Portal Instruments

Drug Delivery Forum 2018

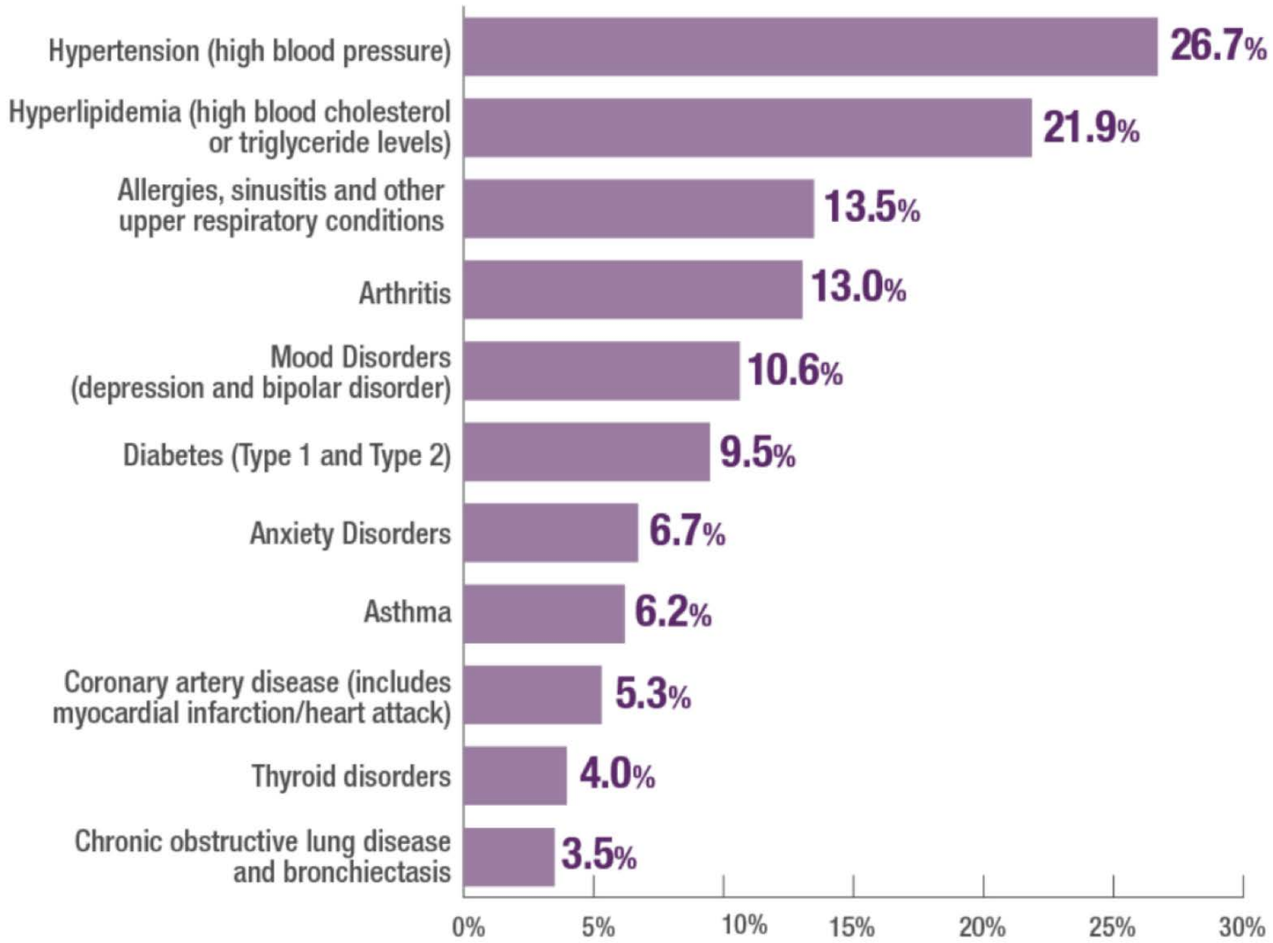
Berlin, March 13, 2018

Our Mission
is to improve the experience for patients on life-changing therapies

1 in 2 American Adults Suffers from a Chronic Disease

Source Data: CDC, 2016

Prevalence of Chronic Diseases in US Adults



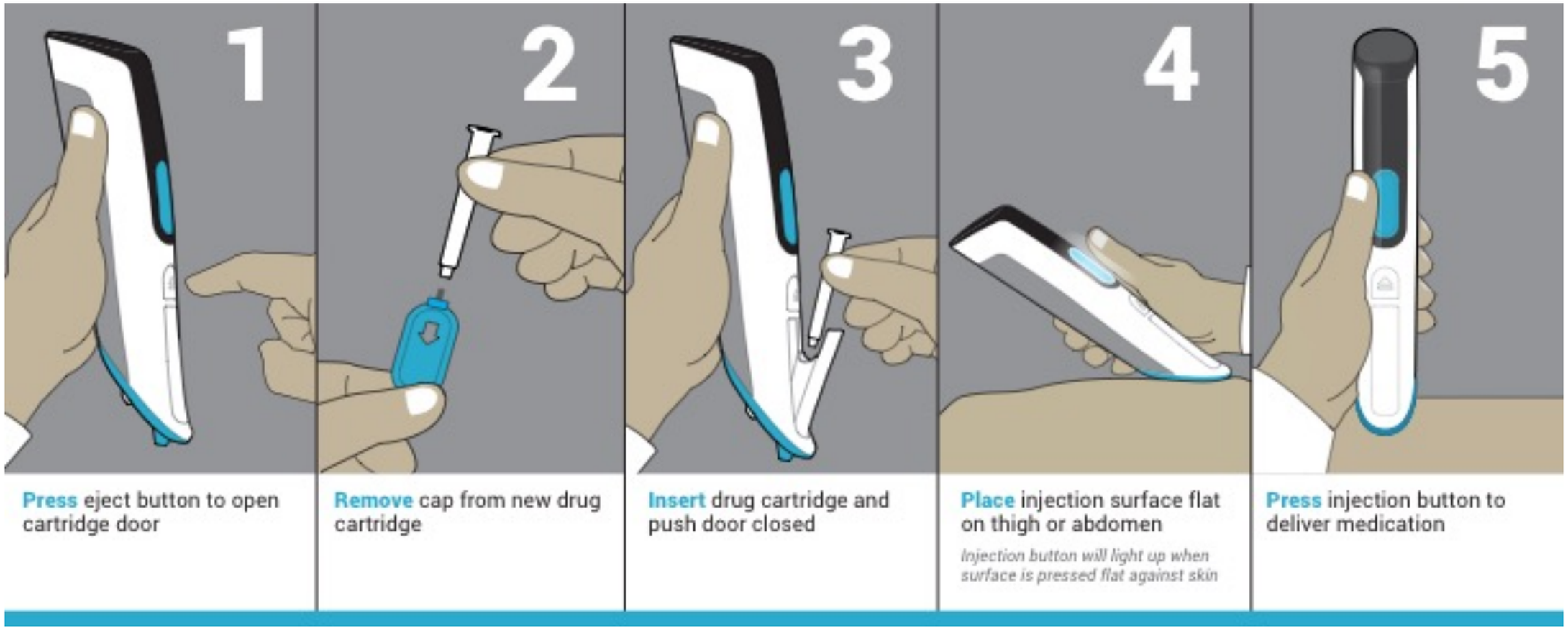
Source: Agency for Healthcare and Quality, U.S. DHSS, 2014

Only 30% Adherence Rates with Biologics

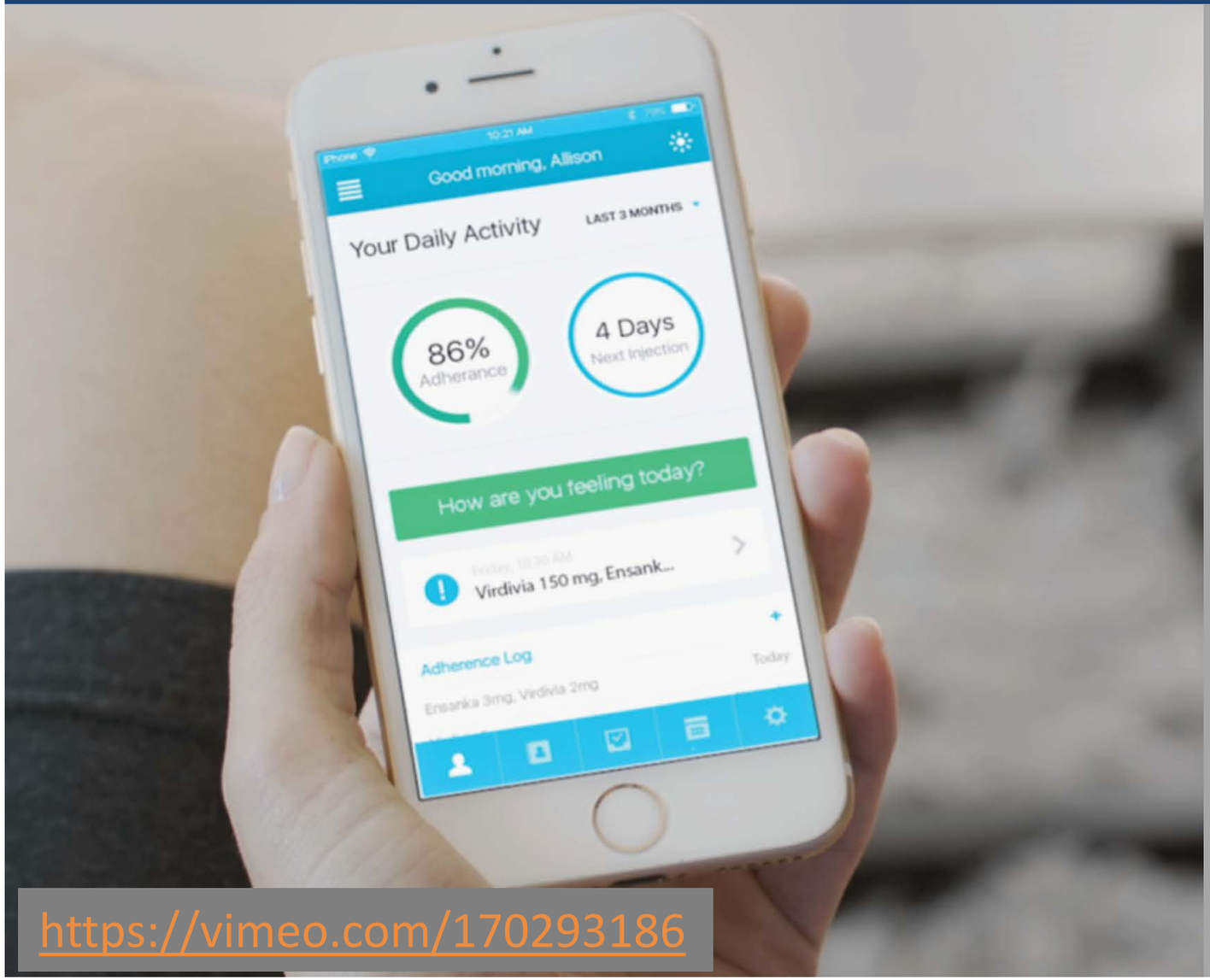
Source Data: CDC 2016

Our Technology is from Star Trek

PRIME Simple, Easy, and Connected



Integrated with the Patient's Digital World



https://vimeo.com/170293186

- Nurse in your pocket™
- Treatment data is automatically collected in real-time
- Patients receive reminders to encourage compliance
- Users get tailored feedback on how well they are doing on the therapy

Portal has Built an Ecosystem Augmenting the Patient's Treatment and Care with the Goal of Improving Outcomes

Each Injection gets Recorded with no Patient Input Required

Injector

Patient Tools

3G Hub

Injector Data Transmitted Wirelessly via 3G Cellular:

- Injection date/time
- Injection profile
- Self-test results
- Battery life

Portal CLOUD

Health Information Exchange

ACO

Physician X

Community Hospital or doctor's office

Physician Y

Portal Instruments Operations, R&D

Pharmaceutical Company

Payers

Pharmacies

Data is then processed and distributed to all stakeholders through a scalable, secure Cloud platform

Availability: **now**

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Needle-Free Viscous Drug Injections: Interview with CEO of Portal Instruments

JUNE 30TH, 2017 EDITORS EXCLUSIVE, MEDICINE, PEDIATRICS

Facebook Twitter

High viscosity biologic drugs gener
uncomfortable around long needles
Instruments, a company out of Cam
injector that reminds us of somethi
Anquetil, CEO of **Portal Instrume**
body without a needle, what this me

SXSW INTERACTIVE INNOVATION AWARDS 2017 WINNER

RED HERRING N. AMERICA 100 WINNER

Portal Instruments

biopharmadealmakers profile

Portal Instruments, Inc.
www.portalinstruments.com

Needle-free: solving challenges viscous biologic self-injections

Portal Instruments' needle-free and digitally controlled device can help i tolerability and adherence of self-injections via a 'smart' needle-free dru

The challenge with biologics

The advent of large-protein biologics enabled the creation of breakthrough treatments for many chronic conditions, and this represents a multi-billion-dollar market. However, challenges exist with the delivery of biologics to be effective, these biologics often need to be delivered at high doses, but regulatory bodies impose limits on the inject-able volumes of drug formulations. The result is high-viscosity drug solutions. High viscosity solutions, however, pose new challenges both at the technical level—for example, with respect to needle size and the force needed to administer the injection—and at the patient-comfort level, owing to increased pain, anxiety about 'doing it right', and potentially the need for repeated injections to achieve an effec-tive therapeutic dose.

The challenge with needles

Patient adherence and persistence with injection-based chronic therapy regimes are notoriously low owing to, among other factors, needle anxiety and injection-related pain. Needle phobia, a condition officially recognized by the American Psychiatric Association in its *Diagnostic and Statistical Manual of Mental Disorders*, affects up to 10% of the population and is associated with a spectrum of mild to severe symptoms of distress. Because the condition is trig-gered by the presence of a needle, no easy solution to the problem exists beyond helping patients relax or avoiding injections altogether.

The Portal platform: a simple and 'smart' solution

Portal Instruments, founded in 201 2, can solve some of these challenges with its needle-free, connected drug delivery device. The technology, currently being developed under a global licensing agree-ment with the Massachusetts Institute of Technology (MIT), allows for comfortable, fast and safe medica-tion administration, including high-concentration and high-viscosity biologics (Fig.1).

The device also allows data related to drug, dos-age, injection frequency and other relevant param-eters to be collected automatically by the device and shared (as desired) with physicians or other health care providers and stakeholders. Insights into patient adherence and symptom progression will enable health care providers to more accu-rately assess the effectiveness of the medication and, if needed, make changes more quickly. The Portal solution gives clinicians the confidence to

Figure 1: Portal's connected, handheld, nee free drug delivery device. This device is desig to deliver high-viscosity drugs quickly and prec

modify treatment, as they will have current relevant insights into their patients' medica patterns.

Cutting-edge technology

To allow the delivery of precise amounts of subcutaneously, the Portal platform leverag unique intellectual property portfolio of paten a jet-injector-based technology developed a over the past ten years.

The Portal platform consists of an electromag actuator controlled by a computer that gener jet of liquid with a diameter that is about 1/3 th a 27 gauge hypodermic needle, which is app mately the diameter of a human hair. It is th of liquid, which contains the drug of interest, pierces the skin to reach the desired subcut ous space, without the intervention of any phy component to puncture the skin. The effect fo patient is less pain sensation than experienced a traditional needle and syringe.

The actuator enables precise control of the s of the pressurized jet of liquid, thus resultin accurate targeting of the desired subcutane space with the exact amount of drug needed high adaptability of the system further allows jet-injection device to accommodate the d ery of low to very high liquid viscosities and concentrations without any changes to the de The design of the device currently support subcutaneous administration of up to 1 ml of preparation in 0.4 s.

"The unique technology from MIT allows full trol of the jet via a computer-controlled feed mechanism, thus decreasing sensation when paired with needle and syringe," said Patrick Anq CEO of Portal Instruments.

Portal Instruments

Drug Development & Delivery

June 2017 Vol 17 No 5 www.drug-dev.com

Digitally Controlled Jet Injection

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Patrick Anquetil, PhD
Portal PRIME: A Digitally Controlled, Cloud-Integrated Jet Injection System

Aaron Goodwin, PhD
Particle Engineering of Spray Dried Dispersions: Considerations for Downstream Processing

AAPS PharmSciTech (© 2017)
DOI: 10.1208/s12249-017-0779-0

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Research Article

An Innovative Needle-free Injection System: Comparison to 1 ml Standard Subcutaneous Injection

Nikola Kojic,[1,3] Pragun Goyal,[1] Cheryl Hamer Lou,[2] and Michael J. Corwin[2]

Received 17 February 2017; accepted 7 April 2017

Abstract. A needle-free delivery system may lead to improved satisfaction and compliance, as well as reduced anxiety among patients requiring frequent or ongoing injections. This report describes a first-in-man assessment comparing Portal Instruments' innovative needle-free injection system with subcutaneous injections using a 27G needle. Forty healthy volunteer participants each received a total of four injections of 1.0 mL sterile saline solution, two with a standard subcutaneous injection using a 27G needle, and two using the Portal injection system. Perception of pain was measured using a 100-mm visual analog scale (VAS). Injection site reactions were assessed at 2 min and at 20–30 min after each injection. Follow-up contact was made 24–48 h after the injections. Subject preference regarding injection type was also assessed. VAS pain scores at Portal injection sites met the criteria to be considered non-inferior to the pain reported at 27G needle injection sites (i.e., upper 95% confidence bound less than +5 mm). Based on a mixed effects model, at time 0, accounting for potential confounding variables, the adjusted difference in VAS scores indicated that Portal injections were 6.5 mm lower than the 27G needle injections (95% CI −10.5, −2.5). No clinically important adverse events were noted. Portal injections were preferred by 24 (60%) of the subjects ($P = 0.0015$). As an early step in the development of this new needle-free delivery system, the current study has shown that a 1.0-mL saline injection can be given with less pain reported than a standard subcutaneous injection using a 27G needle.

KEY WORDS: needle-free jet injections ; subcutaneous injections; injection pain; injection site reactions.

INTRODUCTION

Injections are required for administration of many different medications, including a variety of difficult to inject viscous biologics (e.g., monoclonal antibodies) and other therapies. Reduction of the pain and time of injections may lead to improved patient satisfaction and compliance, as well as reduced anxiety in populations of patients who require frequent or ongoing injections to treat their medical conditions. A needle-free delivery system offers the potential to address a number of these issues.

The essence of needle-free drug delivery is the ability to achieve a fluid (drug) stream or jet with sufficiently high velocity (typically >150 m/s) in order to pierce the skin (1,2). The thin fluid column (typically <300 μm in diameter) can be thought of as being a "virtual needle" since it penetrates the skin. Prior approaches to a needle-free delivery system have been limited by relying largely on either mechanical (e.g., spring-based) or gas-based approaches to generate the high pressures needed to eject the fluid at speeds sufficient to pierce the skin and achieve a successful subcutaneous injection (3–5). These approaches lack the ability to control the injection (i.e., the fluid stream) in real time, meaning that once the mechanism of action is activated, there is no possibility of further modifications to the injection (1). This becomes the limiting factor when attempting to deliver larger volumes, such as 1.0 mL often needed for viscous biologics, to the subcutaneous space in a needle-free fashion. For example, the spring-based approach has the spring generating the force needed to push out the fluid out of an orifice with high speeds (e.g., >150 m/s). Since the spring has a force (or energy) profile that decays during the time of the injection, the fluid velocity will also decay over time (4,6). Similarly, a decaying velocity profile is also characteristic for gas-based injectors (4). The decreasing velocity profile results in the highest velocity being at the onset of the injection followed by a decrease to smaller and smaller velocities, which for a 1.0-mL injection of a viscous biologic may be insufficient to achieve a successful subcutaneous injection.

To overcome these restrictions, Portal Instruments (Cambridge, MA) has developed new technology that has the ability to control (and modify) in real time the fluid

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Published online: 01 May 2017

Quality Management System Ready for Prime Time

- Quality Management System at Portal
  - FDA Compliant QMS verified by external audit Q1 2016
- ISO 13485:2012
  - Notified Body: NSAI National Standards Authority of Ireland
  - ISO 13485 Certification received Q1 2017
  - ISO 13485 Surveillance completed Q2 2017
  - ISO 13485:**2016** target: June 2018

NSAI

Certificate of Registration
of Quality Management System
to I.S. EN ISO 13485:2012

The National Standards Authority of Ireland certifies that:

PORTAL INSTRUMENTS
190 5th Street
Cambridge, MA 02141
USA

has been assessed and deemed to comply with the requirements of the above standard in respect of the scope of operations given below:

The Design, Manufacture and Distribution of Hand Held Needle-Free Injection Devices for Drug Administration

Approved by:
Geraldine Larkin
Chief Executive Officer

Approved by:
Susan Murphy
European Medical Device
Operations Manager

Registration Number: MD19.8046
Certification Granted: Apr 11, 2017
Effective Date: Apr 11, 2017
Expiry Date: Apr 10, 2020

National Standards Authority of Ireland, 1 Swift Square, Northwood, Santry, Dublin 9, Ireland T +353 1 807 3800

13485:2012-US (2.0)

The Delivery of Biologics is Mostly Undifferentiated
Case Study for Rheumatoid Arthritis

	Humira	Enbrel	Simponi	Cimzia	Actemra	Orencia
Auto Injector						
Pre-Filled Syringe					 PFS-S	 PFS-S

The Portal PRIME Device

FEATURES	BENEFITS
Needle Free, no sharps disposal	Patient preference and ease of use
Fast (<0.3 s), simple	Ease of use
Interactivity – reminders, data tracking	Improves compliance; integrates data with Pharma patient support services
Interactivity – patient support	Responds to patient needs, provides support, builds brand loyalty
Does not affect pK or drug integrity	Compatible with biologics
Automatically adjust to any drug dose or viscosity	No long device redesign required for each drug and will operate at wide drug temperature range (straight from the fridge)
Standard primary container	Compatible with standard pharma fill/finish lines. No additional line CAPEX investments required

Overwhelmingly Preferred over the State of the Art

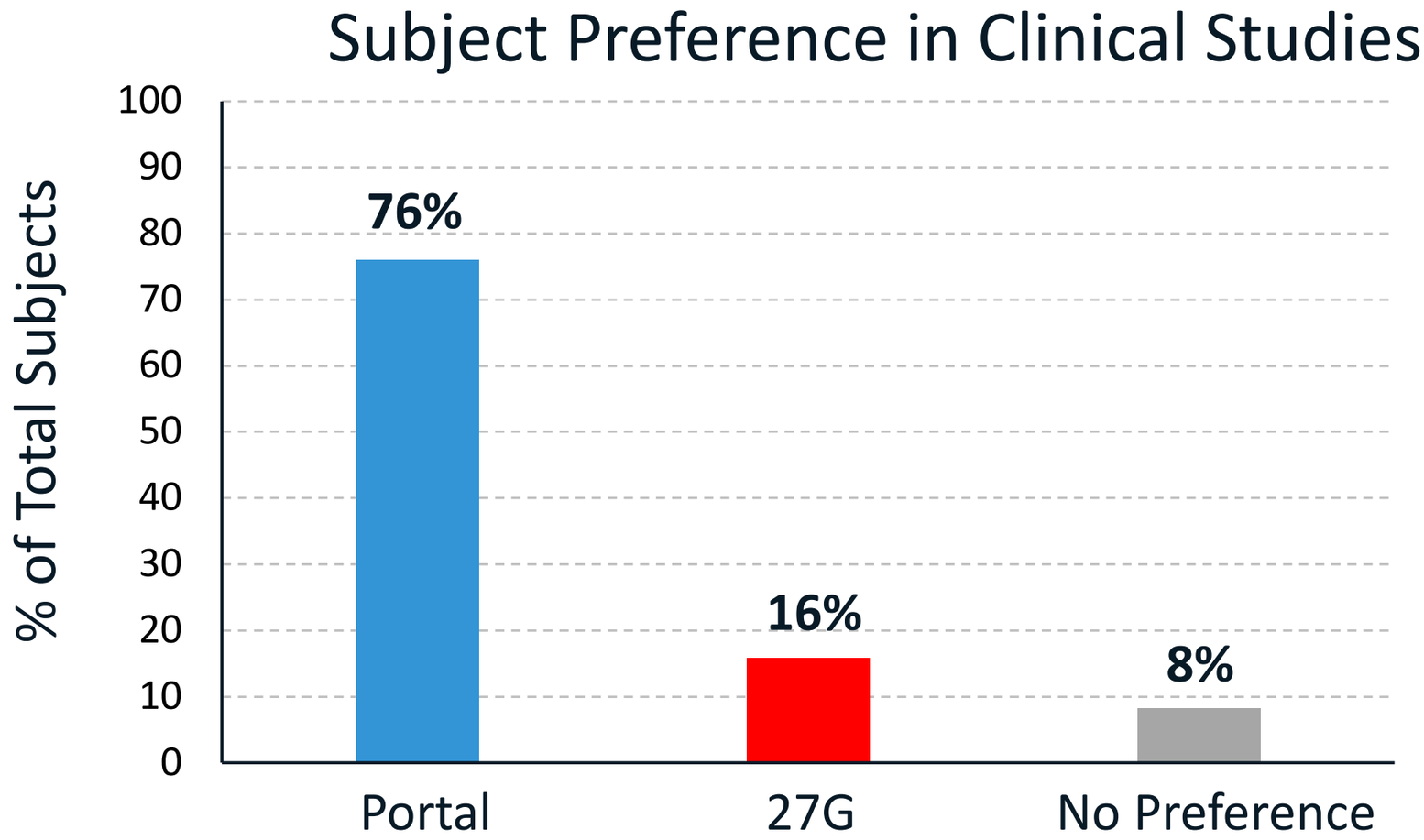
Portal

vs.

Auto Injector

- **Pharma-sponsored human factors study**
- **Subjects**: 9 RA Patients & 14 RA HCPs (4 physicians, 10 nurses)
- **Results:**
  - **8 out of 9 patients** preferred the Portal injector over the auto-injector
  - **12 out of 14 HCPs** would prescribe the Portal injector for self-administration
  - **8 out of 14 HCPs** would still prescribe the Portal injector over the auto- injector if the discomfort was the same
- **Key reasons for preference**: comfort and convenience:
  - Needle-free injection + short injection time = attractive
  - Needle-free cartridge: Higher safety, no sharps disposal, less waste

Subjects prefer PRIME vs. Needle & Syringe when injected with large volume (1 mL) saline solution



N=149 subjects
447 Total Injections
(data excludes Portal employees)

HOW DOES IT WORK?

The Portal Solution

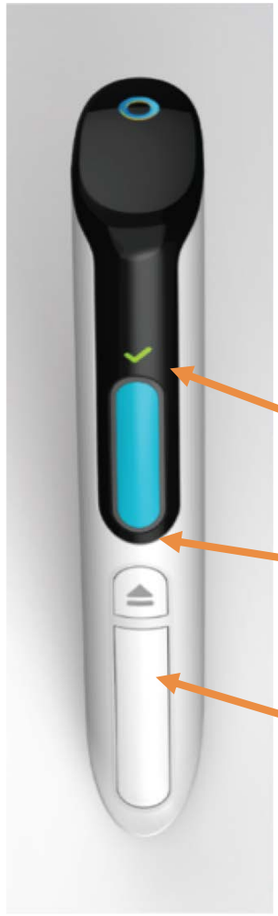
"plug & play" nest & tub format for easy filling

Pre-filled at pharma
(max 1.2 mL)

EPDM + fluoropolymer coating plunger

COP Material

Sterile Cap
(removed at time of use)



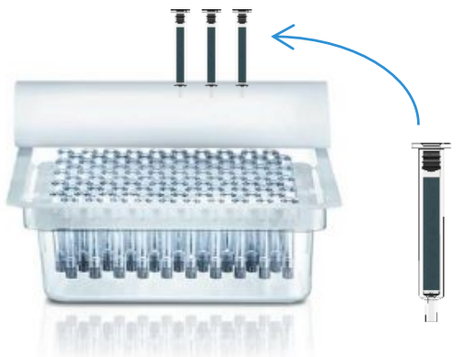
Ready-to-use

Headspace compatible

Cartridge loaded in handheld

Secondary pack
(single or multi)

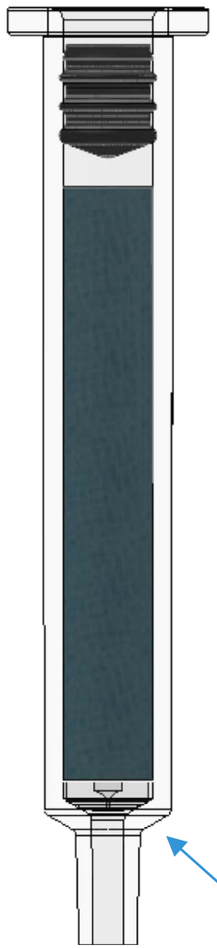
Portal Cartridge is based on 1 mL long PFS



"Plug & Play"
nest & tub format
for easy filling

1.2 mL fill volume

65 mm



2 mm Headspace

40 mm

Nozzle

Cartridge Cap

Partnership with:

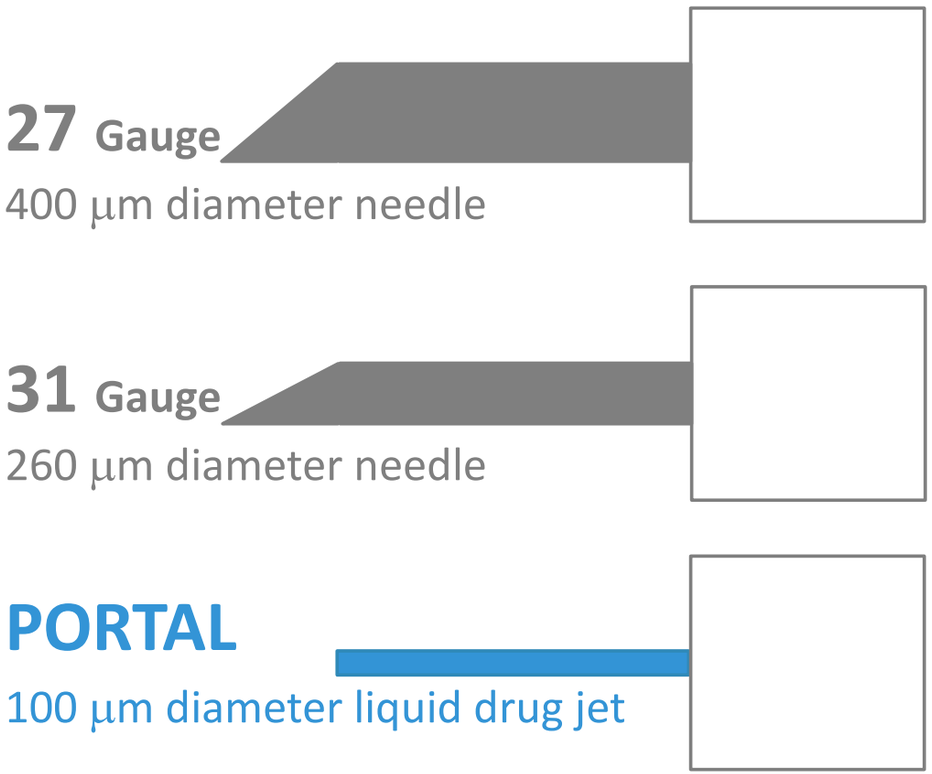
GERRESHEIMER

Choice for rubber components. All are "off the shelf":

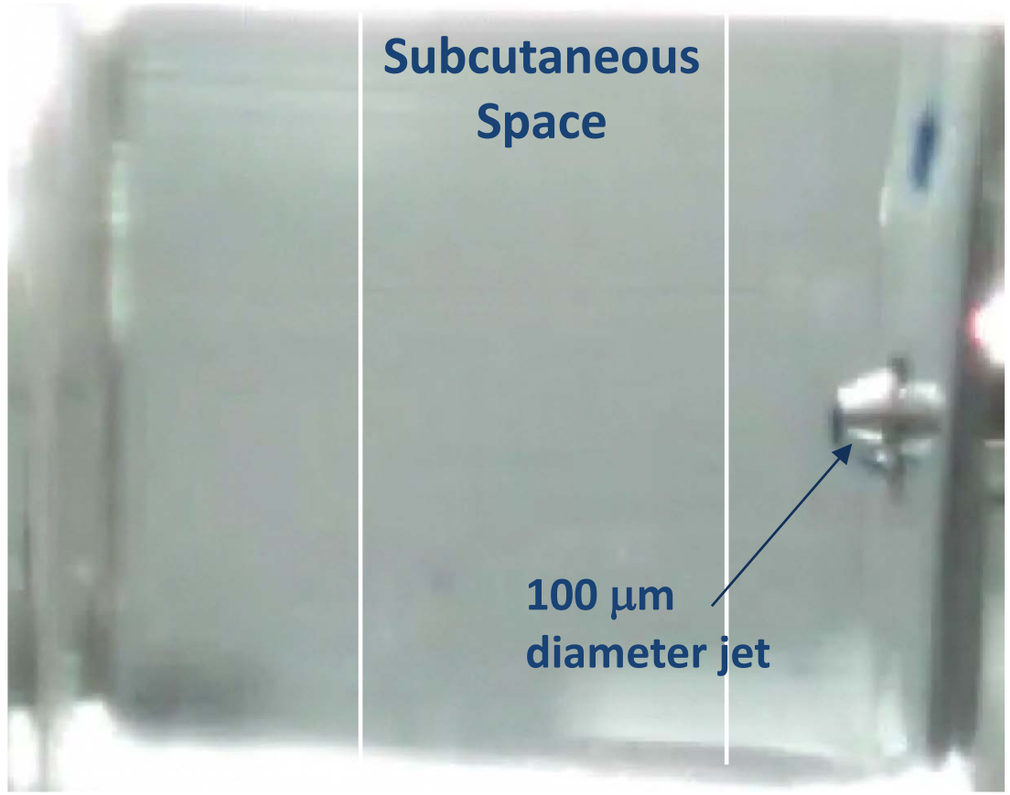
The Needle is Replaced with a Small Liquid Drug Jet

Diameter Comparison

Portal vs. Needle & Syringe



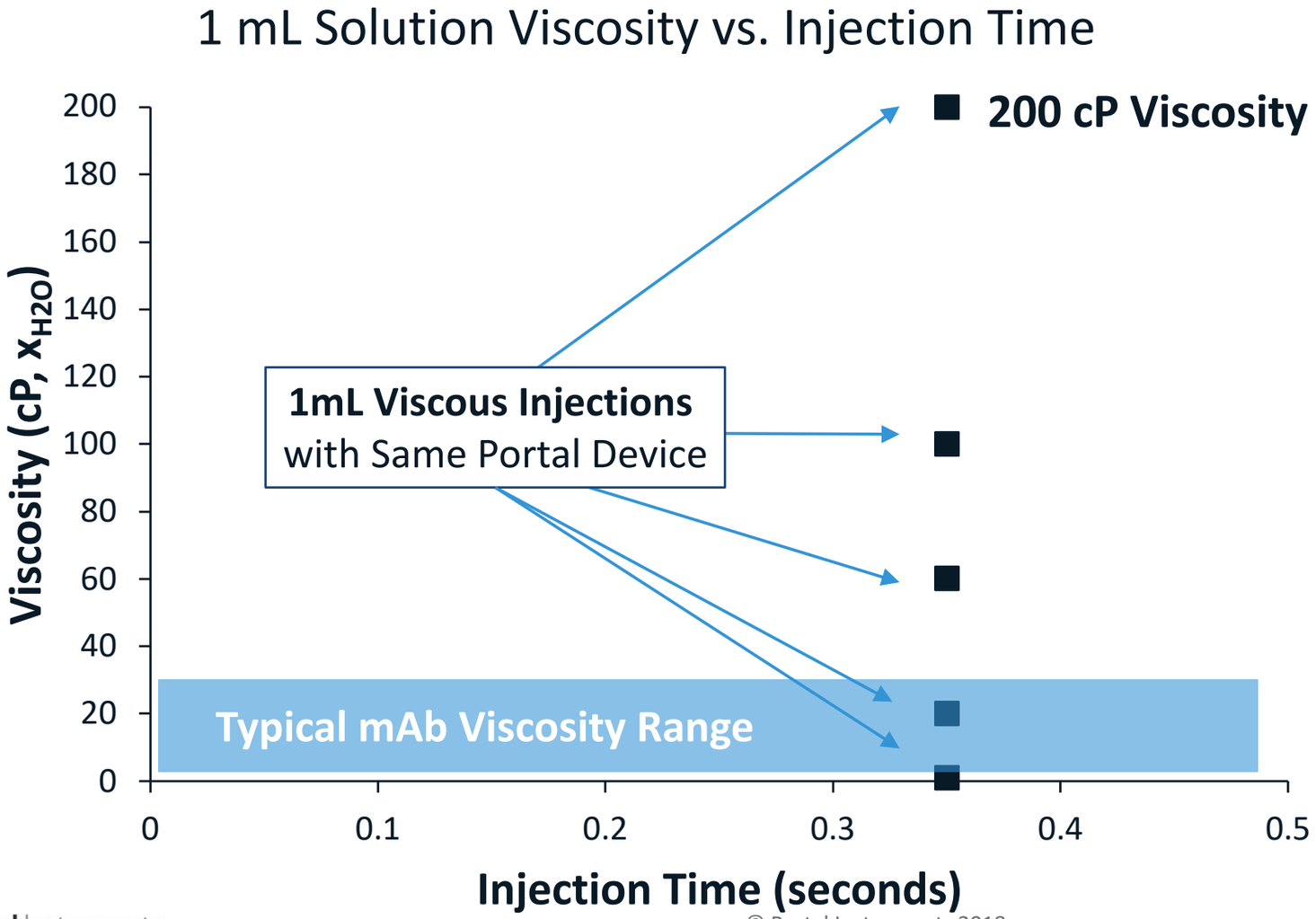
Portal's Needle-Free Injection



Vaccine injection in 0.18 seconds
10,000 frames per second

Portal Instruments

Portal Injector is Agnostic to Drug Viscosity



1mL Viscous Solutions (1 cP – 200 cP) All had a duration of 0.35 seconds

Same Portal device used with no changes in parameters

In traditional drug delivery, each data point would require a different auto-injector

FEASIBILITY DATA

Feasibility Studies Performed at Pharma Partners' Laboratories
8 Partners: 14 mAbs, 2 Proteins Tested, 100% Success Rate

	Drug Development Stage			Physical Integrity	Functional Integrity	Animal pK Study	Pharma Partner Performing Testing & Analysis	Conclusion
	Pre-C.	Ph 1-3	Marketed					
Humira®			✓	✓	✓		Avastus Preclinical Services	✓ Passed
mAb 2	✓			✓	✓	✓	Pharma Partner 1	✓ Passed
mAb 3			✓	✓	✓		Pharma Partner 2	✓ Passed
mAb 4			✓	✓	✓		Pharma Partner 2	✓ Passed
mAb 5			✓	✓	✓		Pharma Partner 2	✓ Passed
mAb 6		✓		✓	✓		Pharma Partner 3	✓ Passed
mAb 7		✓		✓	✓		Pharma Partner 3	✓ Passed
mAb 8		✓		✓	✓		Pharma Partner 4	✓ Passed
Protein 1			✓	✓	✓	✓	Pharma Partner 4	✓ Passed
mAb 9		✓		✓	✓		Pharma Partner 5	✓ Passed
mAb 10			✓	✓	✓		Pharma Partner 5	✓ Passed
mAb 11			✓	✓	✓		Pharma Partner 6	✓ Passed
mAb 12		✓		✓	✓		Pharma Partner 7	✓ Passed
mAb 13		✓		✓	✓		Pharma Partner 7	✓ Passed
Protein 2		✓		✓	✓		Pharma Partner 7	✓ Passed
mAb 14		✓		✓	✓		Pharma Partner 8	✓ Passed

Analytical Techniques Used by our Pharma Partners

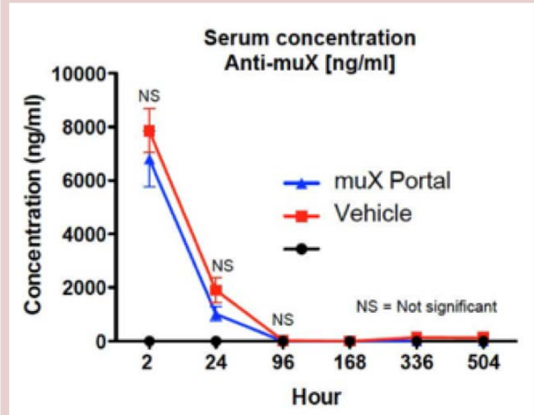
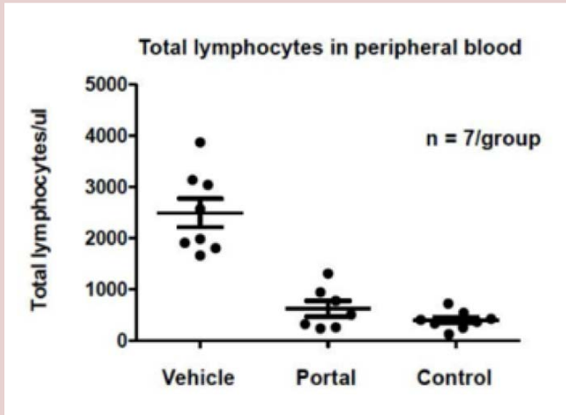
Structural Integrity Testing

- Gel electrophoresis
- UPLC
- MCE-SDS
- MFI
- DLS
- HIAC
- SEC
- Circular Dichroism
- FTIR

Functional Integrity Testing

- ELISA
- Flow cytometry
- Drug specific Bio-assays
- In vivo PK/PD studies (mouse, pig)

pK/PD equivalent to Needle & Syringe

	Pharma Partner	Animal pK Study	Animal pD Study
Anti-muX	**Pharma Partner 1**	No Significant Difference *(C_{max} , AUC , Time Points) Mouse Model* 	Same Degree of Clinical Effect Mouse Model 
TNFα	**Pharma Partner 4**	*Minipig pK study where Portal Device shows pK equivalence to standard administration (see next slide)*	

TNFα pK Study in Mini Pigs
Experimental Design

Group	Product X IP	Dose (mg)	Dose (mL)	No. of Males
1	Needle-free Device	20	0.4	8
2	PFS	20	0.4	8

TNFα pK Study in Mini Pigs
Results: Equivalence to Needle & Syringe

Dependent	CI_90_Lower	CI_90_Upper	Ratio % Portal vs. Ref
$Ln(AUC_{last})$	79.72	132.27	102.68
$Ln(C_{max})$	78.05	131.98	101.49

90% CI; %Ratio: Group 2 (Reference); Group 1 (Portal)

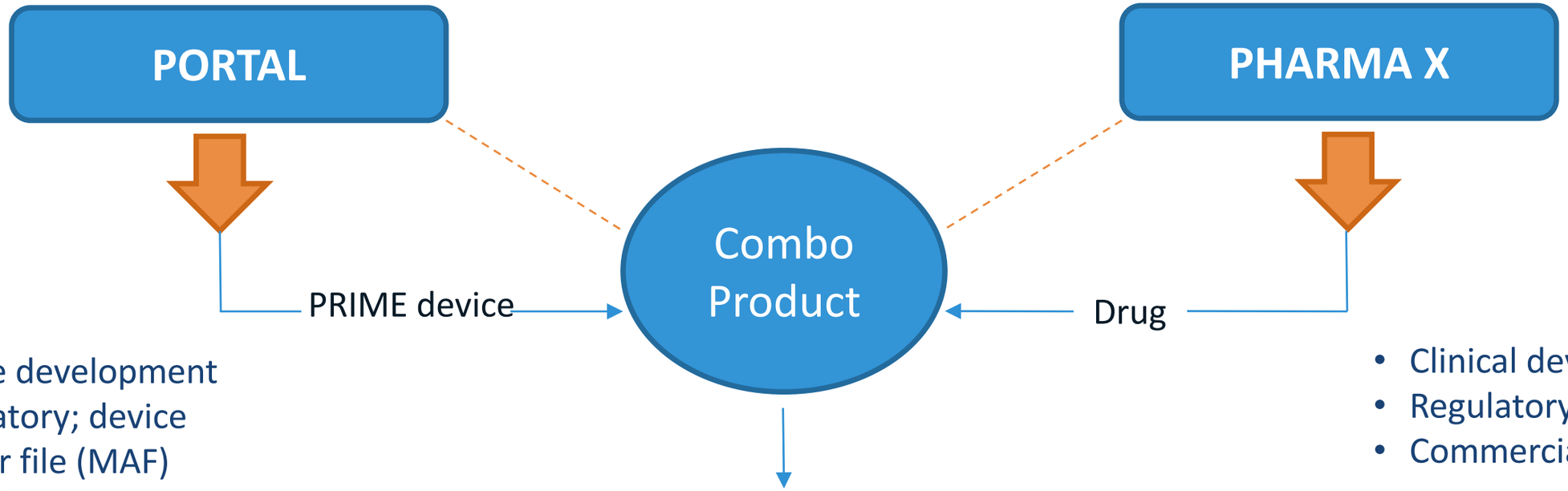
"Preliminary PK data suggest two treatments are comparable in terms of PK exposure"

HOW TO PARTNER WITH PORTAL

How Can Portal Help Pharma?

1. Greater **Market Differentiation** vs. other biologics
2. Enhanced **Market Penetration** via patient preference
3. Increased **Patient Adherence** via connected disease mgmt

Portal's Partnership Model



- Device development
- Regulatory; device master file (MAF)
- Manufacture and supply

- Clinical development
- Regulatory; sBLA
- Commercialization

Traditional Pharmaceutical License (exclusive)

- Joint Committee to oversee clinical development; device design
- Work together on regulatory filings to gain Combo Product approval

FDA Approval Process

- Handheld: Class II
  - Device Master File (MAF) in lieu of 510(k)
    - Pharma partner references MAF as part of Drug submission
    - Simplifies Drug submission by removing need for approval/clearance across FDA Centers
- Prefilled Cartridge:
  - Included in Portal Device MAF and in Combination submission
  - MAF approach supports partner-specific requirements

Enhancing the Takeda IBD Franchise

- Takeda utilizes PRIME to deliver its IBD drug needle free
  - Portal manufactures device, Takeda fills drug, ships the drug and device
  - Patient choice of PRIME “no needle” device drives market penetration
  - Unique interactive experience drives compliance and build brand loyalty
  - Pharma receives treatment insights & intervention effectiveness measures to drive better service offerings
- Biotech deal structure:
  - Exclusive collaboration and license agreement in IBD
  - Upfront, milestones and royalty payments
- $100+ million landmark deal

How to Partner with Portal

Step 1
Goal Setting

Evaluation of target molecule

- NDA
- Drug-Device Evaluation
- Evaluation of Primary Package

Step 2
Planning

Technical expertise provided by Portal

- Collaborative Study Design
- Quote & Protocol
- Material Transfer Agreement

Step 3
Execution

Study completed by partner

- Feasibility Testing
- Training, Support & Recruitment
- Clinical Evaluation

Study Outcomes

Clinical

- Tolerability
- PK/PD Profile
- Compliance

Human Factors

- Preference
- Market Acceptance
- Usability Profile

For more information, please visit **www.portalinstruments.com** or email us at **partnering@portalinstruments.com**

Summary

- Transformative technology, solving the patient experience challenge for self-administration of biologics in chronic diseases
- Unique needle-free jet injection technology augmented by connectivity and digital health solutions driving market penetration, market share and improved compliance
- Successful clinical studies and usability studies support value proposition and rapid adoption
- First pharma commercial deals signed

Patrick Anquetil, PhD, MBA - CEO
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