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Clinical Evaluation Report

On

Infusion Set

comfort™, comfort™ short, Silhouette®, Silhouette® Paradigm, ACCU-CHEK®, Varisoft, Duo™ infusion tubing

For subcutaneous infusion with 20°-45° degree

Contents

Executive Summary

The Clinical Evaluation Report (CER) presents the data to support safety and performance for comfort™ family infusion sets such as comfort™, comfort™ short, Silhouette®, Silhouette® Paradigm, ACCU-CHEK/TenderLink, Varisoft infusion sets. comfort™ family infusion sets with soft cannula insertion at a 20°- 45° degree insertion angle is designed for a single use subcutaneous drug delivery. The infusion set is designed to be used with an external infusion pump.

The comfort™ family infusion sets and cannula are sterile, non-pyrogenic class IIb medical device per Annex IX, Rule 8 of the EC Council Directive 93/42/EEC of 14 June 1993 [2] and amended by Directive 2007/47/EEC also a class II according to Food and Drug Administration (FDA).

Duo™ infusion tubing only offered for P-cap connector is a sterile class IIa medical device per Annex IX, Rule 8 of the EC Council Directive 93/42/EEC of 14 June 1993 [2] and amended by Directive 2007/47/EEC.

comfort™, comfort™ short, Silhouette®, Silhouette® Paradigm, ACCU-CHEK/TenderLink, Varisoft infusion sets are intended to subcutaneous delivery of medication administered by an external pump for the treatment of Diabetes Mellitus (DM) in adults and children.

The purpose of this CER is to verify the safety and performance of aforementioned infusion sets to ensure that the available clinical data is documented in accordance with current regulatory requirements as required by MEDDEV 2.7.1, Revision 4, June 2016 and to make conclusions in regard to compliance with Essential Requirements 1, 3 and 6 of Directive 93/42/EC as amended. The sufficient clinical evidence included in the CER has been identified through manufacturer generated data such as bench testing as well as through a literature review of available clinical data used for relevant clinical indication combined with a review of state of the art/existing knowledge of similar products.

Verification of safety and performance is supported by the examination of post-market surveillance (PMS) data as well as by the data identified in the risk analysis that has accumulated.

Based on successful review of all data included in the current CER, it can be concluded that comfort™, comfort™ short, Silhouette®, Silhouette® Paradigm, ACCU-CHEK/TenderLink, Varisoft infusion sets, all manufactured by Unomedical A/S are well documented in relation to safety and performance and suitable for use as intended. Consequently, there has not been identified any outstanding risks that will justify the enrollment of patients in a clinical investigation of an investigational medical device and as such, a clinical investigation is not necessary to demonstrate conformity with the requirements concerning the characteristics and performance referred to in the MDD 93/42/EEC and amendments.

Few reports on adverse events and no product recalls related to the subject devices were identified, and With a performance-related complaint ratio of 0.00649631%, this CER concludes that using of comfort™, comfort™ short, Silhouette®, Silhouette® Paradigm, ACCU-CHEK/TenderLink, Varisoft is safe, compliant with state of the art as well as the risk associated with the use of the similar device is acceptable when weighed against the benefits to the patient.

The overall benefit vs. risk ratio for comfort™, comfort™ short, Silhouette®, Silhouette® Paradigm, ACCU-CHEK/TenderLink, Varisoft infusion sets remains favourable.

Based on assessment of all available data in respect of aforementioned infusion sets, it is considered that the subject devices fully complies with the conformity assessment requirements of ER1, ER3 and ER6 as set out in the Medical Device Directive 93/42/EEC as amended by 2007/47/EC [2].

1. Scope of this Clinical Evaluation Report

The Clinical Evaluation is performed to evaluate and verify the suitability of the subject device for its intended use as well as its clinical safety, thus fulfilling the essential requirements (ER) for CE-marking (MDD 93/42/EEC Annex I, points 1., 3., and 6) and / or the requirements for registration and marketing in countries outside the EU (e.g. as Canadian MDR).

The Clinical Evaluation is performed according to the guidelines for medical devices provided by the European Commission, MEDDEV 2.7.1 rev 4 [1] and Clinical evaluation: a guide for manufacturers and notified bodies.

This CER will assess and critically analyze following:

- A compilation of all manufacturer generated data and ancillary documentation (e.g. product claim sheets, Instructions for Use (IFU), labels, risk management documentation etc).
- A critical evaluation and an analysis of PMS data from 2011 to the data lock point 2018.
- A comprehensive review of relevant scientific literature, published between January 2007- September 2017.
- All data is assessed and critically analyzed in the context of the risk analysis of comfort™, comfort™ short, Silhouette®, Silhouette® Paradigm, ACCU-CHEK/TenderLink, Varisoft infusion sets, and a conclusion regarding the resulting risk-benefit is drawn.
- The purpose of this clinical evaluation is to identify aspects that need to be addressed during PMS, e.g. in post market clinical follow-up (PMCF). This include estimation of residual risks and uncertainties or unanswered questions (such as rare complications, uncertainties regarding long-term performance, safety under wide-spread use).

Statement of Interest.

Author

I do hereby declare, on my honour that, to the best of my knowledge, the only direct or indirect interests in ConvaTec Limited or affiliate, I have currently (at the time of completion of the form) or have had (in the last 3 years) are those listed below.

Date: 21.06.2018

Signed:

Evaluators

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Date:

Signed: _____ _____ _____ _____

Author name Evaluator name Evaluator name Evaluator name

2. General details and device history

This clinical evaluation is an assessment of comfort™, comfort™ short, Silhouette®, Silhouette® Paradigm, ACCU-CHEK/TenderLink, Varisoft infusion sets with soft cannula infusion at a 20°-45° degree insertion angle. In this CER, this group of infusion sets will be named “comfort™ infusions set product family”.

Infusion sets with an angled insertion and a soft catheter have been on the market for more than 20 years. Unomedical introduced the first 20°-45° degree angled soft cannula infusion set comfort infusion set in 1994, followed by comfort short infusion set in 2003 – In between comfort ™ and comfort ™ short infusion sets, the branded infusion sets, TenderLInk and Silhouette where also launched.

The devices under evaluation are used only for Diabetes mellitus (DM) patients.

3. Characteristics of the device

comfort™ family infusion sets are designed as being functional infusion sets enabling safe and easy 20-45 degree angled insertion and used for continued drug delivery. The aforementioned infusion sets are designed to be used with an external infusion pump with a maximum usage time of 72 hours.

- All infusion sets connect to a pump's reservoir and lock into place to avoid leaks. Most pumps use standard Luer-lock connections, which means they work with any Luer lock–capable infusion set and that's most of them. Some pumps, however, use a different type of connector. comfort™ infusion set (Figure 1) is the original product initially launched by Unomedical. comfort™ infusion set was the first insulin pump infusion set that combined angled insertion with at-site disconnection; however today is also distributed under separate brand names. And with only moderate changes, by redesigning the cannula housing the visible needle is shortened and a shorter needle version of comfort™ has been launched and is today also branded as Silhouette® and Accu-chek/TenderLink (figure 2). Silhouette® with Luer Lock and Silhouette® paradigm (figure 3) infusion set with P-cap connector offered for Medtronic insulin pump. Accu-Chek TenderLink is offered with microdosage insulin pumps and is manufactured by Roche Diabetes Care.
  Varisoft infusion set with T-Cap connector offered for specific Tandem insulin pump (figure 4). ACCU-Chek/TenderLink, Silhouette® with Luer Lock, Silhouette® paradigm and Varisoft are available in 2 versions based on the Comfort™ and Comfort™ short.

Figure 1. The same set of comfort™ family infusion sets

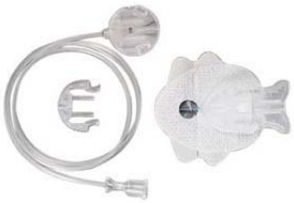


Figure 2. comfort™ short, Silhouette®/ Accu-chek TenderLink

Figure 3. Silhouette®paradigm infusion set with P-cap

Figure 4. Varisoft infusion set with t:lock

3.1. Components

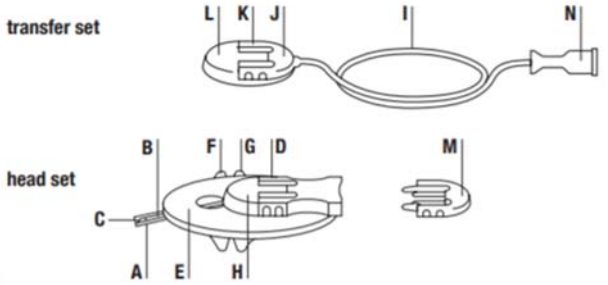
comfort™ infusion set product family consists of a cannula housing, with at pre-attached adhesive tape, a cannula (25-gauge 13mm or 17mm in length), and an introducer needle (27G stainless steel) and a introducer needle hub, this making up the adjustable angled insertion part – individualizing the insertion angle and depth.

The tubing part of the infusion set is secured by a connector and connector needle, which before use is protected by a separate cannula housing. By removing the separate cannula housing the tubing can be connected to the infusion set part and access to the external pump is secured. comfort™ infusion set product family is available in 4 tubing lengths (30, 60, 80 and 110) and two needle lengths (13 and 17 mm).

As the infusion set part (cannula) and the tubing part are delivered in the sterile packaging as two separate parts. comfort™, comfort™ short, Accuchek/TenderLink, Silhouette infusion sets are also available in a "cannula only" version.

Silhouette paradigm is available in "cannula only" and "tubing only/ Duo™ infusion tubing" version. Duo™ infusion tubing with P-cap connector is also in 30, 60, 80 and 110 lengths.

Figure 5. Illustration of components of aforementioned devices



Package 1 (complete set):
- **A** protective cover
- **B** soft cannula
- **C** introducer needle
- **D** side clips of the introducer needle
- **E** self-adhesive
- **F** front half of the adhesive backing
- **G** back side of the adhesive backing
- **H** cannula housing
- **I** tubing
- **J** connector with connector needle
- **K** side clips of the connector
- **L** circular protective cap
- **M** disconnect cover
- **N** luer-lock

The table 1 presents the raw material of comfort™ infusion set product family components, which have different contact with either the patient or the user. Materials in contact with skin/tissue/drug for up to maximum 72 hours are known materials.

Table 1: Materials of construction and material compliance of comfort™ product family

Component	Material
Needle protector	Polypropylene
Introducer needle	Stainless steel (AISI 304)
Catheter	Polytetrafluoroethylene (PTFE)
Adhesive tape	Non-woven polyester
Cannula housing	Polypropylene
Introducer needle hub	Polypropylene
Catheter bushing	Polycarbonate, white
Injection port	Silicone
Segment	Polyoxymethylen (POM)
Connector needle	Stainless steel
Connector	Meta-Acrylonitrile Butadiene Styrene
Tubing	Inner: Polyethylene
	Outer: Polyurethane
Glue	UV-cured Glue
Standard Luer Lock	Meta-Acrylonitrile Butadiene Styrene

comfort™ and comfort™ short infusion set is also delivered to costumer with and external insulin pump with a proprietary tubing connection.

As a consequence of this tubing part of the Silhouette infusion set is with a proprietary connection at the tubing end and also a redesigned introducer needle in the infusion set part.

The connector hub at end of the tubing part is a 3 part component made up by a needle (AISI 304, a membrane (PFTE) and the pump connector – also referred to as a P-cap.

The introducer needle hub has been redesigned with two holes, that fits into a reusable insertion device (called the Sil serter) for the Silhouette infusion set fits with the introducer needle protector part of the infusion set

(Picture 6). The redesigned introducer needle of the infusion set part allows the user to choose between manual insertion or insertion with the aid of a reusable insertion device (n manufactured by Medtronic).

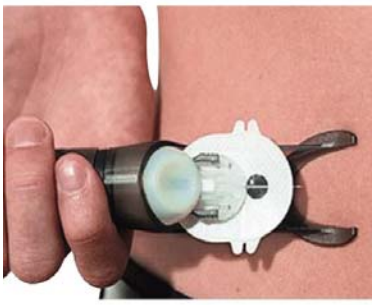


Figure 6: MiniMed Sil-serter

3.1.1. Characteristics

The table 2 presents technical characteristics of comfort™ infusion set product family infusion sets.

Table 2: Characteristics of devices under evaluation

Subject	Definition
comfort™ infusion set product family	A sterile, non-pyrogenic, single use continuous subcutaneous infusion sets with soft cannula insertion at a 20°- 45° insertion angle. Mechanical connection for delivery of medication from an external pump to an infusion set.

3.1.2. Mode of action

The purpose of an infusion set is to constantly deliver the drug in the subcutaneous tissues under the skin. The user (patient and the caregiver or HCP) inserts the infusion set in a site as recommended by the healthcare professional. The user peels off the paper protecting the adhesive pad and carefully inserts the needle beneath the skin. The introducer needle is pushed (inserted) into the subcutaneous tissue below the skin taking the cannula with it. The introducer needle is necessary to puncture the skin to insert the infusion set. After insertion, the introducer needle is removed immediately after. The adhesive tape holds the Soft cannula and the cannula housing securely in place onto the body.

The user must fill a reservoir with the drug according to the pump manufactures instruction. The tubing will be filled/primed with the drug. The connection and lock is with the Connector and the fluid path is established with the needle (through the septum). The pump is ready to infuse the drug through the tubing and the Soft cannula into the patient's subcutaneous tissue.

Directions for use (Figure 7) [6-9]:

A) Inserting the infusion set:

- Wash your hands before inserting infusion sets.
- Use an insertion site as recommended by your healthcare professional. The choice of site depends on treatment and patient specific factors. Check that the insertion site is free of skin irritation such as redness, scar tissue etc.
- Clean the area for insertion with a disinfectant as directed by your healthcare team. Be sure the area is dry before inserting the product. If needed, remove hair around the insertion site to ensure proper attachment of the adhesive tape to the skin.
- Remove the front part of adhesive backing paper and protective needle cover.
- Fold back front edge of self-adhesive.
- Pinch and hold subcutaneous tissue. Insert needle and soft cannula into skin at 20°-45° angle.

- Introducer Needle Removal: Press front half of self-adhesive firmly onto skin to hold self-adhesive in place. Press side clips and pull gently needle out of skin.
- Being careful not to bend the cannula too far forward, remove remaining adhesive backing. Press self-adhesive firmly onto skin.
- Priming: Attach connector to pump. Press side clips of circular protective cap and remove. Prime tubing according to pump's instructions until insulin emerges from connector needle. Do not leave air bubbles in pump cartridge or tubing.
- Connecting With rounded side up, connect tubing to cannula housing. Fill cannula with 0.7 U insulin bolus.
- NOTE: Do not connect tubing to cannula housing before priming.

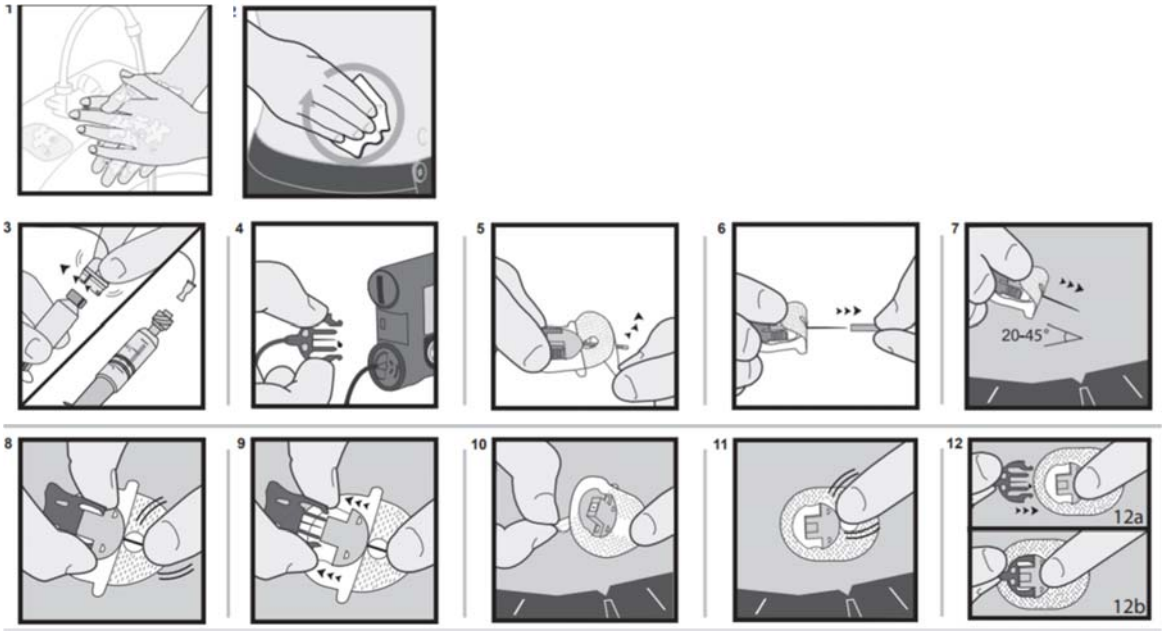


Figure 7: User steps preparation and insertion comfort™ family product IFU [6-9]

3.1.3. Duration of use and body contact

The initial guidelines to change an infusion set every 2-3 days (48-72) were published in 1983 and were based on anecdotal case report. The manufacturer recommends changing infusion sets with soft cannula and infusion sites every 48-72 hours (2-3 days), or per the patients' HCP instructions, in order to avoid skin irritation, infusion sites reaction and other undersides side effects of subcutaneous therapy.

3.2. Intended Use, Indications, Contraindications/Precautions

The subject devices are intended to subcutaneous delivery of insulin administered by an external pump for the treatment of Diabetes Mellitus (DM) in adults and children.

Diabetes Mellitus (DM)

Diabetes mellitus is a metabolic disorder that results in hyperglycemia (high blood glucose levels) due to the body. It is characterised by the body being unable to metabolise glucose (a simple sugar). This leads to high levels of blood glucose which over time may damage the organs of the body.

Contraindications:

The aforementioned infusion sets are not intended for use with blood, blood products or intravenous infusion (I.V.).

Precautions:

- The products are only sterile and non-pyrogenic if the insertion device is unopened and undamaged. Do not use if the insertion device is already open or has been damaged. Ensure sterility by checking if the sterile paper and tamper-proof seal are undamaged.
- Carefully examine the instructions for use before inserting the product. Failure to follow instructions may result in pain or injury.
- When using the product for the first time, do so in the presence of a healthcare provider. Since different individuals have varying amounts of subcutaneous layer, ensure that an appropriate cannula length is chosen to fit your needs.
- If blood is seen in the product, change to a new product and new site.
- Do not in any way bring disinfectants, perfumes, deodorants or other products containing alcohol or disinfectants into contact with the connector or the tubing, as these may affect the integrity of the infusion set.
- The product is a single use device and should be disposed of immediately after use. Do not clean or re-sterilize.
- The product can be disposed of safely after insertion if the lid has been placed back on. Please consult your local pharmacy for sharp containers.
- Be sure that the needle guard is removed before insertion.
- Release the tubing with caution as a hard pull of the tubing can result in damage to the infusion set/introducer needle. Ensure that the infusion set is properly in place when the tubing is fully released.
- Do not position the tubing in the slot prior to loading the infusion set.
- Do not leave air in the infusion set. Make sure to fill the product completely.
- Inaccurate medication delivery, infection and/or site irritation may result from improper insertion or maintenance of your infusion site.
- Change the infusion set after maximum 72 hours in consultation with your healthcare professional. Please also refer to the drug company's instructions for use for recommendations related to usage time for the specific drug.
- If the soft cannula bends during insertion, discard and apply a new product immediately.
- Replace the infusion set if the adhesive tape becomes loose or is displaced from its original site. Since the cannula is soft, it will not cause any pain if it slips out, and this may take place without notice. The soft cannula must always be completely inserted to receive the full amount of medication.
- If your infusion site becomes inflamed, replace infusion set and use new site until the first site has healed.
- Do not re-insert the introducer needle into the infusion set. This could cause a tearing of the soft cannula and unpredictable medication flow.
- Never try to fill or free clogged tubing while the infusion set is inserted. This may result in unpredictable medication flow.
- Consult your healthcare provider on how to compensate for missed medication when disconnected.
- Protect the product from direct sunlight and atmospheric humidity. Store in a dry place at room temperature.
- Never point a loaded insertion device towards any body part, where insertion is not desired.
- Reuse of the product may cause infection, site irritation, or damage to the cannula/ needle. A damaged cannula/needle may lead to inaccurate medication delivery.
- Avoid mechanical stress on the infusion site and on the devices under evaluation.
- Pay attention when carrying heavy weights.
- Prepare the infusion site before insertion according to CDC (Centers for Disease Control and Prevention) guidelines or institutional protocol. •

- Check blood glucose level 1–2 hours after inserting your infusion set and inspect the infusion site on a regular basis.
- When infusing insulin, do not changes the infusion set just prior to bedtime, unless blood glucose can be checked 1-2 hours after insertion.

3.3. Claims

Table 3. Claims for comfort™ family product

Claims	Reference
DM therapy	[5,8,10,11,12]
Skin-friendly adhesive	[22]

3.4. Preclinical tests

3.4.1. Technical tests

The devices have undergone mechanical tests according to EN/ISO standards.

Relevant bench test such as flow test, tensile test and leak test that demonstrate performance of the aforementioned infusion sets was fulfilled on the predicate devices and Silhouette infusion set (table 4, 5) DHF [5].

Table 4. Mechanical test for comfort™ and comfort™ short

Test	Product design verification tests	Internal test criteria
Leak tightness:	The product is designed to withstand a pressure of 4,5 bars in 30 sec. No air bubbles must be observed during the tst period when the Infusion Set is immersed in water.	This set is tested at 3 bars for 30 sec. The set is immersed in water and no air bubbles must be observed.
Flow (occlusion):	Free flow of air must be observed at min. 40 ml/min.	The set is tested at 1 bar and free flow of air bubble observed.
Breaking strength of connection:	Any connections between fluid path components shall withstand a force of no less than 22,5 Newton.	The connections Tubing/Luer Lock and Tubing/Connector must with stand a pull from 1,5kg weight for 15 sec.
Pull test of soft cannula:	The bonding must withstand a force larger than 3 Newton.	-
Pull test of stainless steel needle in tubing connector:	The strength of the bonding must withstand a force larger than 7.5 Newton.	The bonding must min. withstand a pull from a 0.5kg weight for 15 sec.
Pull test of introducer needle:	The strength of the bonding must withstand a force larger than 15 Newton.	-
Transportation test:	The transportation test is to demonstrate that the device remains safe and effective the device has been subjected to a transportation test according to the guidelines in ISTA 2A.	-

Table 5. Mechanical test for Silhouette®

Test	Product design verification tests	Internal test criteria
Leak tightness:	The product is designed to withstand a pressure of 4,5 bars in 30 sec. No air bubbles must be observed during the test periode when the Infusion Set is immersed in water.	This set is tested at 3 bars for 30 sec. The set is immersed in water and no air bubble must be observed.
Flow (occlusion):	The set is tested at 1 bar and free flow at min.40 ml/min is observed.	The set is tested at 1 bar and free flow air bubbles are observed.
Flow test of the p-cap vent membrane:	-	To ensure that the p-cap vent membrane holes are not occluded,

(only relevant for silhouette Paradigm)		the p-cap is flow tested at 0,71 -0,75 psi. The Acceptance criteria : Flow must be grater than or equal to 5 SCCM* (*Square cubic centimetres pr.minute)
Breaking strength of connection:	Any connections between fluid path components shall withstand a force of no less than 22,5 Newton.	The connection between Tubing/Luer Lock is tested must with stand a pull from a 1,5 kg weight for 15 sec.
Pull test of soft cannula:	The bonding must withstand a force larger than 3 Newton.	-
Pull test of stainless steel needle in tubing connector:	The strength of the bonding must withstand a force larger than 7,5 Newton.	The bonding must min. withstand a pull from 0,5 kg weight for 15 sec.
Pull test of introducer needle:	The strength of the bonding must withstand a force larger than 15 Newton.	. -
Transportation test:	The transportation test is to demonstrate that the device remains safe and effective the device has been subjected to a transportation test according to the guidelines in ISTA 2A.	-

The difference between comfort™ infusion set and the Silhouette infusion set is a replacement of connector used with the P-cap connector assembly for the Medtronic pumps. The P-cap is an established component and is included in the various infusion devices i.e. Quick set and Mio™ 30.

The projects introducing T-Cap for Tandem Diabetes Care in already existing Unomedical infusion sets demonstrated performance of the T-Cap connector that replaced the current standard Luer Lock existing in all Unomedical devices. In the Design Verification, all tests performed are related to the T-Cap, the infusion set is not subject for this testing. No changes to the existing concept of the products [5].

The predicate devices fulfill the requirements and expectations demanded by the end-user. Based on the tests performed on predicate devices, it is able to confirm that the devices under evaluation meet the requirements of the EC Directive 94/62/EEC. No additional tests are needed [14].

3.4.2. Biocompatibility

The devices under evaluation have undergone biocompatibility tests according to EN/ISO standards ISO 10993-1:2009. Relevant biocompatibility testing that demonstrates safety of comfort™, comfort™ short, Silhouette®, Silhouette® Paradigm, ACCU-CHEK/TenderLink, Varisoft infusion sets are based on information gathered in the available BRA rapport on previously approved predicate infusion set, comfort™, comfort™ short and summarized in the statements [15].

The adhesive type is the only competent with skin contact. It is therefore classified as surface devices under the category of skin with a contact duration of permanent. These results are categorized in three tests which are Cytotoxicity, Sensitization and Irritation/Intracutaneous (Table 6).

The rest of the components, except for them with no contact defined, are all classified as externally communicating devices under the category of tissue/bone/dentine/communicating, where tissue includes tissue fluid and subcutaneous spaces. The contact duration is classified as permanent. This classification results in testing within several areas, where these areas are Cytotoxicity, Sensitization and Irritation/Intracutaneous. Acute systematic toxicity, Subchronic toxicity, Genotoxicity, and Implantation (Table 6) [15].

Materials which do not have any contact with skin, drug or tissue do not require biocompatibility testing.

Table 6: Overview of device classification

Device Categories	**Biological Effect**

Body contact		Contact duration	Cytotoxicity	Sensitization	Irritation/ Intracotaneous	Acute systematic toxicity	Subchronic toxicity	Genotoxicity	Implansation
Surface device	Skin	Permanent (>30 days)	X	X	X	-	-	-	-
Externally communicating devices	Tissue/ bone/dentin/ communicating		X	X	X	X	X	X	X

Component and contact type:

The names of each of the components are listed in Table 7, and 8 where materials are shown for the different components as well as the type of contact.

Table 7: Biological characteristics of comfort™ family product- cannula set with tubing

Component	Material			
Needle protector	Polypropylene	None	None	None
Introducer needle	Stainless steel (AISI 304)	Yes	None	Yes
Catheter	Polytetrafluoroethylene (PTFE)	Yes	Yes	Yes
Adhesive tape	Non-woven polyester	Yes	None	None
Cannula housing	Polypropylene	Yes	None	None
Introducer needle hub	Polypropylene	None	None	None
Catheter bushing	Polycarbonate, white	None	Yes	None
Injection port	Silicone	None	Yes	None
Segment	Polyoxymethylen (POM)	None	None	None
Connector needle	Stainless steel	None	Yes	None
Connector	Meta-Acrylonitrile Butadiene Styrene	None	None	None
Tubing	Inner: Polyethylene	None	Yes	None
	Outer: Polyurethane	Yes	None	None
Glue	UV-cured Glue	Yes	None	None

Table 8. Biological characteristics of connectors

Component	Material	Skin	Drug	Tissue
Standard Luer Lock	Meta-Acrylonitrile Butadiene Styrene	Yes	Yes	None
T-cap	Methyl methacrylate-acrylonitrile-butadiene-styrene	None	Yes	None
P-Cap Connector	Glycol-modified Polytetrafluoroethylene Terephthalate	None	Yes	None
P-Cap Membrane	Polytetrafluoroethylene	None	None	None
P-Cap Needle	Stainless steel	None	Yes	None
P-Cap Glue	UV-cured glue	None	None	None
P-Cap Connector	Glycol-modified Polytetrafluoroethylene Terephthalate	None	Yes	None

All tests passed successfully.

The testing showed that the relevant parts of infusion set are biocompatible [15].

3.4.3. Drug compatibility test

Drug stability tested with the below listed short acting insulin analog:

- Regular human insulin (Humalog®)
- Aspart (NovoLog®)
- Glulisin (Apidra®)

All tests have been passed successfully [5].

3.4.4. Usability/Human factor testing

In accordance with IEC 62366-1:2015 and the FDA's guidance on human factors, the purpose of the usability study is to evaluate whether the user interface (UI) of the device, including the information for safety (e.g. the Instructions for Use), is safe and effective to use by intended users in intended use environments.

The usability analyze & evaluation, conducted by Unomedical within comfort™ showed that comfort™ infusion set and information to be supplied with the infusion set is found sufficient and easy to understand for the intended users, its intended uses in the intended use environments.

Based on the provided data, product information provided by Unomedical, clinical opinion provided by HCP, it can be concluded that comfort™ product family fulfills the requirements for usability such as an intuitive and unambiguous use, and the design of the user interface has an acceptable, safe usability. Comfort™ product family complies with the Essential Requirements and fulfills the clinical needs and end-user expectations with regard to user-friendliness proficiency, patient safety and technical performance [16].

4. Clinical background, current knowledge, state of the art

4.1. Introduction

In 1926, Prof MacLean, was convinced that "insulin is by far the greatest boon that has ever been discussed on the suffering diabetic patient, for through its proper use he may, in almost every instance, regain a great measure of health and strength [42].

Since, the management of DM focuses on improving glycaemic control by means of lifestyle modification and pharmacological therapy with the aim of reducing risk and progression of microvascular and macrovascular complications [42]. Studies such as the Diabetes Control and Complications Trial (DCCT) in T1DM and the United Kingdom Diabetes Prospective Study (UKPDS) in T2DM have shown that intensive glycaemic control improves patient outcomes especially for complications [42].

Diabetes is a condition in which glucose (sugar) in the blood is too high because the body does not respond to insulin or not enough insulin is made. Insulin is a hormone made by the pancreas, which allows glucose to enter the cells where it is used as fuel by the body. Controlling blood sugar levels is important because levels that are too high or too low can affect the brain and other organs such as cardiovascular and renal systems of the body.

Many people who take insulin find that both use of standards injection (SI) therapy and CSII have inherent drawback. For this reason, many people with diabetes do not take advantage of what insulin therapy can offer [4]. Various literature based evidence indicated that use of infusion sets are a well-known and proven technology and that this technology is safe and effective in treatment of children and adults with T1DM.

4.2. Usage of infusion set in DM

Despite the economic and technological challenges and the complexity of patient training associated with CSII, it is estimated that more than 500 000 patients worldwide are currently being treated with CSII [36]. When applying CSII, the insulin is administered via an infusion set, which is composed of a polymer cannula or steel needle located in the subcutaneous tissue, and which is connected to the insulin container in the pump device by means of a plastic tube. To avoid skin irritation, infusion site reactions and other adverse effects, it is recommended that infusion should not occur for longer than 48 to 72 hours at the same tissue location [36].

The infusion sets differ respectively. Some infusion sets have a steel needle, which is inserted under the skin, and others have a plastic cannula. Plastic cannulas are flexible, to some extent, and may be more comfortable to wear therefore than steel needles. However, cannulas can sometimes kink causing problems with insulin delivery [31]. The needle or cannula commonly varies between about 6 to 9 mm in length. Shorter needle or cannula lengths are more suitable for people with less body fat, larger lengths are more suitable for people with more body fat [4].

Infusion sets can have the cannula facing directly (90 degrees) towards the skin's surface or at an angle (commonly between 10 and 45 degrees) to the skin's surface. Angled infusion sets can be useful for people with less body fat [4].

The infusion sets include also an adhesive tape to keep the infusion set stuck to the skin. Some people may find they are more prone to having the adhesive wear away, typically if the skin gets sweaty or wet, say from showering, sport or hot weather [www.diabetes.co.uk]. The basic requirement for the adhesive patch is to

provide an environment favorable to protect and cover of the injection site to avoid infections and staying firmly in place without causing skin trauma during removal as well as maintaining an optimal moisture balance to maximize the rate of healing. This in turn must be fulfilled in the context of patient comfort by avoiding frequent changes as well as mitigating pain [37, 38, 40].

The manufactures provide the infusion set with a number of different adhesives, e.g. an adhesive that provides a stronger bond with the skin or is for sensitive skin if needed.

The quick disconnection device allows the user to temporarily disconnect the pump and tubing, say for showering, without needing to take out the entire infusion set. Some infusion sets detach but leave a small length of tubing still attached [www.diabetes.co.uk].

Infusion sets are usually changed every 2 or 3 days. If infusion sets are left in longer, there's a higher risk that infections could occur under the skin or occlusions (blockages in the cannula) could occur [www.diabetes.co.uk].

There is also mentioned on different diabetes forums [www.diabetes.co.uk] as well as in the published literature that regularly re-use the same infusion site can lead to the subcutaneous tissue (fatty tissue just under the skin) becoming harder (Lipohypertrophy), which can lead to inconsistent absorption of insulin and could therefore result in unexpectedly high or low blood sugar levels [www.diabetes.co.uk].

Some insulin pumps need particular infusion sets to be used with the pump whereas other pumps are designed to work with a wider range of infusion sets.

4.3. Risk versus benefits for using infusion sets

Specific to usage of infusion sets for drug administration within DM therapy the following risks and benefits has been identified in current literature.

To the risk benefit sections, it is important to mentioned what environmental impact infusion sets have. Since 1980, the potential environmental impact of pharmaceutical device has become (next to safety and efficacy) a major point of consideration in development of new product. The loss or resources with regular continuous subcutaneous infusion therapy is considerably lower than the loss or resources induced by patch pumps.

In literature, the most commonly reported AEs were local skin nodules at the injection site related to the treatment. Some patients develop itching, bruises or pain depending on concentration and infusion time or depth of injection. Development of nodules can be avoided by changing the injection sites frequently. It is recommended to change the infusion set and site every 12 hours [5].

The duration of infusion is individualized which can be more comfortable for the patient and has dramatically improved the patient's quality of life and expanded life [28]. Many patients prefer to perform their infusion during the night, but since this therapy takes time for some patients can give decreased comfort. Furthermore, the subcutaneous route can produce painful skin irritation, but the intravenous route has higher risk of infection or thrombosis of the indwelling central catheter which make the subcutaneous route more safe. However, the increased comfort is high comparing to the aforementioned risk of local side effects.

5. Device under evaluation

5.1. Context of the evaluation and choice of clinical data types

A literature search will be conducted for the period from 2007-2017, with the purpose to investigate data on the performance and safety for devices under evaluation intended for subcutaneous infusion of insulin and based on an existing and well-established technology.

To conduct the present CER of the safety and performance characteristics of devices under evaluation several strategies were chosen. The data used in the present report were based on published scientific literature and clinical data from comfort™ and comfort™ short™ and similar products.

The literature search for current CER has been conducted using PubMed, Medscape, Prospero, Cochrane and ClinicalTrials.gov. For search in PubMed following filter activated: humans, English, published from 01.01.2007 to 01.09.2017. For search in Medscape, Prospero, Cochrane and ClinicalTrials.gov no filter achieved.

The keywords that were utilized for the searches included the following:

1. Diabetes AND infusion set

2. (“infusion set” AND “comfort”) AND safety
3. Infusion set AND insulin AND (contraindication OR “adverse event”)
4. “Infusion set” OR “comfort” AND polyester tape AND skin irritation
5. "comfort” AND "infusion set"
6. "Silhouette" AND "infusion set"
7. "varisoft" AND "infusion set

The information used in the current CER to address safety and performance of subject devices is a collection of both favorable and unfavorable clinical data from published literature and experience of infusion sets. Literature search was performed with use of different databases. For full description of the search strategy, see LSR [Appendix II].

The following clinical data has been evaluated:

- A systematic literature review of PubMed database
- Medscape
- Prospero
- ClinicalTrials.gov
- Cochrane Database of Systematic Reviews
- Regulatory agencies:
  - Medicines and Healthcare products Regulatory Agency (MHRA) database
  - MHRA medical device alerts and field safety notices (FSN): https://www.gov.uk/drug-device-alerts ;
  - Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM) field corrective actions: http://www.bfarm.de/medical_device/field_corrective_actions ;
  - Food and Drug Administration (FDA) Manufacturer and User Facility Device Experience (MAUDE): https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/search.cfm
  - DEAN https://www.tga.gov.au/database-adverse-event-notifications-daen
  - SARA https://apps.tga.gov.au/Prod/sara/arn-entry.aspx
  - MHDP http://www.hc-sc.gc.ca/index-eng.php
- Safety data from clinical experience with Suction Handles and Sets.

5.2. Demonstration of equivalence

A comparison between comfort™ and comfort™ short™, Silhouette®, Silhouette® Paradigm, ACCU-CHEK/TenderLink, Varisoft infusion sets and other available infusion set devices has been made. The equivalent device is identified with equivalent clinical, technical and biological means as defined in MEDDEV guideline 2.7.1 Rev. 4 [1].

Clinical:

Used in same clinical indications and purpose, in the same site in the body, in similar population (including age, anatomy, physiology), and have similar critical performance according to the expected clinical effect for specified intended use.

Technical:

Used under similar conditions of use, similar specifications and properties, similar design, similar deployment methods, sterilization method, materials, critical performance requirements and have similar principles of operation.

Biological:

Use same materials in contact with the same tissue and body fluids.

Conclusion

Equivalent devices may be used to support the safety, performance, and “state of the art” of the subject device when they are used under the same conditions and intended use as the subject device. VariSoft with T-Cap connector, ACCU-CHEK/Tender, Silhouette, with Luer lock connector and Silhouette paradigme® with p-Cap are comparable to Unomedical A/S infusion set: comfort™, comfort™ short, and this comparison has been found relevant in all three aspects [14].

The devices are deemed to be “Equivalent” when they have the same characteristics or the noted variations of characteristics are rationalized to be sufficiently similar with supporting discussion of their clinical impact in relation to each.

The existing differences are not expected to affect the clinical performance and clinical safety of the devices under evaluation. The devices are considered equivalent in regard with their clinical considerations as they are all intended to be used for the similar indications and patient populations, are technically and biologically similar.

6. Summary of the clinical data and appraisal

6.1. Clinical data generated and held by the manufacturer

6.1.1. Sales Data

The resent PMS trends for comfort™ and comfort™ short™ and Silhouette®, Silhouette® Paradigm, ACCU-CHEK/TenderLink, Varisoft from 2011-2018 are included and summarized in table 9.

Table 9. The number of sale

Product	2011	2012	2013	2014	2015	2016	2017	2018 YTD	Total Unit sold
Comfort ™	730,250	696,075	641,985	609,785	631,685	569,640	408,760	251,210	4,539,390
Comfort ™ short	460,110	523,000	485,650	568,995	686,795	623,570	482,830	233,020	4,063,970
Silhouette	677,880	766,550	608,370	615,820	447,180	583,750	478,860	318,900	4,497,310
Silhouette paradigm	9,127,866	9,548,120	8,144,110	7,704,066	8,416,130	8,363,460	9,485,280	3,648,720	64,437,752
Accu-Chek Tender	292,310	178,330	170,494	191,956	143,308	105,260	59,870	20,740	1,162,268
Accu-Chek TenderLink	2,890,384	2,208,270	2,197,270	2,226,700	1,820,290	1,579,084	1,060,330	598,150	14,580,478
VariSoft	NA	NA	NA	NA	NA	NA	279,560	79,880	359,440

Over this review period, at total of 93,640,608 products have been sold.

6.1.2. Complaint databases

Unomedical TrackWise database

The most recent PMS data for predicate and similar devices covered during current search period shows few reportable adverse event incidents (Table 10).

Table 10. Number of complaints for comfort™ family product

Product	Total Unit sold	Complaints received	Ratio	Report	Ratio
Comfort	4,539,390	533	0.0014083	242	0.0006703
Comfort short	4,063,970	447	0.0010013	260	0.0005918
Silhouette	4,497,310	161	0.0003729	87	0.0001911
Silhouette paradigm	64,437,752	6088	0.000857	3427	0.0004981
Accu-Chek Tender	1,162,268	31	0.0007069	22	0.0004936

Accu-Chek TenderLink	14,580,478	100	0.0001111	74	0.0000822
Varisoft	359,440	175	0.00203881	17	0.0014111

During the period 2011 to 2018, 93,640,608 units of subject devices have been sold worldwide. During this time span, Unomedical has received total 7535 product related complaints corresponding to a performance-related complaint ratio 0.00649631%.

The complaints were related to skin irritation/ skin infection/allergy, bent/kinked cannula, leakage and clogged tubing. No complaints related to other biocompatibility issues were reported.

Since low percentage of complaints related to the performance of subject devices were identified, and with a performance-related complaint ratio of 0.00649631%, this CER concludes that comfort™ and comfort™ short™ and Silhouette®, Silhouette® Paradigm, ACCU-CHEK/TenderLink, Varisoft are safe and compliant with state of the art and the overall benefit vs. risk ratio for the device remains favourable.

MAUDE, MHRA, BfArM, DAEN, MHDP data

The United States Food and Drug Association (FDA) publish reports on adverse events (AE) involving medical devices on their website in the Manufacturer and User Facility Device Experience Database (MAUDE). Moreover, the Medicines and Healthcare Products Regulatory Agency (MHRA) in UK also publish reports on adverse events involving medical devices. Likewise, the Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte), - (BfArM) that is an independent federal higher authority within the portfolio of the Federal Ministry of Health has been used. Although MAUDE, MHRA, BfArM, DAEN, MHDP data is not intended to be used either to evaluate rates of AE or to compare AE occurrence rates across devices, the data can be used as a procedure of the type of risks that may be associated with the use of a device type.The data is summarised in LSR.

Review of the MAUDE, BfArM, MHRA, DAEN and MHDP databases on AEs involving the subject devices and similar devices, revealed that more than 92 reports were identified. More than 35 medical device alerts/warning was identified concerning comfort™ and comfort ™ short included in this evaluation.

Full search in safety databased is described in the LSR [Appendix II].

6.1.3. Field corrective actions and other PMS data

A search from Medical Devices Alerts/Warning letters were carried out in the period from January 2011 to June 2018. Manufacturer has identified an increase in reports of the tubing becoming detached at the connect/disconnect location. If tubing detachment occurs, insulin delivery is interrupted and can result in diabetic ketoacidosis (DKA). DKA is a serious condition that can cause a severe impact to health.

Unomedical issued a Field Safety Notice in November 2014 and advising patients to continue to use the infusion sets while following the directions below:

- When changing your infusion set, closely follow the instructions for use included in the product box. Check the tubing at the site connector location to make sure it is not loose.
- Monitor your blood sugar levels frequently using your blood glucose meter. Proactively check your tubing connections occasionally to ensure tubing is secure. It is especially important to check your blood sugar and tubing connections at bedtime to confirm insulin delivery is occurring.
- If you experience high blood sugar, check your tubing connections and infusion site closely to ensure your tubing is secure.

If you discover that the tubing is detached:

- Do not attempt to reattach the tubing. Replace the infusion set immediately.
- Treat any high blood sugar based on guidelines provided by your healthcare professional.
- Call your distributor (see table below) to report the issue and receive instructions on how to return the affected infusion set to the company.
- Call the Medtronic 24-Hour Helpline to report this issue.

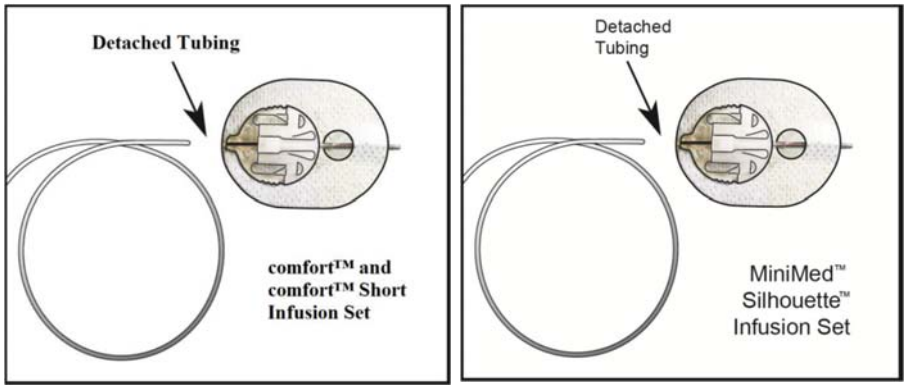


Figure 8. Example of Tubing Detachment

All relevant information is included in the IFU.

6.1.1. Summary of clinical trials conducted by Unomedical

No clinical trials conducted by Unomedical.

6.2. Summary Clinical data from literature

The medical database PubMed was mainly used, since it is the largest database on peer-reviewed medical articles available and found to be adequate for the purpose of this literature search. There has been complemented by search using other databases such as Medscape, Prospero, Cochrane and Clinicaltrials.gov and to support relevant articles that are not available on PubMed.

Only studies in English were included and the data had to be relevant and related to specific characteristics of comfort™ and comfort™ short™, Silhouette®, Silhouette® Paradigm, ACCU-CHEK/TenderLink, Varisoft infusion sets. Furthermore, the literature included use of the device in question and similar devices with respect to clinical, technical and biological characteristics as defined in MEDDEV 2.7.1 rev 4 [1] were included.

References were excluded if similarity in clinical, technical or biological similarity as described in the MEDDEV 2.7.1 rev 4 [1] could not be established. References were also excluded if they were not related with the use in humans.

The data obtained from literature and included in the current CER has been appraised and weighted to determine the suitability to address question comfort™ and comfort™ short™, Silhouette®, Silhouette® Paradigm, ACCU-CHEK/TenderLink, Varisoft infusion and its contribution to demonstrating the safety and performance of the device under evaluation. All publications have been evaluated consistently by the criteria described in LSR.

For this review 52 publications were presumed useful to identify sufficient clinical evidence, 5 articles were appraisal as sufficient to support safety and performance of the aforementioned infusion sets, 19 included in the state of the art section, and a total of 24 of these are referenced [Appendix II].

Articles of level 1 (clinical data of the subject device and/or equivalent device) and 2 clinical data (clinical data of the similar device) has been included, and the available published literature is considered adequate to support the clinical use of comfort™ infusion set product family product due to the long history of use of infusion set for this application.

The datasets demonstrated the overall safety and performance of the subject devices consists of clinical data obtained from published literature on Level 1 and Level 2. One article on Level 1 covering comfort™ and 5 articles on level 2 covering the use of the similar devices in terms of materials, design and clinical indication were identified and critical reviewed and analyzed. Nineteen publications on level 3 that is a collection of data including clinical data, guidance documents and review articles with limiting grading only to be used in state of the art section were included.

The datasets considered being the pivotal dataset or most important to demonstrate the overall safety and performance of the devices under evaluation consists of clinical data from an open-label, case study design,

double-blind cross-over study and cross over study including use of the subject device and non-equivalent infusion sets.

An overall evidence level is assigned to the clinical data (see LSR) based on the equivalence criteria to evaluate its relative contribution to the safety and performance assessment.

6.3. Overall Summary Conclusion of clinical data

Table 11. Summary of performance data

Ref	Purpose	Study Design	Study Objective	Summary of Key Results
Patel *et* al.	To compare steel versus Teflon infusion set (Dupont ™, Quick-Set ™ or Sure-T ™) in people with type T1DM.	A randomized, open-label, single-side, crossover design. 2014	19 (12–45 years old) patients with type 1 diabetes for at least 1 year, who had been using a Medtronic insulin pump for at least 3 months were enrolled in the study.	The outcome of this study showed satisfied efficacy of using the tested infusion sets and concluded that infusion sets are a viable alternative to multiple daily injections. No difference between steel and Teflon infusion sets was found when used for up to 7 days. 15% of Teflon sets failed because of kinking on insertion. The strongest predictor of prolonged 7-day infusion set function was the individual subject, not the type of infusion set.
Bon *et* al.	Comparison of insulin glulisine (GLU) with insulin aspart (ASP) and insulin lispro (LIS) administrated by continuous subcutaneous insulin infusion (CSII) using Medtronic and Roche devices.	An open-label, three-way crossover, controlled multicenter study. 2011	During 39 weeks' study 288 patients were randomized. The outcome measure was unexplained hyperglycemia and/or perceived infusion set occlusion.	Increased duration of infusion sets showed decreased occurrence of unexplained hyperglycemia and occlusion. The results supported that using of the infusion sets is effective as part of the CSII treatment when used as recommended.

DM therapy

Many of DM patients feel they can wear steel infusion sets for longer time than Teflon infusion sets. In order to prepare a systematic study comparing the length of wear using steel compared with Teflon infusion sets the authors of the recent study paralleled different infusion sets [43]. The study by Patel et al [43] showed that 15% of Teflon sets failed on the first day because of kinking that was associated with use of the Teflon infusion sets. The failures were not recognized by the investigator or subject until there was hyperglycemia and/or high-pressure alarms hours later and can be assumed that were secondary to kinking and could be related to performance of the device. The author referred to other recent published research by Højbjerre et al that demonstrating that a steel infusion set would have an advantage over Teflon [43]. However, when comparing the effect of the type of infusion set (steel vs. Teflon) and the effect of the individual subject on infusion set wear, it was the individual ($P = 0.002$) and not the type of infusion set that was most significant in determining infusion set survival [43]. The reason for individually variability is still unknown. Nevertheless, the study limitations included self-management of infusion site induration and erythema by the participant, which could affect duration of infusion set wear and its performance. However, the study investigated only 90°-angled infusion sets, which are similar to the subject devices. Still, the study by von Bon [44] indicated that the majority of the patients change the infusion set at a time interval greater than 2 days whatever the angle of needle. The mean time noted for routine change was 19.7h and the overall change was 19.3h [44].

The prospective study Mecklenburg et al. [46] recorded the types of and frequencies of cannula defects. The most common malfunction was due to occlusion of the infusion set. This was in agreement with other findings, which have shown that insulin delivery failures due to blockage of the indwelling needle/cannula were the most common cause of acute loss of glycemic control. It was suggested that the occlusion of the cannula might be

due to insulin precipitation [46].

The literature findings support the use of infusion sets in patients with diabetes. The infusion sets seem to facilitate optimal glycemic control in both children and adults with DM. In addition to the clinical benefits in terms of glucose control, insulin systems can improve the quality of life for patients with diabetes. The time for changing infusion sets can be individualized with some patients requiring a change every 2-3 days whereas others can change a set less frequently and indicated that the infusion sets perform sufficient. Furthermore, it is considered effective when patients are well trained and educated by the HCP to follow the recommendation in using the infusion sets and know the importance of changing their infusion set and the infusion site regularly after 72 hours of use in order to avoid skin reactions, and to ensure a stable and reliable efficacy of the applied insulin. In order to attain stable glycemic control, insulin absorption, subcutaneous deposit, length of subcutaneous cannula and infusion set site are similar in importance to the dose of insulin delivered.

These results indicate that the commercially available similar to the devices under evaluation perform sufficient when used as intended.

Table 12. Summary of safety data

Ref	Purpose	Study Design	Study Objective	Summary of Key Results
Patel *et* al	To compare steel versus Teflon infusion set (Dupont ™, Quick-Set ™ or Sure-T ™) in people with type T1DM.	A randomized, open-label, single-side, crossover design. 2014	19 (12–45 years old) patients with type 1 diabetes for at least 1 year, who had been using a Medtronic insulin pump for at least 3 months were enrolled in the study.	The outcome of this study showed satisfied efficacy of using the tested infusion sets and concluded that infusion sets are a viable alternative to multiple daily injections. No difference between steel and Teflon infusion sets was found when used for up to 7 days. 15% of Teflon sets failed because of kinking on insertion. The strongest predictor of prolonged 7-day infusion set function was the individual subject, not the type of infusion set.
Bon *et* al	Comparison of insulin glulisine (GLU) with insulin aspart (ASP) and insulin lispro (LIS) administrated by continuous subcutaneous insulin infusion (CSII) using Medtronic devices.	An open-label, three-way crossover, controlled multicenter study. 2011	During 39 weeks' study 288 patients were randomized. The outcome measure was unexplained hyperglycemia and/or perceived infusion set occlusion.	Local reactions at the infusion site were recorded and divided into four categories: infection; inflammation or erythema; pruritus; and pain. In the analysis, the time to change the infusion set influenced unexplained hyperglycemia and occlusion. For every increase of 6h the chances for hyperglycemia and infusion set occlusion decreased by 9%. No significant differences in percentage of patients were demonstrated between GLU versus ASP (P=1.00) and GLU versus LIS (P=0.70) regarding experiencing one or more site infections or site inflammation/erythema or pruritus or isolated pain. No death occurred during the trial. No differences in serious adverse events were reported for the three insulins: GLU, 10.6%; ASP, 6.8% (P=0.157 vs. GLU);

Ref	Purpose	Study Design	Study Objective	Summary of Key Results
				and LIS, P.4.1% (P=0.0038 vs. GLU). The author concluded that increased duration of infusion sets shows decreased occurrence of unexplained hyperglycemia and occlusion. The results showed that using of the infusion sets is safe as part of the CSII treatment.
Conwell *et* al	To describe the dermatological changes associated with continuous subcutaneous insulin infusion (CSII) therapy in youth with T1DM To assess their association with duration of CSII, age, adiposity, HbA1c, insulin dose, insulin brand, infusion set or site.	A cross-sectional study. 2008		50 children younger than18 years that use of CSII for at least 6 months were enrolled in the study. The exclusion criterion was the presence of a pre-existing skin condition affecting the regions used for CSII (e.g., psoriasis, eczema, or panniculitis). Most of infusion sets used during the study was Quick-set from Medtronic, but also Silhouette, Soft-set and Sure-T were used. The most common change was scars < 3 mm diameter with surrounding hyperpigmentation, which were observed in 94% of subjects. Larger scars were observed less frequently (12%). Erythema was observed either as an isolated finding or in association with subcutaneous nodules. In subjects using infusion sets with a non-metal catheter, those inserted at 90° (Medtronic Quickset, Medtronic Softset) were associated with significantly lower total severity scores than those inserted at a smaller angle. In 1 patient, the erythema was clearly in the distribution of the edge of additional tape used to secure the site. Only 4% of parents and 2.4% of the patients reported considering CSII discontinuation because of dermatological concerns.
Pfützner *et* al	To investigate the tolerability of 2-day use of infusion sets in comparison to 4-day use in a real-world setting.	A prospective randomized controlled crossover study. 2015	24 patients with type 1 patients during 2x 3-month observation periods were enrolled. Patients were trained on the use of the infusion set Mio® or inset™ II and randomized to any of the 2 treatment sequences. Observation parameters included treatment and nature of device-related, and procedure-related	The number of infusion set related adverse events was 290 with 2-day use versus 495 with 4-day use (P < .05). The overall treatment satisfaction was higher with 2-day use (very high/high satisfaction) 90.4% versus 4 day-use 77.3% (P < .05).

Ref	Purpose	Study Design	Study Objective	Summary of Key Results
			adverse events and patient preference.	
Pickup *et* al	To report a survey of patients with T1DM who had been treated by CSII for more than 6 months.	A clinic based survey. 2014		Pump, infusion set, and infusion site Problems remain common with CSII, even with contemporary technology.

DM therapy

One of the complications recognized during use of infusion set found in the literature search was kinking [43, 44, 47, 48]. This complication can result in reduction of the medication administration. Moreover, common problem with CSII therapy is the development of unexplained hyperglycemia that resolves with changing the infusion set. What triggers this problem is not clear but unappropriated use of the device can increase glucose level. However, problems are not related to the type of infusion set but only to the unappropriated use of the device [43, 44].

Pickup *et* al. [47] analyzed responses on perceived complications of SCII therapy from 92 patients who have been treated by CSII for more than 6 months, and the mean duration of infusion set use was 3.2 +/- 0.7 days. The commonest problem reported was kinking and the Quick™ Set and Inset™ II infusion set was the common infusion set in use (64.1% of subjects at some time, with 12% of the total number of patients observing frequent kinking). They found the infusion set kinking and blockage were common - about 10 % of patients experience this problem. It is possible that some patients misinterpreted blocking as kinking, and vice versa, because early blockage is often caused by kinking and late blocking by insulin aggregation /precipitation [47].

In general, part of the technical issues with infusion sets is related to the type of needle used. In particular, perpendicularly inserted soft cannulas entail the risk of kinking, bending, or crimping. This may go unnoticed either during the insertion process or during use. To minimize the risk of an incorrect insertion, the authors recommend for Teflon infusion sets use of an insertion devices with integrated inserter [48]. Clinicians report a significant number of failure rates (up to 10%) with autoinserters [48]. If the attachment of the infusion set on the skin shifts laterally (e.g., in case of profound sweating), this can result in an infusion set occlusion [48]. During use, ensuring proper application of the adhesive can reduce the risk of soft cannula kinking and crimping. However, the authors of this review pointed that use of the infusion sets are well-established and safe option [48].

Other complications recognized as failed correction dose, pruritus, pain at the infusion site and adhesive tape issues as well as infection and erythema were reported and described by the authors as common incidents [43, 44]. The adhesives associated problems and strip the superficial layer of the skin when the adhesive is removed can occur during use of infusion set [43]. However, it was not possible to concretize level of injuries as the local reactions at the infusion site and serious adverse events were not described in the article reviewed.

Dermatological complications, specifically Lipohypertrophy and Lipoatrophy, have been associated with subcutaneous insulin injections and use of infusion sets. Dermatological complications may be important to consider because of cosmetic effects but they may also be associated with acute effects, long-term effects on insulin absorption and glycemic control, or both [41, 45].

The study by Conwell et al [45] described dermatological changes and severity of these changes associated with CSII therapy in youth with T1DM using infusion sets as Comfort™, Quick™ Set, Sure-T which all are based on the Unomedical infusion set technology but branded by Medtronic company. The most common change was scars < 3 mm diameter with surrounding hyperpigmentation, which were observed in 94% of participants. Larger scars were observed less frequently (12%) [45]. Furthermore, erythema not associated with nodules and inflammation was also observed. Possible reason of the erythema associated with catheter, adhesive tape, or topical agents was not differentiated in the scoring and is unclear. In only 1 patient, the erythema was clearly in the allocation of the edge of adhesive tape used to secure the site which can be associated with an allergic reaction. However, this is not concluded. Only 4% of parents and 2.4% of the patients reported considering

CSII discontinuation because of dermatological concerns [45]. The author emphasizes that dermatological complications occurred are possibly not associated with use of the infusion sets or the adhesive tape but are rather complications associated with insulin treatment [45].

The prospective, randomized, controlled cross-over study by Pützner *et* al [41]. Investigated the tolerability of 2-days use of Inset™ II in comparison to 4 days use in real-world setting. The results showed that use of the Inset™ II infusion set as recommended by Unomedical A/S manufacture is safe where prolonged use resulted in clinically relevant increase in treatment related tolerability harms and a decrease in treatment efficacy [41]. For use with insulin pumps the predicate device comfort™ is recommended for use of 2-3 days as stated in the IFU at the same tissue location to avoid local skin reactions otherwise tolerability problems can occur [5].

Based on above, it can be concluded that using infusion set is safe when used as intended and recommended by HCP.

7. Risk management

Risk assessments have been formed for the entire product range of soft cannula infusion set inserted in an 90 degree angle in the subcutaneous tissues, to identify the risks associated with the infusion set and how such risk have been addressed. Following these evaluations, all risks were considered acceptable.

A risk analysis on comfort™, comfort™ short™, Silhouette®, Silhouette® Paradigm, ACCU-CHEK/TenderLink and Varisoft has been performed in accordance with Unomedical A/S Risk Management procedure describing process and planning of the risk managing, and the risk management covering devices under evaluation and manufacturing processes in the Unomedical A/S [17].

This risk analysis is a component of the risk analysis process and is used to identify risks of the device. The risk analysis includes aspects associated with the medical procedure for which the device is intended, technical solution adopted, design, process and aspects specific to the use of the particular device. The risk analysis in conjunction with conclusions drawn from the evaluation of pertinent technical characteristics and literature-based clinical data for comfort™, comfort™ short™, Silhouette®, Silhouette® Paradigm, ACCU-CHEK/TenderLink, Varisoft infusion sets have been used to demonstrate compliance with the EN/ISO 14971 – Application of Risk Management to Medical Devices.

No new potential risks were identified in the CER that have not been identified through the bench testing performed on the subject devices and associated with the use of the similar device for its intended purpose. The potential risks identified in the literature includes:

- Insertion issues due to use error
- Lack of adhesion
- Leakage
- Skin irritation
- Lipodystrophy and scar tissue formation
- Infection and inflammation
- Unexplained elevated blood glucose level due to intra patient variation

All identified risks have been found to be well known and at an acceptable level for the use of infusion sets.

The potential risks identified in the risk analysis have been addressed by bench testing and clinical data, and additional means of risk migration and no additional risk reduction activities are required. The potential clinical risks associated with use of the infusion sets identified in the literature are all taken into consideration in the materials for devices under evaluation held by the manufacturer [17].

All identified risks have been found to be well known and at an acceptable level for the use of infusion sets. The potential risks identified in the risk analysis have been addressed by non-clinical tests, available clinical data, and additional means of risk migration and no additional risk reduction activities are required.

During the lifetime of devices under evaluation continuous monitoring of varies elements will be carried out. Elements that will be monitored are following [18]:

- Information from manufacturing, installation and maintenance.
- New or revised standards.
- Failures on competitor devices.

- Previously unrecognized hazard or hazardous situation.
- Risk that is higher than previously estimated or no longer accepted.

Details can be found in the Risk Management File (RMF) for aforementioned infusion sets.

It can be concluded that the residual risks related to devices under evaluation have been mitigated to an acceptable level and the overall residual risk is considered safe for its intended use.

8. Analysis of the clinical data

8.1. Requirement on performance (MDD ER3 / AIMDD ER2)

According to Annex IX, Medical Device Directive 93/42/EEC confirmation of conformity with the requirements concerning the characteristics and performance of class IIb devices can be based on existing clinical data when this can be duly justified [2].

The clinical data underpinning the performance of the subject devices are data based on the device under evaluation and the non-equivalent infusion sets manufactured by Unomedical, and report data to confirm the expected performance characteristics of comfort™ and comfort™ short™, Silhouette®, Silhouette® Paradigm, ACCU-CHEK/TenderLink, Varisoft, in particular with respect to DM treatment.

The data available is considered to support the assessment that devices under evaluation to achieve their intended performances during normal conditions of use and this is supported by sufficient clinical evidence in the context of the overall state of the art and the paucity of clinical data available in this particular field. Therefore, it fulfils the essential requirement on performance (MDD ER3).

8.2. Requirement on safety (MDD ER1 / AIMDD ER*)

Based on the assessment of all the available (manufacturer and scientific literature) data in respect of comfort™ and comfort™ short™, Silhouette®, Silhouette® Paradigm, ACCU-CHEK/TenderLink, Varisoft, it is considered that the subject devices complies with the conformity assessment requirements of ER1, as set out in the Medical Devices Directive (93/42/EC) as amended.

Information supporting the devices, specifically the Instructions for Use (IFU) have been assessed within the context of the available supporting data including bench-top tests as well as the RMR, PMS and complaint data for the period 2011-2018. The IFU and product literature have been reviewed to make sure that product information about contraindications, warnings and precautions have been addressed and described. The proposed IFU and product literature are consistent with the sufficient clinical evidence reviewed in this CER. All relevant clinical information has been incorporated to make sure that patient hazards and other clinical information that may impact the use of comfort™, comfort™ short™, Silhouette®, Silhouette® Paradigm, ACCU-CHEK/TenderLink, and Varisoft are described.

Together, these data are considered sufficient to adequately assess the performance and safety of devices under evaluation and to conclude that the information materials supplied by the manufacturer remain appropriate.

8.3. Requirement on acceptable benefit/risk profile (MDD ER1)

The subject devices are medical devices that are based on existing, well-established infusion set technology and their use during medical procedures have been common for many years. Clinical data described is available to support usage of comfort™, comfort™ short™, Silhouette®, Silhouette® Paradigm, ACCU-CHEK/TenderLink and Varisoft infusion sets used for their intended use.

Based on an assessment of benefit provided within the evidence of risks associated with the device from clinical trial data, it is considered that infusion sets under evaluation has an acceptable benefit-risk profile within the context of its intended use and is consistent with that for similar infusion sets currently used.

It is concluded that comfort™ and comfort™ short™, Silhouette®, Silhouette® Paradigm, ACCU-CHEK/TenderLink, Varisoft infusion sets complies with the conformity assessment requirements of ER 1 in respect of an acceptable benefit-risk profile.

8.4. Requirement on acceptability of side effects (MDD ER6)

Any undesirable side effect must constitute an acceptable risk when weighed against the performances intended.

As set out in the MEDDEV 2.7.1, Revision 4 guidance, a reasonable probability (80%) of observing at least one event of an undesirable side effect at the 1% level would require a minimum of 161 subjects. Based on sales, equivalent to 93,640,608 devices there is a significant side-effect information from PMS data. Using these data, an Adverse Event (AE) frequency, based on PMS information has been calculated to be 4,129 product exposures with performance-related ratio of 0.003927% . All were mild application site reactions.

The combined PMS and available clinical data support conformity with ER6.

9. Post market surveillance

An important step to monitor risks pertaining to a medical device on the market is to capture customer feedback and review this feedback on a regular basis. comfort™ and comfort™ short™, Silhouette®, Silhouette® Paradigm, ACCU-CHEK/TenderLink, VariSoft infusion set is based on well-known infusion set technology and the product family has been on the market for several years with safety records and has been used in clinical application and is well investigated within clinical safety and performance.

Safety or performance issues have been identified with the subject and equivalent devices in the vigilance databases such as FDA Databases MAUDE, BfArM, MHRA, DAEN, SARA, MHDP.

The user feedback included relates to all aspects of the handling, wear and disposal of any kind of Unomedical A/S infusion sets.

Post Market Surveillance Plan

The PMS plan for the device will ensure design reviews to be held as required by regulations and company Standard Operating Procedures (SOP) whereby adverse event reports, customer complaints and any additional internal or externally derived clinical evidence (whether investigative, literature-based or otherwise) will be assessed. The frequency of on-going reviews will be based on risk management principles. The risk assessment will be updated accordingly. If required the CER will also be updated.

Unomedical has an implemented PMS plan [20] ensuring that Unomedical is kept informed about specific user feedback in connection with the usage of infusion sets. Feedback from patients, HCPs and distributors are included in the PMS plan.

The internal procedures for the PMS comfort™ and comfort™ short™, Silhouette®, Silhouette® Paradigm, ACCU-CHEK/TenderLink, VariSoft infusion sets are established through the implemented procedure CS-10777 Post Market Surveillance for Medical Devices. Hereby, Unomedical follows the guidelines stipulated in the MDD 93/42 EEC, Annex IX and amendments, the European Union (EU) NB-MED/2.12/Rec1 guidance document, “Post-Marketing Surveillance (PMS)” and as appropriate, the MEDDEV 2.12-2 guidance document, “Guidelines on Post-Market Clinical Follow-Up”.

Post Market Clinical Follow up

PMCF activities on comfort™ and comfort™ short™, Silhouette®, Silhouette® Paradigm, ACCU-CHEK/TenderLink, Varisoft infusion sets are not required, as it is recognized that the infusion set in general has an acceptable level of risk associated with their use and the clinical evidence presented showed that subject devices complies with the conformity assessment requirements of ER1, 3 and 6. Consequently, there has not been identified any outstanding risks that will justify the enrollment of patients in a clinical investigation of an investigational medical device and as such, a clinical investigation is not necessary to demonstrate conformity with the requirements concerning the characteristics and performance referred to in the MDD 93/42/EEC and amendments.

10. Conclusions

This clinical evaluation addresses comfort™ and comfort™ short™, Silhouette®, Silhouette® Paradigm, ACCU-CHEK/TenderLink, Varisoft infusion sets. This report demonstrates ongoing support for the safety and performance of subject devices verified by bench testing performed and held by the manufacturer prior to this evaluation as well as clinical data obtained from literature review and PMS data giving sufficient clinical evidence. The use of infusion sets is still a well-established and considered state of the art for medical procedures. State-of-the-art in the intended indication DM therapy, as set out in this document, indicates that use of an infusion set is important and have shown a clinical benefit in terms of performance and safety, comfort™ and comfort™ short™, Silhouette®, Silhouette® Paradigm, ACCU-CHEK/TenderLink, VariSoft are considered to be fully consistent with state of the art.

No new or unknown patient risk connected with the use of infusion sets have been reported during this evaluation.

11. Date of the next clinical evaluation

The clinical evaluation should be updated according to the interval for clinical evaluation review as defined.

The risk class for medical devices according to MDD 93/42/EEC has been chosen as the criterion to determine the frequency for regular reviews of clinical evaluations. As a class IIb medical device the regular revision for comfort™ and comfort™ short™, Silhouette®, Silhouette® Paradigm, ACCU-CHEK/TenderLink, Varisoft infusion sets should be performed annually.

However, in order to fully demonstrate conformity with the requirements concerning the performance referred to in the MDD 93/42/EEC and amendments the next revision will be performed when PMCF data are available.

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49. Appendix I: Literature search report
50. Appendixe II: CV for responsible person writing the report
51. CV's for Evaluators

Useful manufacture websites

https://www.diabetes.co.uk/

https://www.tandemdiabetes.com/products/infusion-sets/tlock-connector

https://www.diabetesdaily.com/blog/tandem-launches-tlock-connector-for-pump-cartridges-and-infusion-sets-479830/

https://www.medtronicdiabetes.com/download-library

Abbreviations

Item	Description
AE	Adverse Event
BfArM	Das Bundesinstitut für Arzneimittel und Medizinprodukte
BRA	Biological Risk Assessment
Clinical Data	Clinical data are sourced from: - Clinical investigation(s) of the MD concerned; or - Clinical investigation(s) or other studies reported in the scientific literature, of a similar MD for which equivalence to the MD in question can be demonstrated; or - Published and/or unpublished reports on other clinical experience of either the MD in question or a similar MD for which equivalence to the MD in question can be demonstrated.
Clinical Evaluation	A methodologically sound ongoing procedure to collect, appraise and analyze clinical data pertaining to a MD and to evaluate whether there is sufficient clinical evidence to confirm compliance with relevant ER for safety and performance when using the MD according to the manufactures instructions for use.
Clinical Evidence	The clinical data and the CER pertaining to a MD
CEP	Clinical Evaluation Plan
CER	Clinical Evaluation Report
CSII	Continuous Subcutaneous Insulin Infusion
DHF	Design History File
DM	Diabetes Mellitus
EO	Ethylene Oxide
ER	Essential Requirements
FDA	U.S. Food and Drug Administration
GCP	Good Clinical Practice
HCP	Healthcare Professional
IFU	Instruction for Use
i.v.	Intravenous
LSR	Literature Search Report
MAUDE	Manufacturer and User Facility Device Experience
MD	Medical Device
MDD	Medical Device Directive
MDR	Medical Device Regulation
MHRA	Medicines and Healthcare Products Regulatory Agency
P-cap	P-cap Connector
PMCF	Post Market Clinical Follow up
PMS	Post Market Surveillance
RMF	Risk Management File
SI	Standard Injection
SOP	Standard Operating Procedure
T1DM	Type 1 Diabetes Mellitus
T-Cap	T-cap Connector
T1DM	Type 1 Diabetes Mellitus

Version History

Change Control			
Rev.	**Date**	**Author Name**	**Change Description**
1.0	21.06.2018	Anna Tomanek Christensen	Set up a new document in accordance with MEDDEV2.7.1 revision 4

13. Appendix I:

Equivalence matrix from R&D

14. Appendix II:

Literature Search Report

(LSR)

1. Background and scope

This literature search report (LSR) is performed based on a template set out in MEDDEV 2.7.1, Revision 4 of June 2016, to support Essential Requirements 1, 3 and 6 of Directive 93/42/EC (updated by 2007/47/EC) along with device claims made in the respective Design History File (DHF) [1]. Furthermore, the objective of this literature review is updating the current knowledge regarding infusion sets.

2. Identification of data

The databases presented in table 1 were searched for scientific information. The medical database PubMed was mainly used, since it is the largest database on peer-reviewed medical articles available and found to be adequate for the purpose of this literature search. There has been complemented by search using other scientific and clinical journals and articles and systematic reviews for health care databases such as Medscape, Prospero, Cochrane and ClinicalTrials.gov to support other relevant articles that are not available on PubMed.

Table 1. Databases used to search for scientific information.

Type of Database	Databases Name	Web address	Country
Medical database (Scientific and clinical journals and articles)	NCBI	http://www.ncbi.nlm.nih.gov/pubmed	N/A
	Medscape	http://www.medscape.com/	
	Prospero	https://www.crd.york.ac.uk/prospero/	
	Cochrane	http://www.cochranelibrary.com	
	Clinical Trials Database	https://clinicaltrials.gov/	
Incident Reports	MAUDE database	www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/search.cfm	US
	BfArM	https:// www.bfarm.de	GR
	FDA	www.fda.gov	US
	MHRA database	http://www.mhra.gov.uk/Publications/Safetywarnings/MedicalDeviceAlerts/index.htm	UK
	DAEN	https://www.tga.gov.au/database-adverse-event-notifications-daen	AU
	SARA	https://apps.tga.gov.au/Prod/sara/arn-entry.aspx	AU
	MHDP (Health Canada)	http://www.hc-sc.gc.ca/index-eng.php	CA

PubMed/MedLine, published by the US National Library of Medicine (NLM)

This database is considered to be the principal online bibliographic citation database of NLM's MEDLARS® system and is used internationally to provide access to more than 5000 titles. The majority of the publications covered in MedLline are scholarly journals; a small number of newspapers, magazines, and newsletters considered useful to identify relevant publications.

Cochrane

The Cochrane Library is a collection of six databases that contain different types of high-quality, independent evidence to inform healthcare decision-making, and a seventh database that provides information about Cochrane groups: Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Methodology Register (CMR), Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment Database (HTA), NHS Economic Evaluation Database (EED), and About The Cochrane Collaboration. Together these databases offer more than 1 million records. The Cochrane Collaboration is a global independent network of 37,000 researchers, professionals, patients, carers, and people interested in health, represented from more than 130 countries. This network produces credible, accessible health information that is free from commercial sponsorship and other conflicts of interest and publishes it in The Cochrane Library.

ClinicalTrial.gov

ClinicalTrial.gov is a registry that provides access to information on publicly and privately supported clinical studies on a wide range of diseases and conditions. Studies listed in the database are conducted in the United States and in 195 countries around the world. The site was created in 1997 and made available to the public in February 2000.

Prospero

PROSPERO includes protocol details for systematic reviews relevant to health and social care, welfare, public health, education, crime, justice, and international development, where there is a health related outcome. Systematic review protocols on PROSPERO can include any type of any study design.

Medscape

Medscape is the online global destination for physicians and healthcare professionals worldwide, offering the latest medical news and expert perspectives and providing access to medical-, essential point-of-care drug and disease information and relevant professional education and CME.

3. Extent of search

The databases were searched using keywords for both the publication titles and the full body of the corresponding abstracts. All relevant studies published since 2007/01/01 were considered for inclusion.

The following search terms (see table 2) were used for the literature search to capture sufficient references to achieve objective of LSR and to document attempts to identify all published literature.

Each of the data sets was appraised and assessed collectively to demonstrate compliance with Essential Requirements 1, 3 and 6. This analysis includes:

- When an evaluation is based on limited data this should be described and justified.
- The adequacy of preclinical (bench-top testing) and clinical testing to verify safety and risks to patients or users will be described.
- The adequacy of clinical data to support benefits to patients and that the device performs as intended (performance claims) will be reviewed.
- Reporting of any gaps in evidence, uncertainties or unanswered questions will be reviewed.
- The adequacy of the product information will be reviewed.
- Consistency and alignment between the CER, the product information and Risk Management Report (RMR) will be discussed.

To maximize search sensitivity and results, no initial limitations were placed with respect to language or publication type.

With respect to the published data, the first step was to assess the titles, abstracts and keywords of the studies to identify relevant matches. In a second step, full text of potentially relevant references was assessed. The

studies selected as relevant in step two will be assessed by reading the entire text (See table 4). Each publication from the search results, at either the first or second round of review, will be either included or excluded. The overall search strategy for identifying relevant publications on the devices under evaluation is presented in table 2 and 2a.

Table 2. Keywords used to limit literature searches.

Extent of search - Keywords	
PubMed	
1.	("diabetes mellitus"[MeSH Terms] OR ("diabetes"[All Fields] AND "mellitus"[All Fields]) OR "diabetes mellitus" "diabetes"[All Fields] OR "diabetes insipidus"[MeSH Terms] OR ("diabetes"[All Fields] AND "insipidus"[A "diabetes insipidus"[All Fields]) AND (infusion[All Fields] AND set[All Fields]) AND (("2007/01 "2017/09/01"[PDAT]) AND "humans"[MeSH Terms]) AND English[lang])
2.	("infusion set"[All Fields] AND "comfort"[All Fields]) AND ("safety"[MeSH Terms] OR "safety"[All Fields]) AND (("2007/01/01"[PDAT] : "2017/09/01"[PDAT]) AND "humans"[MeSH Terms] AND English[lang])
3.	(Infusion[All Fields] AND set[All Fields]) AND ("insulin"[MeSH Terms] OR "insulin"[All Fields]) AND (contraindication[All Fields] OR "adverse event"[All Fields]) AND (("2007/01/01"[PDAT] : "2017/09/01"[PDAT]) AND "humans"[MeSH Terms]) AND English[lang])
4.	"Infusion set"[All Fields] OR "comfort"[All Fields] AND (("polyesters"[MeSH Terms] OR "polyesters"[All Fields] OR "polyester"[All Fields]) AND tape[All Fields]) AND (("skin"[MeSH Terms] OR "skin"[All Fields]) AND irritation[All Fields]) AND (("2007/01/01"[PDAT] : "2017/09/01"[PDAT]) AND "humans"[MeSH Terms] AND English[lang])
5.	"comfort"[All Fields] AND "infusion set"[All Fields] AND (("2007/01/01"[PDAT] : "2017/09/01"[PDAT]) AND "humans"[MeSH Terms] AND English[lang])
6.	"silhouette"[All Fields] AND "infusion set"[All Fields] AND (("2007/01/01"[PDAT] : "2017/09/01"[PDAT]) AND "humans"[MeSH Terms] AND English[lang])
7.	"varisoft"[All Fields] AND "infusion set"[All Fields] AND (("2007/01/01"[PDAT] : "2017/09/01"[PDAT]) AND Humans[Mesh] AND English[lang])
Medscape	
1.	(“infusion set” OR “inset II”) AND safety
2.	“comfort” AND “infusion set”
3.	“silhouette” AND “infusion set”
4.	“varisoft” AND “infusion set”
5.	“accuchek” AND “infusion set”
Prospero	
1.	“comfort”
2.	“silhouette”
3.	“varisoft”
4.	accuchek AND “infusion set”
Cochrane	
1.	(“infusion set” OR “comfort”) AND safety
2.	“comfort”
3.	“silhouette”
4.	“varisoft”
5.	accuchek AND “infusion set”
ClinicalTrials	
1.	“comfort”
2.	“silhouette”
3.	“varisoft”
4.	accuchek AND “infusion set”

Table 2a.

Vigilance	
Maude	**Brand name:** Comfort, comfort short, Silhouette, Silhouette paradigm, ACCUCHEK, varisoft
MHRA	**Brand name:** Comfort, comfort short, Silhouette, Silhouette paradigm, ACCUCHEK, varisoft
FDA	**Brand name:** Comfort, comfort short, Silhouette, Silhouette paradigm, ACCUCHEK, varisoft

Bfarm	**Brand name:** Comfort, comfort short, Silhouette, Silhouette paradigm, ACCUCHEK, varisoft
DAEN	**Brand name:** Comfort, comfort short, Silhouette, Silhouette paradigm, ACCUCHEK, varisoft
SARA	**Brand name:** Comfort, comfort short, Silhouette, Silhouette paradigm, ACCUCHEK, varisoft
MHDP	**Brand name:** Comfort, comfort short, Silhouette, Silhouette paradigm, ACCUCHEK, varisoft

4. Inclusion Criteria

Only studies in English were included and the data had to be relevant and related to specific characteristics of comfort™, comfort™ short, Silhouette®, Silhouette® Paradigm, ACCU-CHEK/Tender, varisoft. Furthermore, the literature included use of the device in question and similar devices with respect to clinical, technical or biological characteristics as defined in MEDDEV 2.7.1 rev 4 were included [1]. The definitions used, were as follows:
Data which met one or more of the following criteria were selected for review:

- Inclusion criterion 1: Relevant population and relevant treatment / device
- Inclusion criterion 2: Relevant treatment, not target population, but can be extrapolated

For the current CER a search period covers from 01.01.2007 to 01.09.2017.

5. Exclusion Criteria

Criteria for exclusion:

- Exclusion code NR: Any identified references (based on title or abstract) that do not relate to either the proposed indications or to the specified devices
- Exclusion code MM: Identified references that contain a mere mention to the subject device, but do not provide any pertinent data to assess performance or safety
- Exclusion code GR: Identified references that contain generic information only (e.g. review articles), and do not contribute further to “state of the art”
- Exclusion code P: Identified references, which are protocols for studies and do not provide evidence to assess performance or safety
- Exclusion D: Duplicates

6. Search results

The literature search results are presented in table 3 that provides details of the database searches and the numbers of results returned, specifically reported are:

- The date the search was conducted and/or the date cut-off filters were applied
- The database search and number that indicates the database searched and the numerical identifier attached to the search
- The search term used with any applied filters
- The number of references identified by the search
- The total and selected number of references

Table 3. Results from literature search

7. Literature Appraisal

Databases	Search no.	Search word.	Total identified references	Criteria for exclusion	Useful Articles with procedure
Pubmed	1.	Diabetes AND infusion set	23	NR, MM, P	15
	2.	("infusion set" AND "comfort") AND safety	13	D	0
	3.	Infusion set AND insulin AND (contraindication OR "adverse event")	5	D, NR	2
	4.	"Infusion set" OR "comfort" AND polyester tape AND skin irritation	7	-	2
	5.	"comfort" AND "infusion set"	1	-	1
	6.	"silhouette" AND "infusion set"	0	-	0
	7.	"varisoft" AND "infusion set"	0	-	0
Medscape					
	1.	("infusion set" OR "comfort ") AND safety AND diabetes	12	NR, D, MM	3
	2.	"varisoft" AND "infusion set"	0	-	-
	3.	"Accuchek" AND "infusion set"	0	-	-
		Silhouette AND "infusion set"	0	-	0
Prospero					
	1.	"comfort™"	0	-	0
	2.	"varisoft:30"	0	-	0
	3.	"Accuchek"	0	-	0
	4.	Silhouette AND "infusion set"	0	-	0
Cochrane					
	1.	"comfort™"	11	D, NR	1
	2.	"varisoft:30"	0	-	0
	3.	"Accuchek"	0	-	0
	4.	Silhouette AND "infusion set"	0	-	0
	5.	"comfort™"	0	-	0
ClinicalTrials.gov					
	1.	"comfort™"	0	-	0
	2.	"varisoft:30"	0	MM,NR	0
	3.	"Accuchek"	0	-	0
	4.	Silhouette AND "infusion set"	0	-	0

7.1 Criteria for Appraisal

The identified clinical data will be appraised according to the criteria for suitability and contribution suggested by Global Harmonization Task Force's (GHTF, now IMDRF) Study Group 5 on Clinical Safety/Performance, SG5/N2R8:2007 appendix D devices [2]. The criteria are presented in the tables below.

Table 4. Sample Appraisal Criteria for Suitability and data contribution criteria
Table 4a. Sample Appraisal Criteria for Suitability

Suitability Criteria	Description	Grading system	
Appropriate device	Were the data generated from the device in question?	D1 D2 D3	Actual device Comparable device Other device
Appropriate device application	Was the device used for the same intended use (e.g., methods of deployment, application, etc.)?	A1 A2 A3	Same use Minor deviation Major deviation

Appropriate patient group	Were the data generated from a patient group that is representative of the intended treatment population (e.g., age, sex, etc.) and clinical condition (i.e., disease, including state and severity)?	P1 P2 P3 P4	Applicable Limited Different population (NA: Reserved for bench-top or pre-clinical studies)
Acceptable report/data collation	Do the reports or collations of data contain sufficient information to be able to undertake a rational and objective assessment?	R1 R2 R3	High quality Minor deficiencies Insufficient information

Table 4b. Data contribution criteria
(Grading system used for data contribution criteria was 1 for yes and 2 for no)

Data contribution criteria	Description	Grading system
Data source type (T)	Was the design of the study appropriate?	1 Yes 2 No
Outcome measures (0)	Does the outcome measures reported reflect the intended performance of the device?	1 Yes 2 No
Follow-up (F)	Is the duration of follow-up long enough to assess whether duration of treatment effects and identify complications?	1 Yes 2 No
Statistical significance (S)	Has a statistical analysis of the data been provided and is it appropriate?	1 Yes 2 No
Clinical significance (C)	Was the magnitude of the treatment effects observed clinically significant?	1 Yes 2 No

The sufficient clinical data included in the CER have been appraised and weighted to determine the suitability to address question(s) about the infusion sets, cannula and tubing and the contribution to demonstrate the safety and performance of comfort™ family product infusion set. All clinical data have been appraised consistently using the criteria described in table 4.

Evidence level is defined as following:

- Level 1 contains of clinical data on the device under evaluation and/or equivalent device
- Level 2 includes clinical data on a similar device
- Level 3 is a collection of data including clinical data, guidance documents and review articles on similar device with limiting grading only to be used in state of the art section.

As a general guide, the more level 1 grades, the greater the weight of evidence provided by that particular dataset in comparison to other datasets, however, it is not intended that the relative weightings from each category be added into a total score. For more information about medical device harmonization see www.imdrf.org website since the GHTF website is no longer operational [2].

7.2 Appraisal results

An overall evidence level is assigned to the clinical data (Table 5) based on the equivalence criteria to evaluate its relative contribution to the safety and performance assessment. Level is defined as following:

Table 5: Appraisal results

	Performance (P) and/or safety (S), state of the art		Appraisal criteria for suitability				Appraisal criteria for data contribution					Overall evidence level
Reference	P	S	D	A	G	R	T	O	F	S	C	
Actual device												
Conwell LS. *et* al 2008	-	S	1	1	1	1	1	1	2	1	1	Level 1
Similar device												
Patel PJ. *et* al, 2014	P	S	2	1	1	1	1	1	2	1	1	Level 2
Bon AC. *et* al, 2011	P	S	2	1	1	1	1	1	2	2	1	Level 2
Pickup JC. *et* al, 2014	-	S	2	1	1	1	1	1	2	2	1	Level 2

Pfutzner A. *et* al, 2015	-	S	2	1	1	2	1	1	1	1	1	Level 2
Other similar device with limited grading												
Curley, Ann. 2007	State of the art		2	1	1	2	1	2	2	1	1	Level 3
Engl N. Med J. 1994	State of the art		3	1	1	2	1	2	2	1		Level 3
Levinson Paul D. 2005	State of the art		3	1	1	2	2	1	2	2	2	Level 3
Osterberg Ole. Et al, 2003	State of the art		3	1	1	2	1	2	1	1	1	Level 3
Hanas R. et al, 1990	State of the art		3	1	1	2	1	1	2	1	1	Level 3
Schade David S. 2002	State of the art		2	1	1	2	2	1	2	2	2	Level 3
Agrawal P. et al, 2011	State of the art		3	1	1	2	2	1	2	2	1	Level 3
Gibney M. et al, 2016	State of the art		2	1	1	2	2	1	2	2	1	Level 3
Heinemann L. et al, 2015	State of the art		3	1	1	2	1	2	1	1	1	Level 3
Heinemann L. et al, 2015	State of the art		2	1	1	2	1	1	1	1	2	Level 3
McVey E. et al, 2015	State of the art		3	1	1	2	1	1	1	1	2	Level 3
Pfutzner A. et al, 2011	State of the art		3	1	1	2	2	1	1	1	1	Level 3
Zahid N. et al,2008	State of the art		3	1	1	2	2	1	2	2	1	Level 3
Scheiner G. et al, 2009	State of the art		3	1	1	2	2	1	1	2	2	Level 3
Dumville JC. et al, 2014	State of the art		3	1	1	2	1	1	1	1	1	Level 3
Daecke C. et al, 1993	State of the art		2	1	1	2	1	2	1	1	1	Level 3
Geukens S. et al, 2001	State of the art		3	1	1	2	1	1	2	2	1	Level 3
Stephen-Haynes J. et al, 2014	State of the art		3	1	1	2	1	1	2	2	1	Level 3
Chatterjee S. et al, 2015	State of the art		2	1	1	2	1	2	2	1	1	Level 3

7.3 Appraisal conclusion

For this review 52 publications were presumed useful to identify sufficient clinical evidence, 5 articles were appraisal as sufficient to support safety and performance of the aforementioned infusion sets, 19 included in the state of the art section, and a total of 24 of these are referenced.

The datasets considered being the pivotal dataset or important to demonstrate the overall safety and performance of devices under evaluation consists of clinical data obtained from published literature on Level 1 (the device under evaluation) and 2 (similar device). The literature included with relative contribution to the performance and safety assessment are assigned from the following studies: an open-label, case study design, double-blind cross-over study and cross over study including use of the subject device and non-equivalent infusion sets.

8. Adverse incident reporting

Table 6: Result from search in regulatory body databases on the comfort™, comfort™ short, Silhouette®, Silhouette® Paradigm, ACCU-CHEK/Tender, varisoft. Search period 01-01-2011 to 01-06-2018 for the vigilance database.

Adverse Events/Recall Search	
MAUDE adverse event database (US) – Search period 01.01.2011 –01.06.2018	**Total**
comfort unomedical(advanced search, brand name)	**5**
Death	1

Injury	3
Malfunction	1
Other	0
Comfort short unomedical (advanced search, brand name)	**1**
Death	1
Injury	0
Malfunction	0
Other	0
Silhouette paradigm unomedical (advanced search, brand name)	**26**
Death	14
Injury	10
Malfunction	2
Other	0
AC/ Tender, unomedical (advanced search, brand name, manufacturer)	**5**
Death	3
Injury	1
Malfunction	1
Other	0
Silhouette Minimed (advanced search, brand name)	1
Death	0
Injury	1
Malfunction	0
Other	0
Varisoft Tandem (advanced search, brand name)	0
FDA Recall database (US) - Search period 01.01.2011 – 01.06.2018	
comfort unomedical(advanced search, brand name)	**2**
Death	0
Injury	0
Malfunction	2
Other	0
Comfort short unomedical (advanced search, brand name)	**1**
Death	0
Injury	0
Malfunction	1
Other	0
Silhouette paradigm (advanced search, brand name)	**2**
Death	0
Injury	0
Malfunction	1
Other	1
ACCUCHEK Roche (advanced search, brand name, manufacturer)	**0(3 not relevant)**
Death	0
Injury	0
Malfunction	0
Other	0
Silhouette Minimed (advanced search, brand name)	2
Death	0
Injury	0
Malfunction	0
Other	2
Varisoft Tandem (advanced search, brand name)	0
Bfarm (Germany) - Search period 01.01.2011 - 01.06.2018	
comfort unomedical(advanced search, brand name)	**0(26 not relevant)**
Comfort short unomedical (advanced search, brand name)	**0(4 not relevant)**

Silhouette paradigm (advanced search, brand name)	**0(not relevant)**
ACCUCHEK Roche (advanced search, brand name, manufacturer)	**0**
Silhouette Minimed (advanced search, brand name)	**0(2not relevant)**
varisoft	0
MHRA Alerts and Recalls database (United Kingdom) – Search period 01.01.2011 – 01.06.2018	
comfort unomedical(advanced search, brand name)	**0**
Comfort short unomedical (advanced search, brand name)	**0(8 not relevant)**
Silhouette paradigm (advanced search, brand name)	**0(4 not relevant)**
ACCUCHEK Roche (advanced search, brand name, manufacturer)	**0**
Silhouette Minimed (advanced search, brand name)	**0(2non relevant)**
varisoft	0
DAEN Database of Adverse Event Notifications (Australia) - Search period 01.07.2012 – 03.02.2018 (database goes from 01.07.2012 to 07.06.2017)	
comfort unomedical(advanced search, brand name)	**2**
Death	0
Injury	0
Malfunction	0
Other	2
Comfort short unomedical (advanced search, brand name)	**4**
Death	0
Injury	3
Malfunction	0
Other	1
Silhouette paradigm (advanced search, brand name)	**0**
ACCUCHEK Roche (advanced search, brand name, manufacturer)	**0(2 not relevant)**
Silhouette Minimed (advanced search, brand name)	1
Death	0
Injury	1
Malfunction	0
Other	0
Varisoft Tandem (advanced search, brand name)	0
SARA Recall Actions (Australia) - Search period 01.07.2012 – 02.06.2018(database only goes back to 01.07.2012)	
comfort unomedical(advanced search, brand name)	**0(2 not relevant)**
Comfort short unomedical (advanced search, brand name)	**0**
Silhouette paradigm (advanced search, brand name)	**0**
ACCUCHEK Roche (advanced search, brand name, manufacturer)	**0(2 not relevant)**
Silhouette Minimed (advanced search, brand name)	0
Varisoft Tandem (advanced search, brand name)	0
MHDP (Health Canada) - Search period 01.01.2011 –01.06.2018:	
comfort unomedical(advanced search, brand name)	**More than 10(03/11/2014)**

Manufacturer has identified an increase in reports of the tubing becoming detached at the connect/disconnect location. If tubing detachment occurs, insulin delivery is interrupted and the pump will not alarm to notify patients. The interruption of insulin delivery can cause hyperglycemia, which if left untreated, can result in diabetic ketoacidosis (DKA). DKA is a serious condition that can cause a severe impact to health, including death. Symptoms of DKA may include nausea, vomiting, shortness of breath and excess thirst/urination. Manufacturer is advising patients to seek medical attention immediately if they are experiencing any of these symptoms.	
Comfort short unomedical (advanced search, brand name)	**More than 10(03/11/2014)**
Manufacturer has identified an increase in reports of the tubing becoming detached at the connect/disconnect location. If tubing detachment occurs, insulin delivery is interrupted and the pump will not alarm to notify patients. The interruption of insulin delivery can cause hyperglycemia, which if left untreated, can result in diabetic ketoacidosis (DKA). DKA is a serious condition that can cause a severe impact to health, including death. Symptoms of DKA may include nausea, vomiting, shortness of breath and excess thirst/urination. Manufacturer is advising patients to seek medical attention immediately if they are experiencing any of these symptoms.	
Silhouette paradigm (advanced search, brand name)	**More than 10(11.09.2017) All lots(03/11/2014)**
Medtronic has become aware of recent reports of potential over-delivery of insulin shortly after an infusion set change. The reported incidence rate requiring medical assistance related to this issue is less than 1 in every 2 million infusion sets. Over-delivery of insulin can cause hypoglycemia and in extreme cases, death. Medtronic has received reports of hypoglycemia requiring medical intervention potentially related to this issue. Manufacturer investigation has shown this can be caused by fluid blocking the infusion set membrane during the priming/fill-tubing process. A membrane blocked by fluid may occur if insulin, alcohol, or water is spilled on top of the insulin reservoir, which then could prevent the infusion set from working properly. Infusion sets currently being shipped by Medtronic contain a new and enhanced membrane material that signifcantly reduces this risk.	
ACCUCHEK Roche (advanced search, brand name, manufacturer)	**More than 10(03/11/2014)**
Manufacturer has identified an increase in reports of the tubing becoming detached at the connect/disconnect location. If tubing detachment occurs, insulin delivery is interrupted and the pump will not alarm to notify patients. The interruption of insulin delivery can cause hyperglycemia, which if left untreated, can result in diabetic ketoacidosis (DKA). DKA is a serious condition that can cause a severe impact to health, including death. Symptoms of DKA may include nausea, vomiting, shortness of breath and excess thirst/urination. Manufacturer is advising patients to seek medical attention immediately if they are experiencing any of these symptoms.	
Silhouette Minimed (advanced search, brand name)	**All lots(03/11/2014)**
Manufacturer has identified an increase in reports of the tubing becoming detached at the connect/disconnect location. If tubing detachment occurs, insulin delivery is interrupted and the pump will not alarm to notify patients. The interruption of insulin delivery can cause hyperglycemia, which if left untreated, can result in diabetic ketoacidosis (DKA). DKA is a serious condition that can cause a severe impact to health, including death. Symptoms of DKA may include nausea, vomiting, shortness of breath and excess thirst/urination. Manufacturer is advising patients to seek medical attention immediately if they are experiencing any of these symptoms.	
Varisoft Tandem (advanced search, brand name)	0

A total more than 92 complaints from the regulatory bodies have been reported for the infusion set devices and this data set represents 19 injuries, 19 deaths, 10 malfunctions and 4 other reasons during the search period. Complaints reported included comfort™ and comfort ™ short. Based on the investigation and test results the failure reported in the regulatory bodies cannot be confirmed as failures caused the infusion sets.

9. References

1. MEDDEV guideline 2.7.1, rev 4, 2016. Guidelines on medical devices. Clinical Evaluation: a guide for manufacturers and notified bodies.
2. Global Harmonization Task Force. www.imdrf.org

15. Appendix III:

CV for responsible person writing the report

A brief summary is provided that describes the expertise and suitability of the author of this report.

Anna Tomanek Christensen,

Registered Nurse (RN), Master of education Ma (Ed), Graduate Diploma in Business Administration (HD).

Anna Tomanek Christensen (ATC) has a bachelor's degree in Nursing (2000) and a Master's in Education from Aarhus University in Denmark (2009). Besides, she has supplied her education with a diploma in Business Administration In 2015.

She has years of practice as a nurse from different departments at the Danish University Hospital – Rigshospitalet. She has sufficient knowledge of metabolic diseases such as Diabetes Mellitus and infusion therapy. She has worked with physicians for metabolic diseases procedures requiring infusion therapy and use of infusion set in Pediatric (RH 4053 and 5062 departments), Gastroenterology (RH 3123 and 3124 departments), Diabetes (Department of Dermatology and Wound Healing Centre at Bispebjerg) and with Interdisciplinary Team for Palliative Care at Home Care Setting. Consecutively, she has clinical experience with diagnosis and management of conditions required infusion by infusion sets as well as treatment standards in the aforementioned clinical areas.

Through her Master-level education and research projects for Coloplast and the European Wound Management Association (EWMA), Hollister and Jacobsen Pharma and MedTech Advice, she obtained knowledge with research methodology such as clinical investigation design, scientific projects with use of medical devices as well as a librarianship qualification (e.g. experience with relevant databases as Pubmed, Medline and Embase) and many years of medical writing. Since, she has extended her knowledge with relevant courses within the medical and regulatory fields, e.g. a librarianship qualification course from Aarhus University on EndNote reference management and several clinical evaluation courses conducted by the Medico Industry.

Anna Tomanek Christensen established the medical writing consultancy AML Christensen in 2014 to help medical device companies comply with European Regulation, and the company consisting of 5 employees supports clients by offering medical writing services. Within the company, she cooperates with various sub-contractors in Clinical Operations (ClinOps), Regulatory Affairs (RegAff), Scientific Affairs (SciAff) and Quality Assurance (QA). Since a new guidelines MEDDEV 2.7/1 ver. 4 was released to the European marked in 2016 Anna Tomanek Christen has performed more than 40 CERs (class IIa, IIb and III) of which many are already approved by the NBs. All documents produced by the AML Christensen company undergo an internal quality review to ensure sufficient compliance within all relevant bodies.

Through her Master-level education, training and many years of professional experience with relevant clinical areas, Anna is suitably qualified to prepare clinical evaluations for medical device companies, including Unomedical A/S.

16. Appendix IV:

CV`s for Evaluators