti applicati durante la fabbricazione del prodotto finito – Altra variazione

Table 1.2-9. Comparison between Current and Proposed IPCs Parameters and Acceptance Criteria, Epirubicin Hydrochloride Injection 2 mg/mL

	A
	Fill volume: Within the target limits to achieve the required overfill. Acceptance criteria for the different fill volumes and nominal vial head space volumes are as in the Approval Decree.

Tipo IA B.II.d.1.c Modifica dei parametri di specifica e/o dei limiti del prodotto finito - Aggiunta di un nuovo parametro di specifica alla specifica con il corrispondente metodo di prova

Identification (Chloride); Positive for Chloride; Ph. Eur. / USP <191> (release and shelf-life);

Visual inspection; Complies; PLC-C01173 (release and shelf-life).

Tipo II B.II.e.1.b.2 Modifica del confezionamento primario del prodotto finito - Modifica del tipo di contenitore o aggiunta di un nuovo contenitore - Medicinali sterili e medicinali biologici o immunologici

Table 1.2-11. Comparative Description of Container Closure System, Epirubicin Hydrochloride Injection 2 mg/mL

<table>
<tr><th>DA
Section 3.2.P.7 Container Closure System</th><th>A
Section 3.2.P.7 Container Closure System</th></tr>
<tr><td>Container description

Vials

The product is contained in colourless glass vials, Type I.

....

Rubber stoppers

Teflon-faced gray chlorobutyl rubber stoppers.
The rubber stoppers are the same for Epirubicin Hydrochloride RTU solution for injection 2 mg/mL.

....

Snap-caps

The snap-caps consist of an aluminum seal with an inset polypropylene disk.
The snap-caps are the same for Epirubicin Hydrochloride RTU solution for injection 2 mg/mL.</td><td>Epirubicin Hydrochloride Injection 2mg/mL is packaged as outlined in Table 3.2.P.7.1-1. The vials are packed into cartons with the prescribing information enclosed.

Table 3.2.P.7.1-1. Packaging Description for Epirubicin Hydrochloride Injection 2 mg/mL in Polypropylene Vials
<table>
<tr><th>Strength</th><th>Count</th><th>Description</th></tr>
<tr><td>10 mg in 5 mL</td><td>1 vial</td><td>5 mL medical-grade polypropylene vial closed with a siliconised, halobutyl rubber stopper (FluroTec® Plus-faced) and sealed with a plain aluminium crimp (or cap) with an opaque, coloured, plastic, flip-off top.</td></tr>
<tr><td>20 mg in 10 mL</td><td>1 vial</td><td>10 mL medical-grade polypropylene vial closed with a siliconised, halobutyl rubber stopper (FluroTec® Plus-faced) and sealed with a plain aluminium crimp (or cap) with an opaque, coloured, plastic flip-off top.</td></tr>
<tr><td>50 mg in 25 mL</td><td>1 vial</td><td>25 mL medical-grade polypropylene vial closed with a siliconised, halobutyl rubber stopper (FluroTec® Plus-faced) and sealed with a plain aluminium crimp (or cap) with an opaque, coloured, plastic flip-off top.</td></tr>
<tr><td>200 mg in 100 mL</td><td>1 vial</td><td>100 mL medical-grade polypropylene vial closed with a siliconised, halobutyl rubber stopper (FluroTec® Plus-faced) and sealed with a plain aluminium crimp (or cap) with an opaque, coloured, plastic flip-off top.</td></tr>
</table></td></tr>
</table>

Tipo IB B.II.f.1.d Modifica della durata di conservazione o delle condizioni di stoccaggio del prodotto finito - Modifiche delle condizioni di stoccaggio del prodotto finito o del prodotto diluito/ricostituito DA : 2 – 8°C, protected from light A 2 – 8°C

Titolare AIC: Pfizer Limited con sede legale e domicilio in Ramsgate Road - Sandwich, Kent CT13 9NJ (Regno Unito)