smiths medical
bringing technology to life

Clinical Evaluation Report

Graseby MS Syringe Drivers

(Infusion Systems)

(CER 006/040 Rev 001)

January, 2013

Smiths Medical

Signature Page

Jordan Greenberg, PhD Manager, Clinical Marketing and Scientific Affairs Smiths Medical ASD St. Paul, MN	Signature: Code A	Date: 14-Jan-2013
Jim Johnson Sr. Regulatory Affairs Specialist Smiths Medical ASD St. Paul, MN	Signature: Code A	Date: 11 JAN 2013
Kulwant Kaur Clinical Marketing and Scientific Affairs Smiths Medical ASD St. Paul, MN	Signature: Code A	Date: 14-Jan-2013

This Clinical Evaluation Report has been completed in reference to MEDDEV 2.7.1, "Guidelines on Medical Devices, Evaluation of Clinical Data: A Guide for Manufacturers and Notified Bodies" and the Medical Devices Directive 93/42/EEC as amended by Directive 2007/47/EC. Although legally not binding, this document reflects position taken by representatives of interested parties in the medical industry community.

Table of Contents

1. Summary of the Clinical Evaluation

1.1 Objectives

Review and revision, as appropriate, of existing clinical evaluations to satisfy the clinical data requirements of the Medical Device Directive 93/42/EEC as amended by Directive 2007/47/EC.

This clinical evaluation will identify and assess the relevance and weighting to be attached to the available clinical data, whether favorable or unfavorable, from a number of sources and critically evaluate the clinical data in relation to the Graseby® MS Syringe Drivers, in order to:

- Verify the performance of the devices is in accordance with the claimed intended purpose(s) under normal conditions of use
- Evaluate the clinical benefits as well as the risks and side effects, and specifically the acceptability of the benefit/risk ratio associated with the intended use of the subject devices
- Evaluate the appropriateness and substantiation of all product claims for the subject devices
- Support demonstration of conformity with relevant "essential requirements" of the Medical Device Directives (as amended) as set out in the appropriate Smiths Medical "Essential Requirements Checklists"
- Identify any significant trend in use or emerging problem(s) apparent from a review of the recent clinical data.

This report should further be used to support the sales of new and continuing ranges of Graseby® MS Syringe Drivers, and to help identify opportunities for new or improved products.

1.2 Scope

The Clinical Evaluation includes all parts of the Smiths Medical Graseby® MS Syringe Drivers (see section 2.1 for the list of parts). Refer to St. Paul technical file TF018 for the list of applicable codes. No products have been excluded from the scope for any reason.

1.3 Conclusion

1.3.1 ***Safety and Performance:***

Graseby® MS Syringe Drivers are safe and perform as intended. The defined objectives of this Clinical Evaluation have been met, and no prospective clinical investigations are required for these devices.

1.3.2 ***Acceptability of the Risk/Benefit Ratio:***

The MS Series Syringe Drivers represent well-established medical devices; the risks of these devices are well established and are acceptable when weighed against the benefits. No new risks have been identified by this Clinical Evaluation.

1.3.3 ***Post-Market Surveillance***

There have been no significant changes for the subject devices since the last CER 001/020 Issue 01.

1.3.4 Published Scientific Literature

Within the current published scientific literature there does not appear to be any trends related to the safety, performance, design characteristics, and intended use of the Graseby® MS Syringe Drivers. The available clinical data reviewed support the conclusions of the Clinical Evaluation Report that the Graseby® MS Syringe Drivers are similar in their performance and intended use as other similar commercially available devices.

1.3.5 Unpublished Reports and Market Experience

Unpublished data from internal sources were reviewed, including complaint files and risk analysis reports. The risks appear to be well established and complaints reported for the subject devices are of an acceptable level with no adverse trends.

2. Products Relating to this Clinical Evaluation

2.1 Scope

This clinical evaluation includes all parts of the Smiths Medical Graseby® MS Series Drivers and accessories. Refer to technical file TF018 for the list of applicable product codes. No products have been excluded from the scope for any reason.

- Graseby® MS Series Drivers and Accessories

2.2 Main Markets

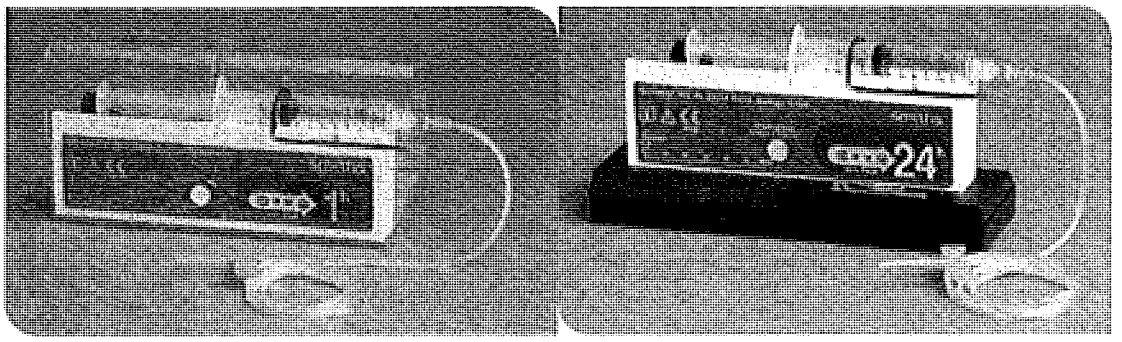
The Graseby® MS Series Drivers and/or accessories are sold in 40 different countries with the largest market being the United Kingdom.

2.3 Description of Device and Intended Use

Smiths Medical Graseby® MS Series Drivers are classified as Class II in Europe, United States, and Class III in Canada. The associated accessories to MS Syringe Drivers are classified as Class I in Australia, Canada, and Europe, as Class II in United States.

The Graseby® MS16A, MS 26 and MS 32 Syringe Drivers ("MS Syringe Drivers") are compact non-sterile devices designed to deliver liquids from syringes with more control and over much longer periods than could be achieved by injecting by hand. The MS Syringe Drivers are battery powered ambulatory devices and utilize screw drive to push the plunger of the installed syringe. The continuous fluid delivered is measured by distance traveled by the plunger.

The Graseby MS 16A, MS 26 and MS 32 Syringe Drivers are provided as packed sets. Each pack contains: syringe driver, clear plastic syringe cover, syringe holster, rate adjuster, instruction manual, and battery (type MN1604). A lightweight and portable Graseby MS Driver Lock Box may be used with all three syringe drivers to minimize the risk of tampering with the infusion. The Lock Box consists of a hard polycarbonate material incorporating clear viewing windows for monitoring the syringe and rate settings and a key lock. The key lock access offers complete control to the authorized clinician. A suitable sterile syringe with a sterile pathway is also required to deliver medication to the patient. The devices are intended for use under medical supervision.



Graseby MS16A MS 26 Syringe Driver

2.3.1 Graseby® Syringe Driver MS 16A

The Graseby® Syringe Driver MS 16A is intended for administration of infusions lasting between 30 minutes and 24 hours. The rate set in millimeters (mm) of syringe plunger movement every hour. The MS 16A is known as the *hourly rate* syringe driver.

2.3.2 Graseby® Syringe Driver MS 26

The Graseby® Syringe Driver MS 26 is for slower infusions, and is intended for administration ranging from periods 1 day and longer. The rate setting is in milliliters (mm) of syringe plunger movement every 24 hours. The MS 26 is known as the *daily rate* syringe driver. At the slowest setting, the MS 26 would take 60 days to move the actuator over the full length of travel. The MS 26 can also be used to give manually administered boost doses during the administration.

2.3.3 Graseby® Syringe Driver MS 32

The Graseby® MS 32 Syringe Driver can be set to deliver volumes of liquid between 0.1 milliliters (ml) and 9.9 milliliters every hour (h) from a B-D PLASTIPAK brand 20 ml syringe. The MS 32 is known as a *volumetric rate* syringe driver.

2.4 Contraindications

The pump is not to be used in any intra-articular space infusion.

2.5 Predicates or Equivalent Devices

The Graseby® MS Syringe Driver series has been on the market for many years. The MS Syringe Drivers are legally marketed devices in the United States that have been compared to the predicated devices through FDA premarket notification process. The intended use of MS Syringe Driver is comparable to the referenced predicate devices listed below:

- MS 16 Syringe Driver, Princeton Medical Instruments, Inc.
- Syringe Driver MS-16, Intermedics, Inc.
- Auto-syringe AS-2F Syringe pump

The MS16 Syringe Driver is also substantially equivalent to the listed predicate devices in terms of clinical use to infuse intravenous fluids from a syringe.

2.6 Applicable Standards

The following standards were used in whole or part in the development of the Graseby® MS Syringe Driver:

Standard Number	Description
ENISO 13485:2003	Medical devices -- Quality management systems -- Requirements for regulatory purposes
ISO 9001:2008	Quality management systems – Requirements
EN ISO 14971:2007	Medical Devices – Application of risk management to Medical Devices
EN 1041:1998	Information Supplied By The Manufacturer With Medical Devices
EN 980:2003	Graphical symbols for use in the labeling of Medical Devices
EN IEC 60601-1, (1990)	Medical Electrical Equipment, Part 1: General Requirements for Safety. Amendment A1 (1993) Amendment A13 (1996) Amendment A2 (1995)
EN IEC 60601-1-2, (2001)	Medical Electrical Equipment, Part 1-2: General Requirements for Safety – Collateral Standard: Electromagnetic Compatibility – Requirements and Tests
MEDEV 2.7.1 Rev 3: Dec 2009	Clinical Evaluation: A Guide for Manufactures and Notified Bodies

3. The purpose of conducting this Clinical Evaluation and relevant context

3.1 Objectives

In order to evaluate whether these products are suitable for the purpose(s) and the population(s) for which they are intended, the objective of this Clinical Evaluation is to identify and assess the relevance and weighting to be attached to available clinical data from a number of sources (see Section 4), critically evaluate the clinical data, and relate the results to the subject devices in order to:

- Verify that under normal conditions of use the performance of the devices is in accordance with Smiths Medical's claimed intended purpose
- Evaluate the clinical benefits as well as the risks and side effects, and specifically the acceptability of the benefit/risk ratio associated with the intended use of the subject devices
- Evaluate the appropriateness and substantiation of all product claims for the subject devices
- Support demonstration of conformity with relevant "essential requirements" of the Medical Device Directive (as amended) as set out in the appropriate Smiths Medical "Essential Requirements Checklist(s)"
- Identify any significant trend in use or emerging problem(s) apparent from a review of the recent clinical data (i.e., last 3 years).

3.2 Context

This Clinical Evaluation is being performed to actively update the previous evaluations. This Clinical Evaluation Report also concludes that Graseby® MS Series Drivers and associated accessories are safe and perform as intended and the risks associated with these devices are well established and acceptable when weighed against the intended benefits.

4. Risk-based decision on the nature and extent of clinical data needed for this Clinical Evaluation

The device technologies are well established in terms of safety and performance in the world market, this Clinical Evaluation follows a combined approach of reviewing the published literature, relevant clinical studies, and market experience for the same or similar devices, with particular regard being paid to the various sources of data on the market experience.

This Clinical Evaluation report is based on inclusively known published clinical investigations and other studies in the scientific literature, market experience, clinical experience, and unpublished Smiths Medical data, whether favorable or unfavorable. In addition to the MEDDEV guidance, this report is consistent with the approach described in GHTF GS5/N2R2 for well established devices in regard to identifying relevant published references. Data were extracted from the following sources for review:

- Complaints process data, including Field Safety Corrective Actions / Notices
- MDV/MDR reportable incidents and review reports
- Risk review documents
- Product catalogs
- Compliance with recognized standards
- Published literature

Based on the extensive history of device use, these data sources have been determined as appropriate and sufficient to satisfy the defined objectives of this clinical evaluation and evaluate the risk/benefit ratio of the subject devices.

5. How this Clinical Evaluation was Conducted

A comprehensive Clinical Evaluation was conducted to assess the relevant information, whether favorable or unfavorable, in order to support the safety and performance of the subject devices when used as intended.

This evaluation was conducted according to MEDDEV 2.7.1, "Evaluation of Clinical Data: A Guide for Manufacturers and Notified Bodies" and the Global Harmonization Task Force ('GHTF') "SG5/N2R8 Clinical Evaluation". This Clinical Evaluation, including the literature review of scientific publications of the same or similar devices and the critical evaluation of the clinical data found, was performed in line with this authoritative guidance.

The primary review of scientific literature was conducted using Pub Med which is a service of the U.S. National Library of Medicine that includes over 19 million citations from MEDLINE and other life science journals. The MEDLINE database contains bibliographic citations and abstracts from more than 5,000 biomedical journals published in over 80 countries. General search terms were utilized in order to broaden the sensitivity of the search. The search specified human studies presented originally in English that reference the subject devices by name or subcutaneous infusion devices generically. A higher level of evidence was given to randomized controlled studies; however, articles discussing the current status of therapy (including competitor products), changes in relevant technology, and/or safety related issues were also to be reviewed. For this Clinical Evaluation, the search included relevant clinical data published from August 2009 through December 2012.

The key search words utilized in the literature searches included the subject device names and therapy/device specific words and phrases selected to increase the sensitivity of the search. A full listing of the search terms and limits is provided in APPENDIX B: Literature Review Specifics.

Each study was graded according to the Harbour and Miller grading system, which allows evaluation of the strength of the available evidence in each article. APPENDIX D provides a description of the grading system. A level is assigned to each article, and from this an overall grade for the body of evidence is determined based on the best available evidence and weighted according to the quality of that evidence.

6. The Results of the Clinical Evaluation

As the device technologies are well established in terms of safety and performance in the world markets, this Clinical Evaluation follows a combined approach of reviewing the published literature, unpublished reports and data, both internal and from government databases and review of market experience for the same or similar devices.

6.1 Unpublished Reports and Market Experience

Unpublished data from internal resources were reviewed, including risk management analyses, sales history, complaints, and post-market surveillance.

6.1.1 Risk Management

A review of current risk management files for the Graseby® MS Syringe Driver series (RA002-01 Issue 5) identified hazards as known or foreseeable using methods defined in ISO 14971:2007. All hazards were mitigated via management controls including design controls and validation, appropriate material selection, manufacturing controls, validation and inspection, clinical training, Instructions for Use, and proper labeling.

Based upon the product performance to date, it has been determined that the medical benefit derived from the product outweighs the residual risk. A review of the Technical File and Conformity Assessment document (St. Paul, TF018) supported the above assessment, and concluded that Smiths Medical Graseby® MS Syringe Driver series performed as intended and their benefits outweighed the remaining residual risks.

6.1.2 Sales and Complaints History

A review of complaint history record (CHR 834) of the subject devices, covering August 1, 2009 through July 31, 2012, revealed a total of 141 complaints with 46 reportable and 95 non-reportable complaints and of these:

- 47 complaints were associated with "No Problem Found" (33%)
- 31 complaints were associated with "Can't Duplicate, other problem found" (22%)

There were 46 reportable events for the specified time period and out of 46 complaints, 1% resulted in "serious injury" , 95% resulted in "no injury" or "product malfunction" and 4% resulted in "death". These deaths may or may not be associated with the device because Graseby® MS Syringe Driver is often used in situations in which patients are approaching the final days or hours of life. There is a decreasing trend in overall complaints during the fiscal year 2012 from the previous two years. All complaints are investigated and corrective actions taken appropriately by the Smiths Medical Quality Management System. **Table 6-1** presents a summary of the reported complaints.

A preliminary assessment of these complaints revealed that the reported items were either known issues covered in risk management analysis or isolated anomalies. The rate of complaints based on sales during this period is 0.75% and 1.55% for reportable and non-reportable complaints, respectively. Complaints were analyzed by compiling the various

complaint types and frequency of occurrence. The detailed breakdown of the complaint history is presented in APPENDIX A.

Table 6-1 Sales and Complaints Summary

Item Number	*FY2010 Direct Units	*FY2011 Direct Units	*FY2012 Direct Units	Total
Sales	2271	2125	1742	6138
Complaints				
Reportable	15	22	9	46
Non-Reportable	30	51	14	95
Complaint/Sales Ratio				
Reportable (%sales)	0.661%	1.035%	0.517%	0.749%
Non-Reportable (%sales)	1.321%	2.400%	0.804%	1.548%
Total Complaints/Sales ratio for this Period				2.297%

***Fiscal Year (FY) begins Aug 1st and ends July 31st the following year**

6.1.3 Recalls and Corrective Actions

There have been no recalls or corrective actions for these products for the last three fiscal years.

6.1.4 Post-Market Surveillance

In addition to Clinical Evaluation Reports, Smiths Medical may conduct post-market studies and periodically invites customers to provide feedback through surveys questioning marketed products' availability, quality, and reliability. These products have a long history of clinical use and uses of such devices are well characterized and understood by the user. Therefore, there have been no significant changes for the subject devices since the last CER.

6.2 General Market Safety Issues

A general search of government websites for safety warnings, alerts, and recalls pertaining to the subject devices was conducted covering August 1, 2009 to December 2012. The search included the United Kingdom's MHRA (Medicines and Healthcare products Regulatory Agency), Australia's TGA (Therapeutic Goods Administration), Canada's Health Canada, and the US FDA (Food and Drug Administration) websites.

There were no safety warnings or recalls listed in the MHRA, TGA, and Health Canada websites concerning the subject device during the prescribed time period.

6.2.1 *FDA*

A search of FDA database specific to the Graseby® MS Syringe Drivers by brand name and product codes covering August 1, 2009 through December 30, 2012 found no reported recalls for the subject device but identifies 24 individual reports. Of these, 2 reports are associated with the event type "injury", 17 with the event type "malfunction" and 5 reports associated with "death". The five reports of death are summarized in the **Table 6-2.**

A general search of FDA website revealed no additional information regarding safety warnings, alerts, or recalls concerning the subject device but the FDA presented a webpage dedicated to infusion pumps, with links to various documents and information.[h] FDA is launching the proactive ***Infusion Pump Improvement Initiative*** to address the safety issues and FDA will:

- Establish additional requirements for infusion pump manufacturers
- Proactively facilitate device improvements
- Increase user awareness via the new infusion pump website

A general search of the subject devices revealed safety alerts issued by NHS. Although these devices have been available for some time, it was mentioned that the safety features of the Graseby® MS Series Syringe Drivers were not upgraded to comply with current standards as recommended by international regulators.

6.3 Published Data

The literature search, which addressed Graseby® MS Series Syringe Drivers, identified 15 potential, non-duplicated, articles. After reviewing the abstracts and a few full text articles, 4 articles are exclusively on syringe drivers' use in hospitals, nursing care homes and palliative care. No published accounts of clinical trials using the Graseby® MS Syringe Driver or equivalent devices were identified during this review period and the results are summarized in APPENDIX C. This may be a reflection of the length of time the devices have been available for use. All of these articles addressed the syringe driver experiences by patients or carers using the Graseby® MS Syringe Driver or equivalent devices. One of the studies also investigated an association between drugs administered via a syringe driver and the occurrence of site reactions.

In attempt to gain insight on current use of technology and to further support this Clinical Evaluation, published Clinical Practice Guidelines from clinical and professional groups were reviewed through general internet search using a widely available search engine.

6.3.1 *Safety and Efficacy In General*

The syringe drivers have played a role in enabling ambulatory and is commonly used in the care of patients who are reaching the end of their life in health-care settings in the UK and internationally. For many years, the mostly widely used syringe drivers in the UK have been the Graseby® MS 26 and MS16A. In 2008, the Risk Management Committee of one large NHS teaching hospital expressed concern at the number of clinical incidents relating to syringe drivers.[1] Clinical engineering specialists are particularly concerned about the number of deaths related to ambulatory syringe driver and the lack of safety

feature, particularly - the Graseby® MS16A syringe driver. A clinical evaluation was performed on two new devices along with the MS16A syringe driver. Although both new devices evaluated more favorably than the Graseby 16A, but making the change to ambulatory syringe drivers with additional safety features is a complex process and it may take longer to implement the change.

In December 2010 the National Patient Safety Agency (NPSA) released a Rapid Response Report citing evidence of harm and death and need to address safety issues related to ambulatory syringe drivers.[9,g] Between January 1, 2005 and June 30, 2010 the NPSA received reports of eight deaths and 167 non-fatal reports involving ambulatory syringe drivers. Four of these deaths were reported in 2009. In February 2011, the NPSA has also issued guidance to NHS organizations in England and Wales, recommending that they phase out ambulatory syringe drivers over the next five years.[g] Longer periods of transition will reduce the cost, as devices would generally only be replaced at the end of their expected functional life.

Two of the articles reviewed ambulatory syringe drivers for their use in palliative care and nursing care homes.[1,12,15] A baseline review conducted by nurses highlighted that the use of syringe drivers may not be the most appropriate way of managing symptoms during the dying phase in very frail and old people. When patients, carers and nurses experienced were reviewed about the use of syringe drivers in palliative care setting, there were a few patient barriers to the use of the devices. Nurses or patient carers reported an increases challenge when syringe drivers were used in rural, at-home settings and the need for training.

7. Relating the results of the Clinical Evaluation to the Smiths Medical devices

The Graseby® MS Syringe Drivers have a long history of clinical use and there was a time when the most widely used syringe drivers in the UK had been the Graseby® Syringe Drivers. These devices, however, have been determined to no longer meet the current international standard for syringe drivers stipulated in BS EN/IEC 60601-2-24 (International Electrotechnical Commission (IEC), 1998). This concern seemed justified as these older types of device had been removed from the market in Australia and New Zealand due to safety issues. Smiths Medical provides a safety Lockbox free of charge with every purchase of the Graseby® MS 16A and MS 26 Syringe Drivers to address some of the safety issues and concerns raised by NPSA. Smiths Medical is planning to phase out Graseby® MS Syringe Driver by the end of year 2014 and will continue to provide maintenance and service support for the devices in the market.

In addition, unpublished data, including complaints and internal documentation, was reviewed and no new trends related to the safety, performance, or intended purposes of the Graseby® MS Syringe Drivers were identified. Customer complaints are trended and reviewed by Smiths Medical on a regular basis for reoccurring events or events that may present unreasonable risks. Corrective action plans are developed and implemented as appropriate. All complaints, safety data reported to government agencies and previously issued corrective action plans were also reviewed and no new trends were apparent. The ratio of reportable complaints to sales is as low as 0.75%. This low rate of reportable complaints within these well established medical devices demonstrates a high level of safety and reliability.

7.1 Product Claims

7.1.1 *Graseby® MS Series Syringe Drivers*

Source: http://www.smiths-medical.com/, Smiths Medical Lit No. LIT/MD2536

- Famed for their simplicity and reliability, the choice of healthcare professionals in hospitals, nursing homes, palliative care and community settings for over 25 years
- Suitable for both IV and subcutaneous infusion

7.1.2 *Graseby® MS Driver Lock Box*

Source: http://www.smiths-medical.com/, Smiths Medical Lit No. LIT/MD2536

- Key lock access, lightweight and portable
- Complete control and increases confidence

8. Conclusions

As per the objectives defined in Section 1.1 and based upon this Clinical Evaluation, the following conclusions can be drawn regarding the Smiths Medical ASD Graseby® MS Series Syringe Drivers:

- Under normal conditions of use, the performance of the devices is in accordance with the claimed intended purposes. Product claims are appropriate for the intended use and purpose and no new risks were identified as a result of this clinical review.
- No significant problems in product use were identified and Graseby® MS Series Syringe Drivers and have been used for the administration of medications since 1983. Smiths Medical also provides a safety Lockbox with the devices to address safety concerns.
- The main benefits provided by the subject devices remain unchanged, as does the safety profile and associated risks with the use of these devices. No prospective post-market clinical follow-up studies or clinical investigations are required.
- The risks of these devices are well established when weighed against the intended benefits, however, the risk analysis on these devices should be updated to address the safety concerns related to the device.
- The devices have a low complaints rate as a function of sales with no trends identified in the complaint types. Even though MAUDE database search revealed five complaints associated with patient deaths, there is no report of device malfunction in these complaints and it is very important to note that the Graseby® MS Syringe Driver is often used in situations in which patients are approaching the final days or hours of life.
- There is an increased emphasis by NHS to implement new but similar devices and phase out the old syringe drivers and Smiths Medical elected to discontinue distribution of the devices by the end of 2014.

9. Recommendations

The Graseby® MS Syringe Driver has been in the market for many years and there are no new changes in design characteristics and intended use of subject devices. There are no recommendations for the subject device at this time.

10. References

1. Wallace EM, Tiernan E. Referral Patterns of Nonmalignant Patients to an Irish Specialist Palliative Medicine Service: A Retrospective Review. *The American journal of hospice & palliative care.* Jul 18 2012.
2. Sardin B, Lecour N, Terrier G, Grouille D. [About safety parameters for patient-controlled analgesia (PCA) devices]. *Annales francaises d'anesthesie et de reanimation.* Oct 2012;31(10):813-817.
3. Paratz ED, Flynn E. Rapid death after admission to palliative care. *Internal medicine journal.* Apr 5 2012.
4. Momen N, Hadfield P, Harrison K, Barclay S. Managing Pain in Advanced Cancer: A Survey of United Kingdom General Practitioners and Community Nurses. *Journal of pain and symptom management.* Nov 27 2012.
5. Mitchell K, Pickard J, Herbert A, Lightfoot J, Roberts D. Incidence and causes for syringe driver site reactions in palliative care: A prospective hospice-based study. *Palliative medicine.* Dec 2012;26(8):979-985.
6. Mauch J, Jurado OM, Spielmann N, Bettschart-Wolfensberger R, Weiss M. Resuscitation strategies from bupivacaine-induced cardiac arrest. *Paediatric anaesthesia.* Feb 2012;22(2):124-129.
7. Franci P, Bertamini A, Bertamini O, Pilla T, Busetto R. Clinical evaluation of an end-tidal target-controlled infusion closed-loop system for isoflurane administration in horses undergoing surgical procedures. *Veterinary journal (London, England : 1997).* May 2012;192(2):206-211.
8. Mauch J, Martin Jurado O, Spielmann N, Bettschart-Wolfensberger R, Weiss M. Comparison of epinephrine vs. lipid rescue to treat severe local anesthetic toxicity - an experimental study in piglets. *Paediatric anaesthesia.* Nov 2011;21(11):1103-1108.
9. Freemantle A, Clark D, Crosby V. Safer ambulatory syringe drivers: experiences of one acute hospital trust. *International journal of palliative nursing.* Feb 2011;17(2):86-91.
10. Miller E, Rotea M, Rothstein JP. Microfluidic device incorporating closed loop feedback control for uniform and tunable production of micro-droplets. *Lab on a chip.* May 21 2010;10(10):1293-1301.
11. Menahem S, Shvartzman P. Continuous subcutaneous delivery of medications for home care palliative patients-using an infusion set or a pump? *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer.* Sep 2010;18(9):1165-1170.
12. Kinley J, Hockley J. A baseline review of medication provided to older people in nursing care homes in the last month of life. *International journal of palliative nursing.* May 2010;16(5):216-223.
13. Harper GK, Stafford MA, Hill DA. Minimum volume of local anaesthetic required to surround each of the constituent nerves of the axillary brachial plexus, using ultrasound guidance: a pilot study. *British journal of anaesthesia.* May 2010;104(5):633-636.
14. Griffith R, Tengnah C. Prescribing and administering unlicensed medicines. *British journal of community nursing.* May 2010;15(5):232-235.
15. Cruickshank S, Adamson E, Logan J, Brackenridge K. Using syringe drivers in palliative care within a rural, community setting: capturing the whole experience. *International journal of palliative nursing.* Mar 2010;16(3):126-132.

Other Published and Unpublished Documents:

a. Smiths Medical Risk Management Reviews (RA002-01 Issue 5)
b. Smiths Medical Essential Requirements Checklists (ER-035 Rev 003)
c. Smiths Medical Technical File & Conformity Assessment (TF018 Rev 005)
d. Smiths Medical Complaints History Reviews (CHR834)
e. Smiths Medical Instruction Manual and IFU (IM-0105-0920-102 and SM-0113-2)
f. National Patient Safety Agency (2010). Rapid Response Report: Safer Ambulatory Syringe Drivers. http://www.nrls.npsa.nhs.uk/resources/type/alerts/?entryid45=92908
g. National Patient Safety Agency (2011): NPSA calls for safer ambulatory syringe drivers. http://www.npsa.nhs.uk/corporate/news/npsa-calls-for-safer-ambulatory-syringe-drivers/
h. "Letter to Infusion Pump Manufacturers". Retrieved from FDA website: http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/GeneralHospitalDevicesandSupplies/InfusionPumps/ucm206000.htm
i. FDA Website: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/textsearch.cfm
j. U.K. Medicines and Healthcare products Regulatory Agency (MHRA) website
k. Australia's Therapeutic Goods Administration (TGA) website
l. Health Canada

11. Revision History

Document No.	Issue No.	Issue Date	Reason
DHF #: Product Family 002	01	11 April 2007	Initial Review
CER 001/020*	01	30 September 2010	Review and revision, as appropriate, of the existing clinical evaluation (previously referred to as "Clinical Data Reviews") to satisfy the clinical data requirements of the Medical Devices Directive 93/42/EEC as amended by Directive 2007/47/EC.
CER 006/040**	001	January 2013	Review and revision, as appropriate of the existing clinical evaluation

* Document numbers changed to signify the introduction of the revised format.
** Document numbers changed to match Graseby product family.

Table 6-2: FDA MAUDE database: Reports of death associated with the Graseby MS Syringe Driver series

Event Date	Device	MDR Report Key	Device Problem	Summarized Description of Event	Manufacturer Narrative
9/7/2012	GRASEBY MS16ASYRINGE DRIVER	2747243	Unknown	Received notice via emergency care research institute that the device was in use with a pt in home care setting. According to reporter, the pt was in "end of life" care and device was being used for infusion of pain control medication. Program settings and medication info were not made available. According to the reporter, the pt expired and the pump was seized by coroner's office.	The reporter brought device to smiths medical (b)(4) for investigation. The device was given delivery testing and was found to deliver within specifications. The root cause of the reported issue could not be established as the device was found to be delivering within specifications. The reported issue could not be confirmed to be device-caused.
6/2/2011	GRASEBY MS26 SYRINGE DRIVER	2307979	Unknown	User facility reported that the device was in use for pain relief on an end-stage terminally ill pt. Infusion was started at 12:20 pm and checked at 1:20 pm with no problems noted. At 4:20 the pt was "deteriorating" and "required urgent suctioning". Pump check showed that device was stopped and not running. Device was removed from use and replaced with a functional device. Pt expired at 5:05 pm. Confirmation on cause of death has been requested but not received at this time.	Customer has not yet returned the device to the manufacturer for device evaluation. When and if the device becomes available and is returned and evaluated the manufacturer will file a follow-up report detailing the results of the evaluation.
5/19/2011	GRASEBY MS26 SYRINGE DRIVER	2158346	Over delivery	The manufacturer received notification that a pt death occurred while the manufacturer's device was in use for palliative care for end stage sigmoid cancer. The pt was to receive 24 hour diamorphine infusion. The pump was set to deliver 2mm/hr over 24 hours; a 48mm infusion for 24 hour. The infusion was initiated at 1100 on (b)(6) 2011. According to the report the pump infusion ended at 2300 on (b)(6) 2011. Pt expired at approx 0300 on (b)(6) 2011. The syringe was discarded; the pump was seized by the coroner. At the time of this report, the device has not been made available to the manufacturer for evaluation and the cause of death was unknown..	Customer has not yet returned the device to the manufacturer for device evaluation. When and if the device becomes available and is returned and evaluated, the manufacturer will file a follow-up report detailing the results of the evaluation.
3/4/2010	GRASEBY MS26 SYRINGE DRIVER	1635870	NA	The mfr received notification that a pt death occurred while the mfr's device was in use. No product is available, the user facility did not record the pump serial number at the time of the event and they claim to have lost track of the device. According to coroner report, death was of natural causes and the incident was not due to a problem with the product.	Customer has not yet returned the device to the mfr for device evaluation. When and if the device becomes available and is returned and evaluated, the mfr will file a follow-up report detailing the results of the evaluation.
10/9/2009	GRASEBY MS16ASYRINGE DRIVER	1522616	Excess flow or overinfusion; Use of Device Issue	Terminally ill patient given 24 hours to live. Nurse went to patient's home to set up the syringe driver for pain relief. Syringe driver set to 02ml/hr. In 2009, patient died at night. Different staff nurse came with the doctor to pronounce that the patient had died. When the iv was removed, the device was set to 60ml/hr. The police were called, and seized the pump and patient notes. Device now is at the forensic laboratory being tested for fingerprints and DNA. Customer to contact the facility, when the device is released by the police, to investigate the pump in conjunction with the facility. Device not alleged to be involved in the patient's death.	Method: device not returned for evaluation by manufacturer - return of device anticipated. Device not alleged to be involved in the patient's death.

smiths medical
bringing technology to life

APPENDIX A: Sales and Complaints Data

Item Number	Direct Units			Total Sales	Complaints (reportable)				Complaints (non-reportable)			
	FY2010	FY2011	FY2012		FY2010	FY2011	FY2012	Total	FY2010	FY2011	FY2012	Total
0105-0504	881	802	862	2,545	6	3	0	9	14	27	9	50
0105-0702	3	62	12	77	0	0	0	0	0	0	0	0
0105-0712	27	88	53	168	0	0	0	0	0	0	0	0
0105-0717	1	0	0	1	0	0	0	0	0	0	0	0
0105-0718	54	57	36	147	0	0	0	0	0	0	0	0
0105-0725	0	0	3	3	0	0	0	0	0	0	0	0
0105-0755	0	0	0	0	0	0	0	0	0	0	0	
0113-0001	934	430	190	1,554	9	19	9	37	15	17	5	37
0113-0705	32	101	77	210	0	0	0	0	0	0	0	0
0113-0707	15	0	2	17	0	0	0	0	1	7	0	8
0113-0712	200	510	434	1,144	0	0	0	0	0	0	0	
0113-0717	28	13	11	52	0	0	0	0	0	0	0	0
0113-0718	49	56	62	167	0	0	0	0	0	0	0	0
0113-0725	0	6	0	6	0	0	0	0	0	0	0	0
FA09CN50NNA076N	5	0	0	5	0	0	0	0	0	0	0	0
FA09CN50NNA076S	12	0	0	12	0	0	0	0	0	0	0	0
FA09CN50NNA138N	12	0	0	12	0	0	0	0	0	0	0	0
FA09DN40NNC101N	4	0	0	4	0	0	0	0	0	0	0	0
FA09DN50NNC051N	2	0	0	2	0	0	0	0	0	0	0	0
FA09DN55NNA161N	12	0	0	12	0	0	0	0	0	0	0	0
Grand Total	2371	2125	1742	6238	15	22	9	46	30	51	14	95

smiths medical
bringing technology to life

Reportable and Non-Reportable Complaints with Short Description

Product Code	Product Name	Short Description	Complaints (reportable)				Complaints (non-reportable)			
			FY2010	FY2011	FY2012	Total	FY2010	FY2011	FY2012	Total
0105-0504	MS16A SYRINGE DRIVER	Fluid Ingression		1		1				
		Can't Duplicate, other Problem found	1	1		2	1	3	1	5
		Customer Induced	1			1				
		Damaged/Broke/Broken					1			1
		Handling Damage/Problem/Dropped					1			1
		Workmanship		1		1		3		3
		No Problem Found/Could not Duplicate	1			1	6	15	1	22
		Manufacturability Condition						1		1
		Other	1			1		1	1	2
		Corrosion/Rust/Contamination						1	1	2
		Inaccurate						1		1
		Inoperable						1		1
		Noisy Mechanism							1	1
		No Product Returned	2			2	1	1	1	3
		Non-Functional					2			2
		Out of Specification					1			1
		Sticking							1	1
		Bent							1	1
		Improperly Assembled							1	1
		Unknown					1			1
0113-0001	MS26 SYRINGE DRIVER	Alignment					1			1
		Cracked Casing		1		1				
		No Product Returned	1	4	1	6	2	3		5
		Can't Duplicate, other Problem found	2	7	3	12	1	3	1	5
		Fluid Ingression					1	2		3

Product Code	Product Name	Short Description	Complaints (reportable)				Complaints (non-reportable)			
			FY2010	FY2011	FY2012	Total	FY2010	FY2011	FY2012	Total
		High Current		1		1				
		Inaccurate		1		1				
		Inoperable								
		Insufficient					2			2
		Intermittent			1	1		1		1
		Low Occlusion			1	1				
		No Problem Found/Could not Duplicate	5	5	3	13	1	7	3	11
		Observed Customer Problem/Can't Duplicate					1			1
		Other	1			1	1	1	1	3
		Unknown					5			5
0113-0707	MS32-G.M.F. SYRINGE DRIVER	Improperly Assembled								
		No Product Returned					1	7		8
Total			15	22	9	46	30	51	14	95

APPENDIX B: Literature Review Specifics

Device name/model: Graseby® MS Series Syringe Driver

Methods: Date of Search: Jan 01-Jan 02, 2013

Period Covered by Search: 3 years

Literature sources of data/databases used to identify data: Pub Med, International Regulatory Agency Websites, Smiths Website, and Internet

Step	Action	Rationale
1	Search: Pub Med Internet/Manufacturers Web Sites International Regulatory Agency Web sites	Peer reviewed journals European and Canada Reporting Websites Google for keywords Promotional literature
2	Clinical Studies of Graseby® MS Series Syringe Driver	Evaluation of Clinical Studies Author's background and expertise
3	Guidelines and Standards for Infusion sets and Pumps	To establish up to date guidelines and standards of practice
4	Exclusion of Clinical Data	Non-relevant literature excluded

Key Search Words: *Syringe Driver, Palliative and Syringe Driver, Pain Management and Syringe Driver, Continuous drug delivery and Syringe Driver*

Search Limits: English; Human, Clinical trial, meta-analysis, practice guideline, Randomized controlled trial, controlled trial; comparative study; controlled clinical trial; guideline

Culling Protocol: After completing the comprehensive literature review, culling was performed objectively using following guidelines, in order to avoid subjective exclusion of scientifically relevant evidence. The guidelines were:

- The article must describe human clinical experience or HFE. Animal or in vitro was excluded but some specific laboratory testing or simulation study will be included depending on the level of evidence.
- Case reports/case series were excluded unless there were at least 5 subjects included in the analysis.

- The article must describe clinical evaluation of the device according to its labeling, i.e. the same intended use and procedure. If the abstract pertained to another therapy and mentioned the device as an alternative therapy or the abstract described 'off-label' usage for another indication, the article was culled from the set of articles to be reviewed.
- Articles which described research not in compliance with applicable ethical standards or regulations, e.g. Declaration of Helsinki, were culled.
- Articles which described poorly designed studies or which did not clearly state the outcomes for the device were culled.
- In the case of multiple publications on the same data set, only the most recent paper summarizing the safety and efficacy of the device was included in this review, unless there was a unique hazard or safety concern included in an earlier manuscript.

All studies obtained via the literature search process were considered for inclusion; studies were not excluded based upon whether the article described favorable or unfavorable evidence on the device. The literature was sorted and categorized according to the culling requirements. A listing of all articles and their categorization, i.e. reason for exclusion or type of evidence provided, is included in APPENDIX C.

Grading of Literature: Each article has been assessed and graded according to the Harbour and Miller classification system. APPENDIX D provides a description of the grading system. A level is assigned to each article, and from this an overall grade for the body of evidence is determined based on the best available evidence and weighted according to the quality of that evidence. In the case of unfavorable evidence, this was considered in the overall body of evidence. Outcomes were noted and highlighted in the table, as were complications.

APPENDIX C: Abstracts and Reasons for Culling from Literature Review

Abstract No.	Author	Title	Journal	Full Article Review	Exclusion Justification
1	Wallace EM, Tiernan E.	Referral Patterns of Nonmalignant Patients to an Irish Specialist Palliative Medicine Service: A Retrospective Review.	*The American journal of hospice & palliative care.* Jul 18 2012.	No	Review article
2	Sardin B, Lecour N, Terrier G, Grouille D.	[About safety parameters for patient-controlled analgesia (PCA) devices].	*Annales francaises d'anesthesie et de reanimation.* Oct 2012;31(10):813-817.	No	Article in French
3	Paratz ED, Flynn E.	Rapid death after admission to palliative care.	*Internal medicine journal.* Apr 5 2012.	No	Non-relevant article
4	Momen N, Hadfield P, Harrison K, Barclay S.	Managing Pain in Advanced Cancer: A Survey of United Kingdom General Practitioners and Community Nurses.	*Journal of pain and symptom management.* Nov 27 2012.	No	Non-relevant article
5	Mitchell K, Pickard J, Herbert A, Lightfoot J, Roberts D.	Incidence and causes for syringe driver site reactions in palliative care: A prospective hospice-based study.	*Palliative medicine.* Dec 2012;26(8):979-985.	Yes	A prospective evaluation study
6	Mauch J, Jurado OM, Spielmann N, Bettschart-Wolfensberger R, Weiss M.	Resuscitation strategies from bupivacaine-induced cardiac arrest.	*Paediatric anaesthesia.* Feb 2012;22(2):124-129.	No	Pharma Study
7	Franci P, Bertamini A, Bertamini O, Pilla T, Busetto R.	Clinical evaluation of an end-tidal target-controlled infusion closed-loop system for isoflurane administration in horses undergoing surgical procedures.	*Veterinary journal (London, England : 1997).* May 2012;192(2):206-211.	No	Non-relevant article
8	Mauch J, Martin Jurado O, Spielmann N, Bettschart-Wolfensberger R, Weiss M.	Comparison of epinephrine vs. lipid rescue to treat severe local anesthetic toxicity - an experimental study in piglets.	*Paediatric anaesthesia.* Nov 2011;21(11):1103-1108.	No	Non-relevant article
9	Freemantle A, Clark D, Crosby V.	Safer ambulatory syringe drivers: experiences of one acute hospital trust.	*International journal of palliative nursing.* Feb 2011;17(2):86-91.	Yes	Rapid Response Evaluation Report
10	Miller E, Rotea M, Rothstein JP.	Microfluidic device incorporating closed loop feedback control for uniform and tunable production of micro-droplets.	*Lab on a chip.* May 21 2010;10(10):1293-1301.	No	Non-relevant article
11	Menahem S, Shvartzman P.	Continuous subcutaneous delivery of medications for home care palliative patients-using an infusion set or a pump?	*Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer.* Sep 2010;18(9):1165-1170..	Yes	Evaluation Study comparing pump vs. infusion set

Abstract No.	Author	Title	Journal	Full Article Review	Exclusion Justification
12	Kinley J, Hockley J. Ward LG,	A baseline review of medication provided to older people in nursing care homes in the last month of life.	*International journal of palliative nursing.* May 2010;16(5):216-223.	Yes	A retrospective review study
13	Harper GK, Stafford MA, Hill DA.	Minimum volume of local anaesthetic required to surround each of the constituent nerves of the axillary brachial plexus, using ultrasound guidance: a pilot study.	*British journal of anaesthesia.* May 2010;104(5):633-636.	Yes	Off topic
14	Griffith R, Tengnah C.	Prescribing and administering unlicensed medicines.	*British journal of community nursing.* May 2010;15(5):232-235.	Yes	Off topic
15	Cruickshank S, Adamson E, Logan J, Brackenridge K.	Using syringe drivers in palliative care within a rural, community setting: capturing the whole experience.	*International journal of palliative nursing.* Mar 2010;16(3):126-132.	Yes	Qualitative evaluation study/surveys

APPENDIX D: Harbour and Miller Article grading system and overall evidence grade

Levels of evidence	
1++	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews or RCTs, or RCTs with a high risk of bias
2++	High quality systematic reviews of case-control or cohort studies or High quality case-control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal
2+	Well conducted case-control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal
2-	Case-control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal
3	Non-analytic studies, e.g. case reports, case series
4	Expert opinion
Grades of Recommendations	
A	At least one meta-analysis, systematic review, or RCT rated as 1++ and directly applicable to the target population or A systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+ directly applicable to the target population and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++ directly applicable to the target population and demonstrating overall consistency of results or Extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results or Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4 or Extrapolated evidence from studies rated as 2+