Elcam
Drug Delivery Devices

# Flexi-Q

## Elcam Drug Delivery New and Innovative Drug Delivery Devices

## **Animal Study**


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E3D

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Elcam MEDICAL

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## *Abstract*

Biotechnology drugs are on the rise in the pharmaceutical market.. While only a few biotechnology drugs are currently approved for use in the US, many more are in human clinical trials, and others are awaiting FDA approval. The majority of these proteins (drugs) are very fragile, and can only be administered by injection. These injections are typically performed using mostly conventional syringes and needles. Growth of alternative injection devices is driven by a number of factors, including improved patient compliance and patient quality-of-care, and the trend toward **self-administration** drug therapy. The selection of **drug delivery devices** is dependent on several factors such as formulation, dosing and usage. The devices available for choice range from pre-filled syringes to automatic injectors including pen-injectors and needle-less devices.
**E3D ,** a sister company of Elcam Medical, a leading provider of disposable medical devices to the U.S. and European OEM markets, has developed a new and innovative line of drug delivery devices designed for administration of biopharmaceutical drugs.
**The Flexi-Q Drug Delivery line** includes a range of **Disposable Auto-Injectors (AI)** and **Reusable Auto-Injectors (AI).** The devices were designed addressing the trends and requirements of the rapidly growing self-injection market.

In response to pharmaceutical companies demand, Elcam Medical has conducted an **animal study** in order to show in-vivo that the drug release in E3D's line of both disposable and semi-disposable Auto-Injectors is initiated AFTER the needle has penetrated the cutis, (<1.0 cm) where the least skin irritation is expected, and to compare the above results to E3D's competitors. **The results** clearly show that in both disposable and semi-disposable versions **- the drug delivery had taken place only after the needle has been fully inserted,** while the competitors' devices tested did not display a distinction between the needle insertion and the drug injection.

## *Background*

**Biotechnology based drugs**

Biotechnology drugs are on the rise in the pharmaceutical market. The majority of these drugs are proteins or peptides manufactured through recombinant DNA technology.
While only a few biotechnology drugs are currently approved for use in the US, many more are in human clinical trials, and others are awaiting FDA approval. Approximately one-half are being tested for use in the treatment of cancer or cancer-related conditions, and are expected to have a major impact in the future health care of cancer patients (1).

**Drug delivery devices - current trends and methods**

Drug delivery methods and devices range from oral delivery to intravenous delivery and are diverse and complex (2). When it comes to biotechnology drugs, the complexity and instability of the compound often mandates delivery by injection (1). Today's most common injection techniques are subcutaneous (SC), intramuscular (IM) and intravenous (IV).
Multiple injection device platforms have already become increasingly prevalent in the competitive



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markets. Over the last few years there has been a rapid growth of the self- injection market (Pen-injectors for Diabetes and Growth Hormone Deficiency and Auto-Injectors for emergency antidotes and anti-migrane drugs). New markets in the last 5 years include Multiple Sclerosis, Fertility, Osteoporosis, Hepatitis, Rheumatoid Arthritis, Oncology and Anemia (3).

Over a third of pipeline drugs will be injectable formulations (see figureA). Many pipeline drugs will be available in a device on launch date or during their life-cycle management program (4)

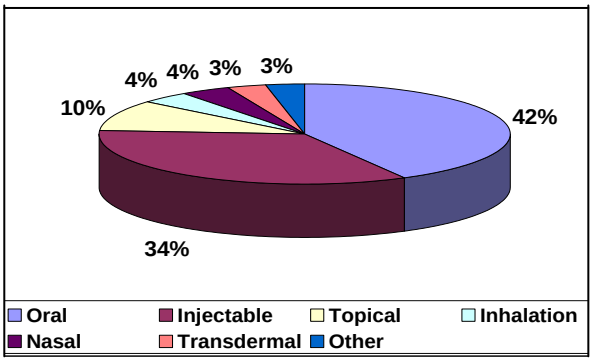


***Fig.A: Segmentation of pipeline drugs by route of administration (4)***

As pharmaceutical companies struggle to position their products in the direct-to-consumer marketing era, the trend towards combining functionality and packaging in drug delivery systems is growing. Innovative drug delivery systems allow pharmaceutical companies to differentiate their drug products from competitors. This is essential at a time when many patents are expiring and competition among the manufacturers of generic medicines is increasing (5).

**Administration trends**

As patients live longer and are diagnosed with chronic and often debilitating ailments, the result will be a dramatic increase in self-administration of drug therapies in non-traditional settings for a number of conditions (5). This trend is creating an increased interest in routes of administration that are patient-friendly and cost-effective.
Pharma company decision makers have come to the realization that new drug product success no longer only depends on the medication itself but also on achieving a patient-friendly form of application.
New injectable delivery device designs currently being developed will create new opportunities for alternative injection methods. Reusable injectors designed to accept pre-filled syringes or drug cartridges have improved ease-of-use and increased alternative device share of the growing self-injection market.

Disposable pre-filled models will penetrate selected practitioner segments. Partnerships between device suppliers and pharmaceutical companies will foster market acceptance of new injection devices for a host of new therapies such as therapeutic vaccines, DNA-based drugs, and protein-derived biologics (5).

**Growth of alternative injection devices will be driven by a number of factors, including improved patient compliance and patient quality-of-care, and the trend toward self-administration drug therapy**.



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**Drug Delivery Methods**

Device evolution features devices with more convenience and fewer steps to operate –
The devices currently available for choice include:
**Pre-filled Syringe (PFS)** – including needle stick prevention devices for PFS that are currently on the rise.
**Pen-Injectors** – reusable and disposable devices for multi dose use. Provide easy dose dialing.
**Auto-Injectors** –automatically insert the needle into the skin and inject the drug – both reusable and disposable systems are available. The newest products are pre-filled disposable systems.
**Reconstitution aids** – for lyophilized drugs, options range from simple vial adaptors to systems with injection capabilities, and include dual-chamber pre-filled syringes.
**Needle-free devices** – the drug is forced by high pressure through a small orifice into the skin, pre-filled disposable and reusable devices available (6).
The selection of a drug delivery device is dependent on several factors: Formulation – liquid vs. lyophilized, single vs. multi-dose, viscosity, existing vs. new primary container. Dosing – route of administration, frequency, volume, fixed vs. variable. Usage – home vs. clinical environment, manual dexterity issues (6).

## *Flexi-Q*

**E3D's new and innovative Drug Delivery product line**

E3D, a sister company of Elcam Medical, a renowned provider of disposable medical devices to the US and European OEM markets, has developed a new and innovative line of drug delivery devices designed for administration of biopharmaceutical drugs that are predominantly stored in pre-filled syringes and vials. These drugs are commonly delivered by self-injection at home.
**The Flexi-Q Drug Delivery devices** (see figure B) were designed addressing several trends and requirements of this evolving market: 1. an **automatic injector** that by the push of a button automatically inserts the needle into the skin and injects the drug, and 2. a **protected needle** that is hidden at all stages of operation providing protection against needle sticks and also addressing needle phobia.

**The Flexi-Q line** includes **Disposable Auto-injectors(AI):** the *PFS* – for prefilled syringes, *DV* – for drugs in vials, *HV*- for high viscosity drugs; and **Reusable Auto-injectors (AI)**: *MMU* - a mechanical multi use AI , and *eMU* – electronic multi use AI. Both the **Disposable AIs** and the **Reusable AI**s are intended for administration of biotechnology drugs that are packaged in PFS or in vials with an included reconstitution mechanism (a unique vial adaptor (VA)). The needle penetration and the drug injection are activated by a push of the button.
The needle is hidden and protected during all operation stages. The **Disposable AI**s are for single use, while the **Reusable AI**s include a disposable single-use cassette that contains the PFS and a needle shield.



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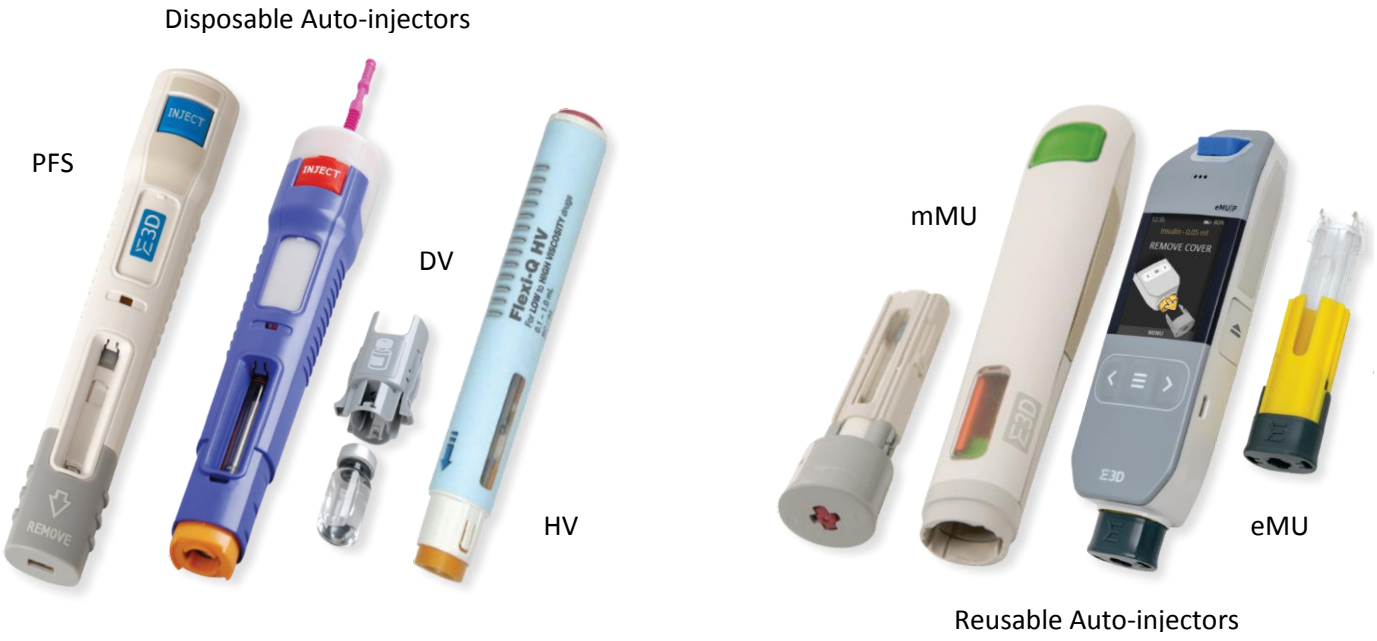


***Fig.B: E3D's Flexi-Q product line***

## *Animal Study*

Two important features in an automatic drug delivery device are the **timing of the drug delivery**, and the **depth of the needle penetration** (into the subcutaneous tissue), where the medication is absorbed in the body.
These features are important due to their effect on skin irritation and drug efficacy.
Elcam Medical's **Disposable AI** is designed to provide a **two-phase injection** in order to assure that the drug delivery takes place only after the needle penetrates the skin and completes its movement; the first phase is the needle penetration and the second phase is the drug delivery.

**Study objectives**

In response to pharma-companies demand, Elcam Medical has conducted an animal study using pigs to show in-vivo that the drug release in E3D's Disposable AI is initiated AFTER the needle had penetrated the cutis, (<1.0 cm) where the least skin irritation is expected, and to compare the above results to E3D's Reusable AI and competitors' auto-injectors (7).



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**Study Protocol**

The pigs were put under general anesthesia and injection sites were shaved, sanitized and marked (pig A or B and numbers). The devices were filled with the diluted contrast media according to the test tables 2 (0.5 or 1 mL).

The injections were given while recording the sequence with the video X-ray (at 15 frames per second). The number of repetitions conducted according to device type are outlined in table 2.

| | Item | Details | Quantity |
|---|---|---|---|
| 1 | Disposable AI for DV | | 2 |
| 2 | Disposable AI for PFS | | 2 |
| 2 | Reusable (non-electronic) AI (with 2 cartridges) | | 2 |
| 4 | Competitor 1 | A marketed disposable AI for PFS | 1 |
| 5 | Competitor 2 | A marketed reusable AI for PFS | 1 |
| 6 | Digital Still Camera | | 1 |
| 7 | Video X ray | 15 frames per second | 1 |
| 8 | Pigs | 12-14 kg/each | 2 |
| 9 | Contrast Media Used For Injection | "Omnipaque" 350 mg/ml manufactured by Amersham Health Cork. Ireland.<br>The active ingredient is Iohexol which is non-ionic, triionated, water soluble x-ray contrast media.<br>Used as the "drug solution" after being diluted to 10% concentration in order to achieve a viscosity close to water, while still allowing the x-ray to detect it. | |

***Table 1: Study materials***



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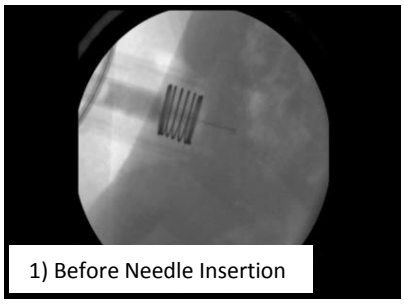
| Device | Injection Volume [mL] | n | Remark |
|---|---|---|---|
| Disposable AI -DV | 0.5 | 6 | 2 injectors,3 injection each |
| Disposable AI -DV | 1.0 | 6 | 2 injectors,3 injection each |
| Disposable AI - PFS | 1.0 | 4 | 2 injectors,2 injection each |
| Reusable AI | 1.0 | 3 | |
| Competitor 1 | 0.5 | 2 | |
| Competitor 1 | 1.0 | 3 | |
| Competitor 2 | 0.5 | 2 | |

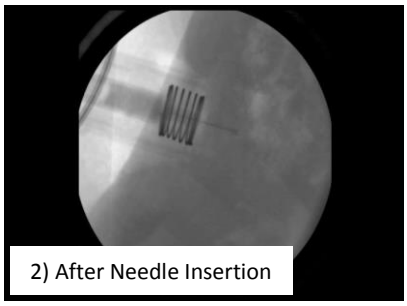
***Table 2: Repetitions according to device type***

## *Result & Conclusions*

As can be seen in figures C1 – C3 during injection with the Disposable AI DV, Disposable AI PFS and Reusable AI - **the drug delivery (3rd frame) had taken place only after the needle has been fully inserted (2nd frame)**.

The results of competitor 1 and competitor 2 as shown in the x-ray video frames (figures C4 – C5) do not show that the needle was fully inserted before starting the drug delivery. However, it cannot be unambiguously claimed that the drug delivery of the tested competitors has started before the needle was fully inserted due to the relatively low frame-rate of the x-ray video.


1) Before Needle Insertion


2) After Needle Insertion

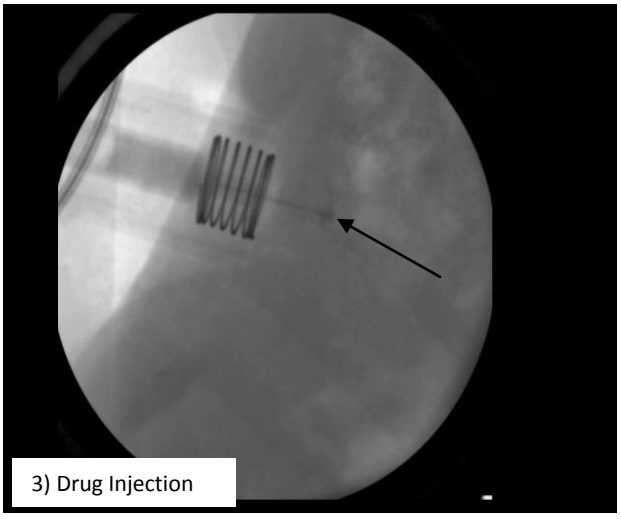

3) Drug Injection

***Fig. C1: Injection with Disposable AI for Drugs in Vials***



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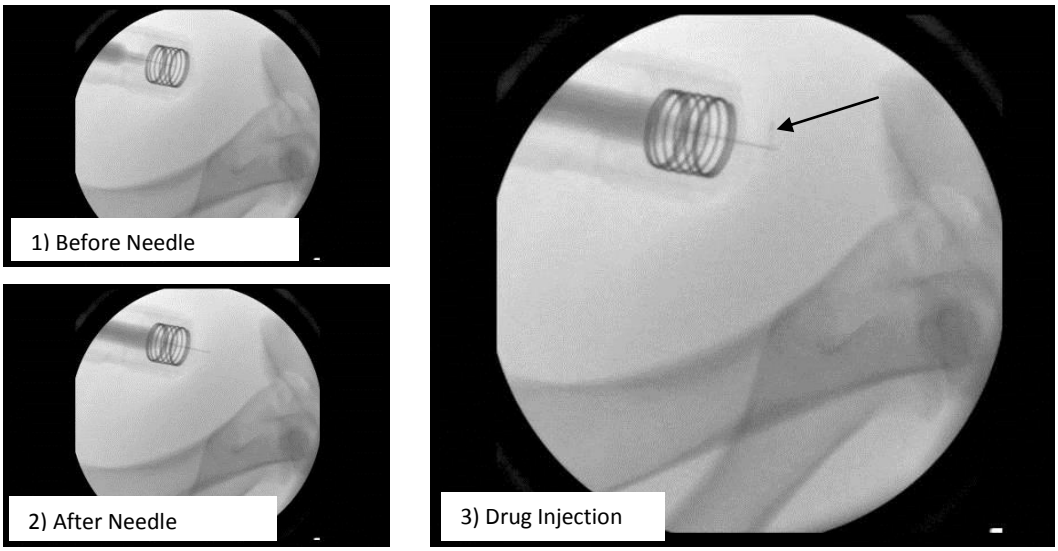


***Fig. C2: Injection with Disposable AI for Pre-filled Syringe***

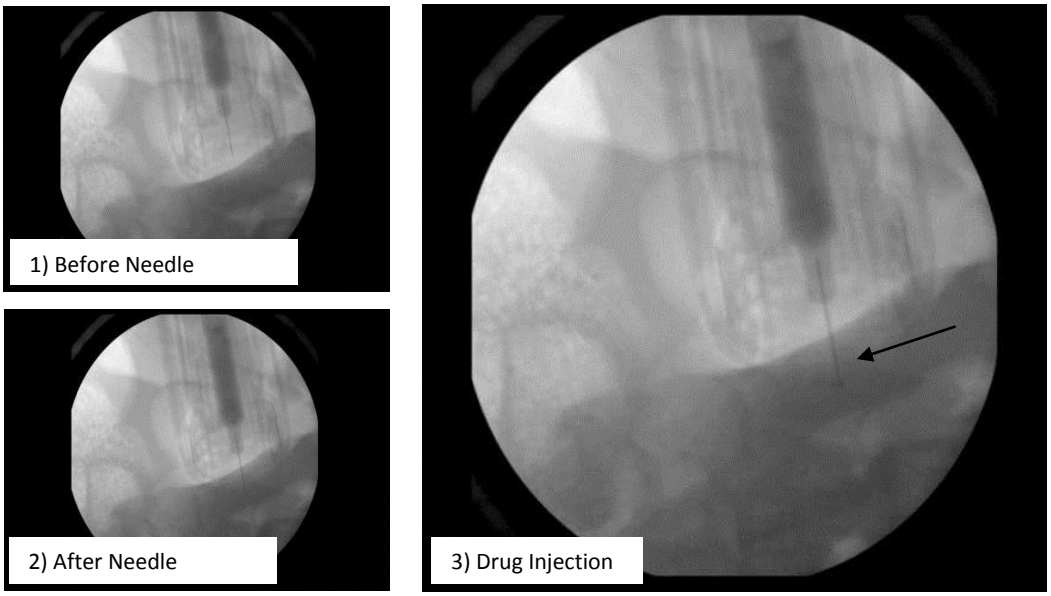


***Fig. C3: Injection with Reusable AI***



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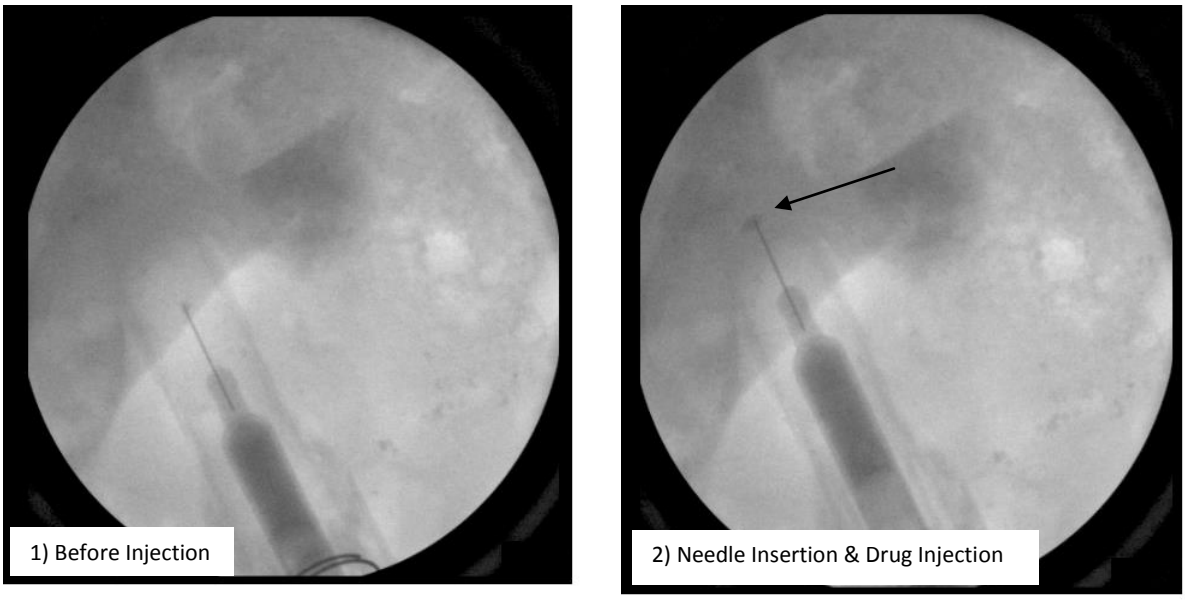


***Fig. C4: Competitor 1 (disposable, for pre-filled syringe)***

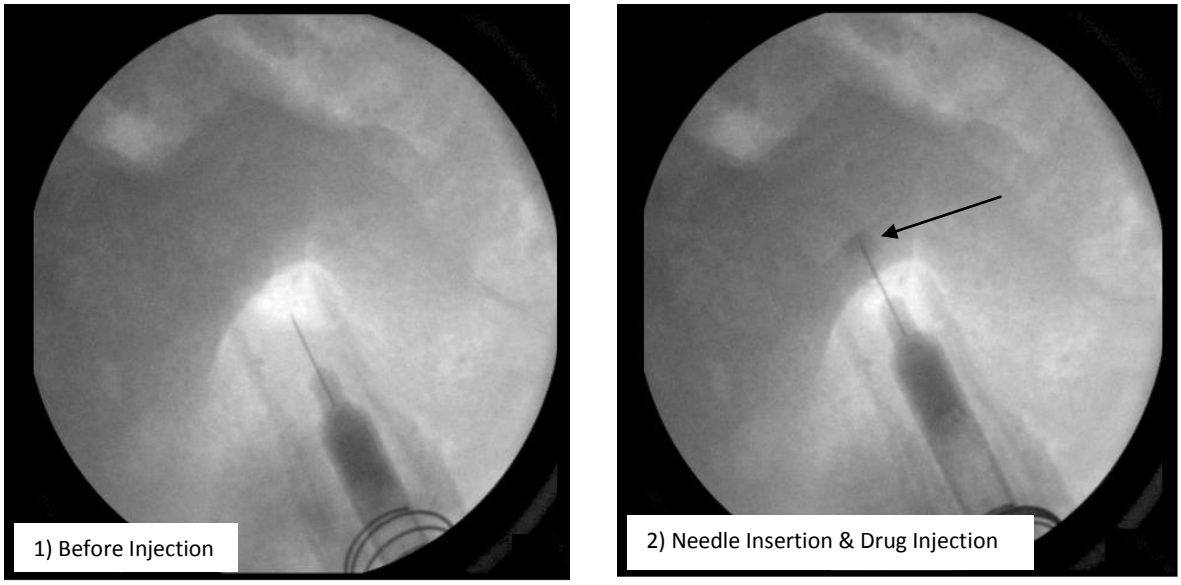


***Fig. C5: Competitor 2 (reusable, for pre-filled syringe)***



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## *Regulatory status:*

The Flexi-Q DV is FDA 510(k) cleared
Device Master File was submitted to the FDA (# MAF-1638) For the Flexi-Q PFS

Flexi-Q HV, mMU and eMU are under development

**E3D is a sister company of Elcam Medical.**
**Elcam Medical** is a world class producer of disposable medical devices and a provider of innovative solutions for specialized flow control needs. The company has been manufacturing various stopcocks for the medical market during the past 25 years infull compliance with FDA 21 CFR 820 Quality System Regulations and ISO 13485. Elcam Medical is a premier provider of stopcocks and manifolds to the US and European OEM markets. Elcam holds marketing approvals from the US FDA, the European MDD (Medical Devices Directive) - Annex II
Section 3 of the Council Directive 93/42/EEC, and from the Israeli Ministry of Health.

## *Acknowledgments*

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