All About Prefilled Syringes

Christa Jansen-Otten, Klaus Ullherr, Bernd Zeiss

PDA Parenteral Drug Association Training and Research Institute

Agenda –
DAY 2

Technical Aspects of Prefilled Syringes
- Syringe meets formulation
- Physical performance
- Pharmaco-chemical performance

Regulatory and Pharmaceutical Aspects
- Short overview on regulatory guidelines and technical standards: EU / US / ISO / …
- Short overview and Introduction into Drug-Syringe Interactions

Manufacturing Aspects Regarding Filling, Finishing and Assembly
- Rod insertion and labeling
- Combi filling
- Robot filling
- New trends

Introduction into Autoinjectors

Questions and Answers

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All about Pre-Filled Syringe Systems

From Initial Development to Final Fill Finish

Introduction into Autoinjectors

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23-24 October 2025

Vienna, Austria

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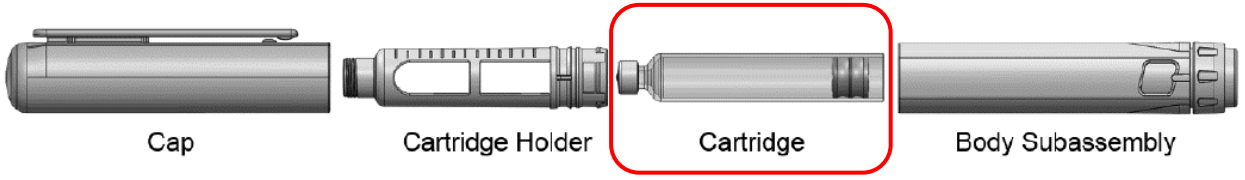
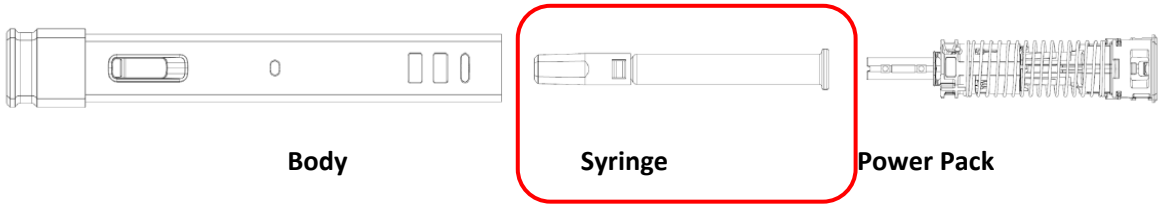
Difference between Autoinjectors and Pens

Pens



Auto-Injectors



From Manufacturers web pages

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Drug Delivery System Treatment Areas

Indications for Pens

- Diabetes (Insulin, GLP-1)
- Growth disorders (hGH)
- Fertility (FSH)
- Osteoporosis (PTH)
- Parkinson's (Apomorphine)

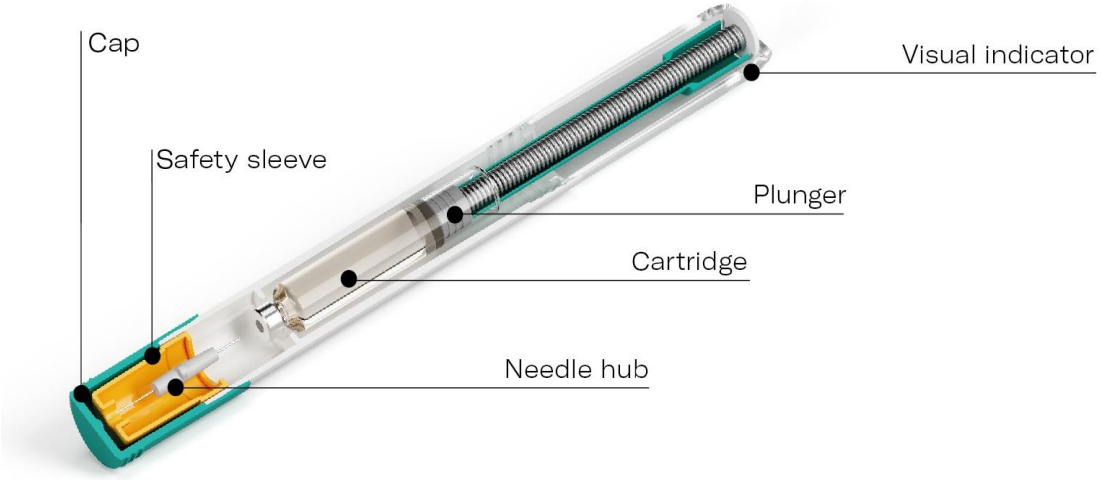
From Manufacturers web pages

Indications for Autoinjectors

- Diabetes (GLP-1)
- Autoimmune disorders
- Asthma, respiratory diseases
- Immuno-oncology
- Migraine

Autoinjectors - Market

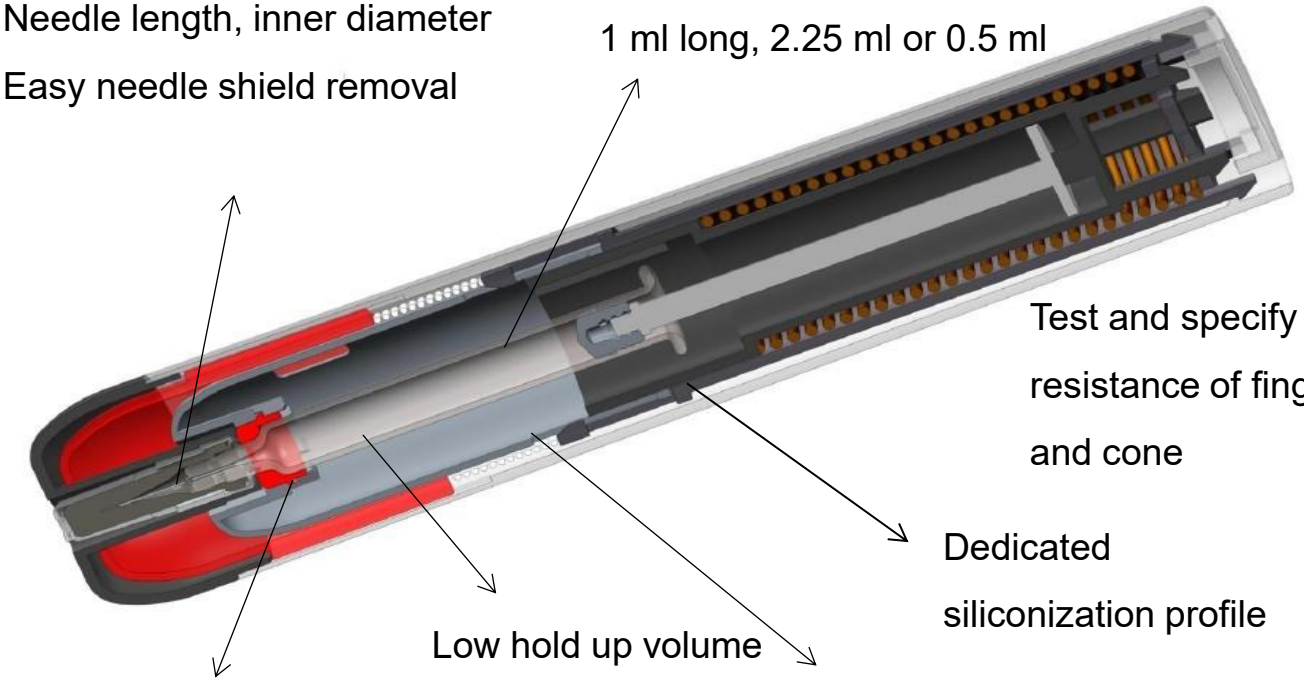
- Self administration and misuse prevention
- Biologics and large molecules
- Larger volumes and high viscosities
- Cartridges and syringes as primary container
- Cartridge based autoinjectors possible
- CAGR USD 8.35 billion in 2023 and is projected to grow at a CAGR of 14.4% from 2024 to 2030*



Gerresheimer Inbeneo: example of a cartridge based autoinjector

*From grandviewresearch.com

Syringe system requirements inside an Autoinjector



Current limits of syringes in autoinjectors are pushed futher

- Dose volume < 3 ml → 5 ml and more
- Viscosity < 10 cP → >10 cP
- Subcutaneous application - → im
- Mechanical (spring), ~10 s → 30 s and more

→Wearables

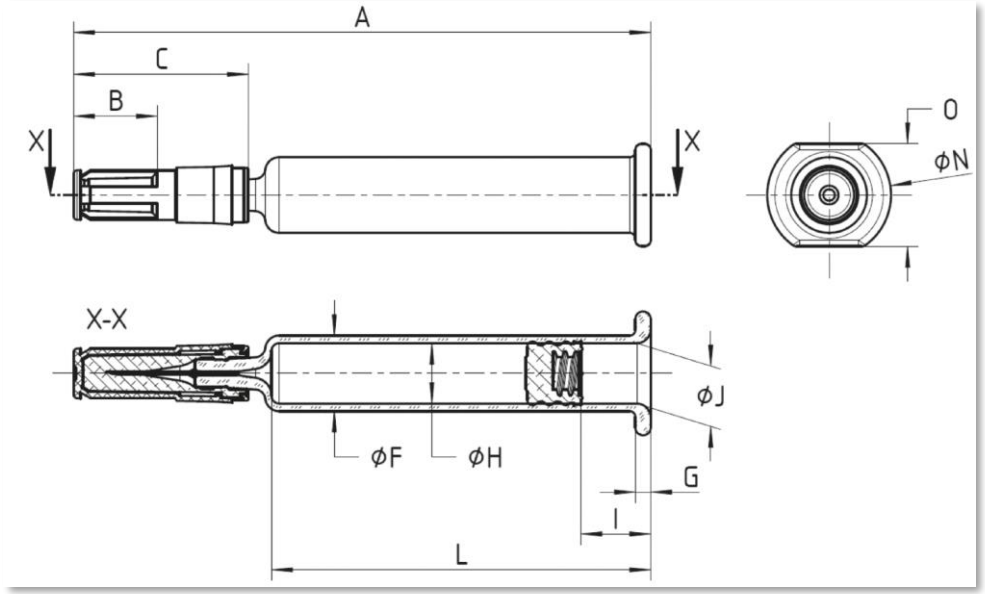
- Dose volume > 3ml
- Viscosity > 10 cP
- Subcutaneous
- Electric drive, minutes

→Infusion

- Intraveneous (vial + disposable syringe)
- home use limited

Advait V Badkar, Rajesh B Gandhi, Shawn P Davis & Michael J LaBarre (2021) Subcutaneous Delivery of High-Dose/Volume Biologics: Current Status and Prospect for Future Advancements, Drug Design, Development and Therapy, 15:, 159-170, DOI: 10.2147/DDDT.S287323

1. Dimensional fit of Syringe into Autoinjectors



All the functionality tests need to follow ISO 11608-1 and ISO 11608-5. Other dimensional aspects may be considered for specific AI designs

Example: Dimension I influenced by Fill& Finish

Dimension	Glass Syringe Dimensions Including RNS	Autoinjector Device Dimensions
A	✓	✓
B	✓	–
C	✓	✓
F	✓	✓
G	✓	–
H	✓	–
I	n/a	✓
J	✓	✓
L	✓	✓
N	✓	✓
O	✓	✓

From Zeiss, B, Cordier, S,. Lee; L. A partnership worth more than the sum of its parts. PDA Phoenix 2024

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2. Essential Performance requirements (EPR)

EPR for Auto-Injectors

- Cap removal force
- Activation force
- Needle penetration depth
- Delivered volume (Dose accuracy)
- Injection time
- Audio and visual and tactile feedback

Life Saving Treatment:
Cap Removal Force is an EPR

Non-Life Saving Treatment:
Cap Removal Force is not an EPR

ISO 11608-5 requirement	Test parameter/value example
Needle cap removal force for user	≤ 30 N
Activation force for user	4-18 N
Subcutaneous injection depth	4-7 mm
Dose accurracy	Weight before and after delivery
Injection time	3-18 s
Needle retraction	Functionality check
Needle shield	Functionality check

Modified from Jamal, H, Köhler C.: Navigating ISO 11608 with Automated equipment for customized pen and autoinjector testing: Ondrug dlivery 2024

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3. Risk Assessment Example Autoinjector

System Performance	Contribution to Essential Performance Requirements	Risk of Failure – Supplier Assessment	Which part of the system contributes Component Syringe Autoinjector	Risk of Failure	Risk Mitigation Strategies Through Suppliers Platform Datasets
Break-loose and Gliding Forces	Functional System Performance	Mostly predictable	✓ ✓ (✓)	Low to moderate	Predict Real Case Results – Spring Force of AI Can Be Adapted
Finger Flange/ Cone break	Mechanical Integrity	Drug independent	✓ ✓	Low	Syringe Breakage Resistance Tests
Needle-Shield / Cap Removal Force	User Experience / Functional System Performance	Drug independent	✓ ✓ ✓	Low	AI and Syringe Functional Test
Dimensional Fit into AI	Regulatory Compliance	Drug independent	✓ ✓ ✓	Low	Comparison of Key Dimensional Requirements and Tolerances
Acceptable Administration Time	User Experience / Functional System Performance	Mostly predictable	✓ ✓ ✓	Low to moderate	Integration of Multiple Parameters: AI Spring Force, BLGF, Needle Size, Drug Viscosity

From Zeiss, B, Cordier, S,. Lee, L. A partnership worth more than the sum of its parts. PDA Phoenix 2024

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Needle-based injection system standards

Standards which address Syringes:

ISO 9626: *Stainless Steel tubing*
ISO 7886-1: *Single use syringes*
ISO 7886-2: *Syringes for syr. pumps*
ISO 11040-5,-6,-8: *Pre-filled syringes*

Other Standards which may apply:

IEC 60601-1: *Medical Elect. Equip.*
IEC 60601-1-8: *Alarms*
IEC 60601-1-11: *Home Healthcare*
EN 62304; IEC 80002-1: *Software*
IEC 15026-1,-2,-4: *Systems & Software Engineering*
IEC 60601-2 IEC 61000-4; *and*
CISPR 11 -14-1: *EMC*
IEC 60812: *Dependability*

Pump-specific Standards:

IEC 60601-2-24: *pumps*

...if the NIS is a rate-based pump

Other Standards which may apply:

EN 1615, 1618: *catheters, tubing*
ISO 594-2, ISO 80369-1: *connectors*
ISO 11070: *IV introducers + guide wires*

...if it requires connectors/catheters

If the device is a Needle-based Injection System (NIS):

ISO 11608 family of standard: *addresses:*

Part 1 *Addresses key requirements for a NIS. The "parent" document for parts 2-7, it covers:*
- *General requirements, Risk Management*
- *Free-fall testing, Dose accuracy*
- *Determining and testing essential functions*
- *Visual inspection & Markings and Labeling.*

The NIS may also have to address the following:

Part 2 *... if, mated with a needle, it becomes a "system".*

Part 3 *... if the NIS contains a finished container or reservoir for the medicinal product. Also addresses the fluid paths (for OBDS systems)*

Part 4 *... if it contains electro-mechanical components, electronics, firmware, software and/or batteries.*

Part 5 *...if the NIS has an automated function (e.g., needle insertion) or the device limits access to a function.*

Part 6 *... if the NIS is an On-Body Delivery System (OBDS)*

Part 7 *...If the NIS is claimed to be appropriate for persons with visual impairment*

+

ISO 23908: *...if the NIS is claimed to provide post-use sharps injury protection.*

If it delivers medication without a needle:

ISO 20072: *Aerosol Drug Delivery Devices*

ISO 21649: *Needle-free Injection Systems.*

... whether it has a needle or not, it may also need:

Process Standards:

ISO 14971: *Risk Management*

IEC 62366: *Usability Engineering*

ISO 10993-3; -10 and -11: *Biological compatibility*

ISO 20069: *Guidance for Change Assessment and Evaluation to Drug Delivery Systems*

ISO 11135: *Sterilization*

ISO 15223: *Symbols*

pending: *Sustainability*

KEY: *ISO = International Organization for Standardization* *IEC = International Electrotechnical Commission* *EN = European Norm*

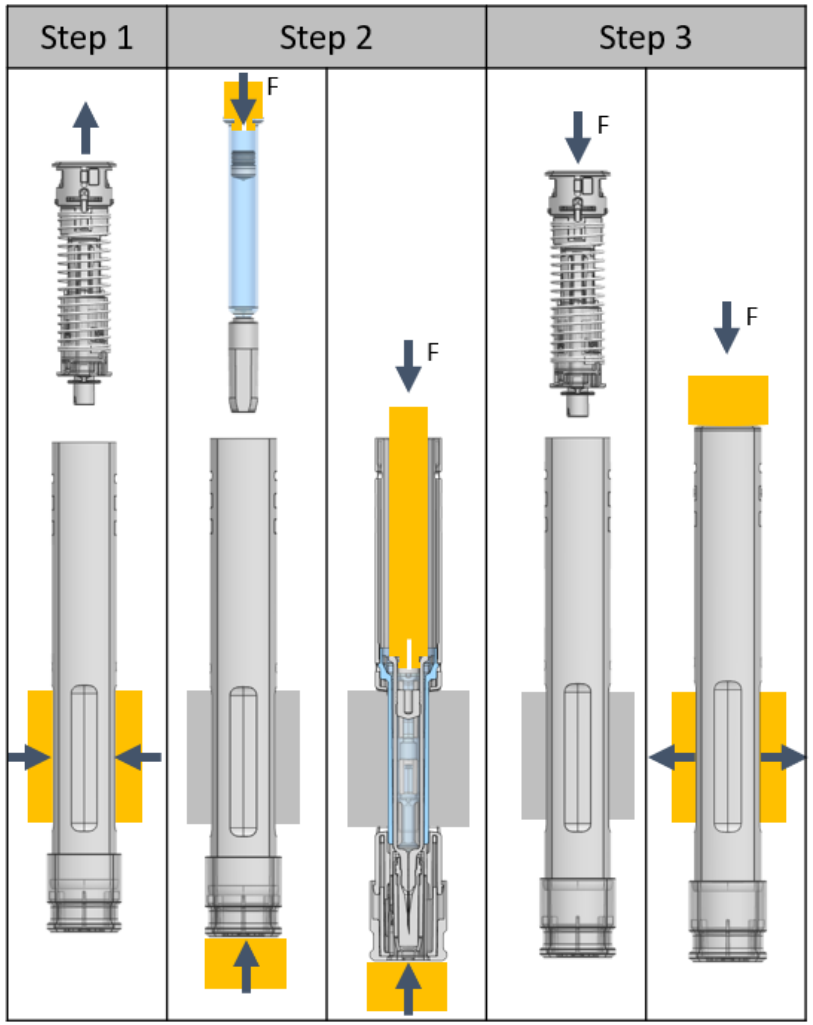
Robert R. Nesbitt, Harold K. Yeager, Michael J. Roe, and Niels Hansen: Standards for Injectable Delivery Devices: ISO 11608 Series and Others. American Association of Pharmaceutical Scientists 2020 729
F. Jameel et al. (eds.), *Development of Biopharmaceutical Drug-Device. Products*, AAPS Advances in the Pharmaceutical Sciences Series 35, https://doi.org/10.1007/978-3-030-31415-6_30

Autoinjectors – Assembly

Advanced Drug Delivery Systems go through rigorous regulatory approval

Final result for machine manufacturers = Assembly Guidelines

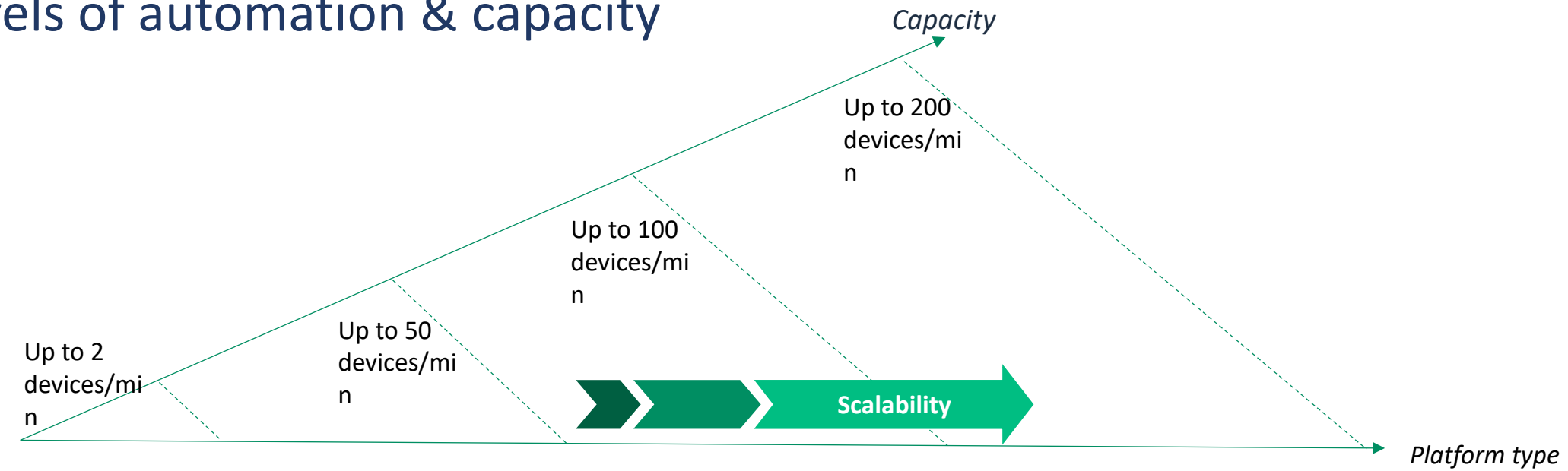
- Assembly sequence
- Travel and force measurements
- Vision quality control
- + specific customer requests

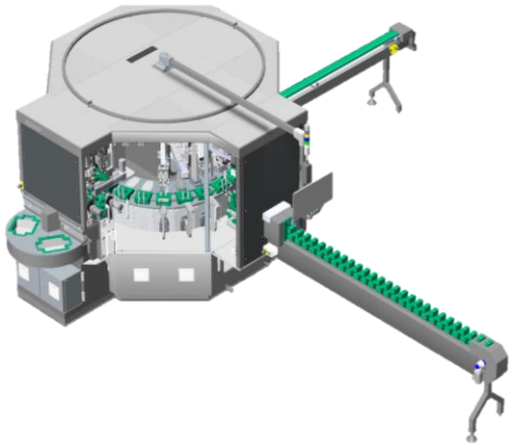


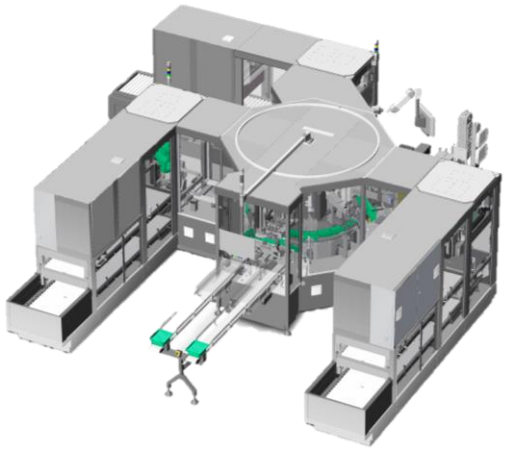
From Syntegon, Ypsomed

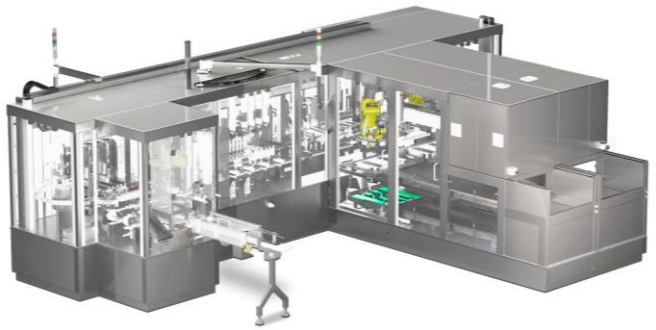
Scalability

Levels of automation & capacity









From Syntegon

Video

Final-Assembly of an Auto-Injector performed on a semi-automatic bench-top machine (RMA)

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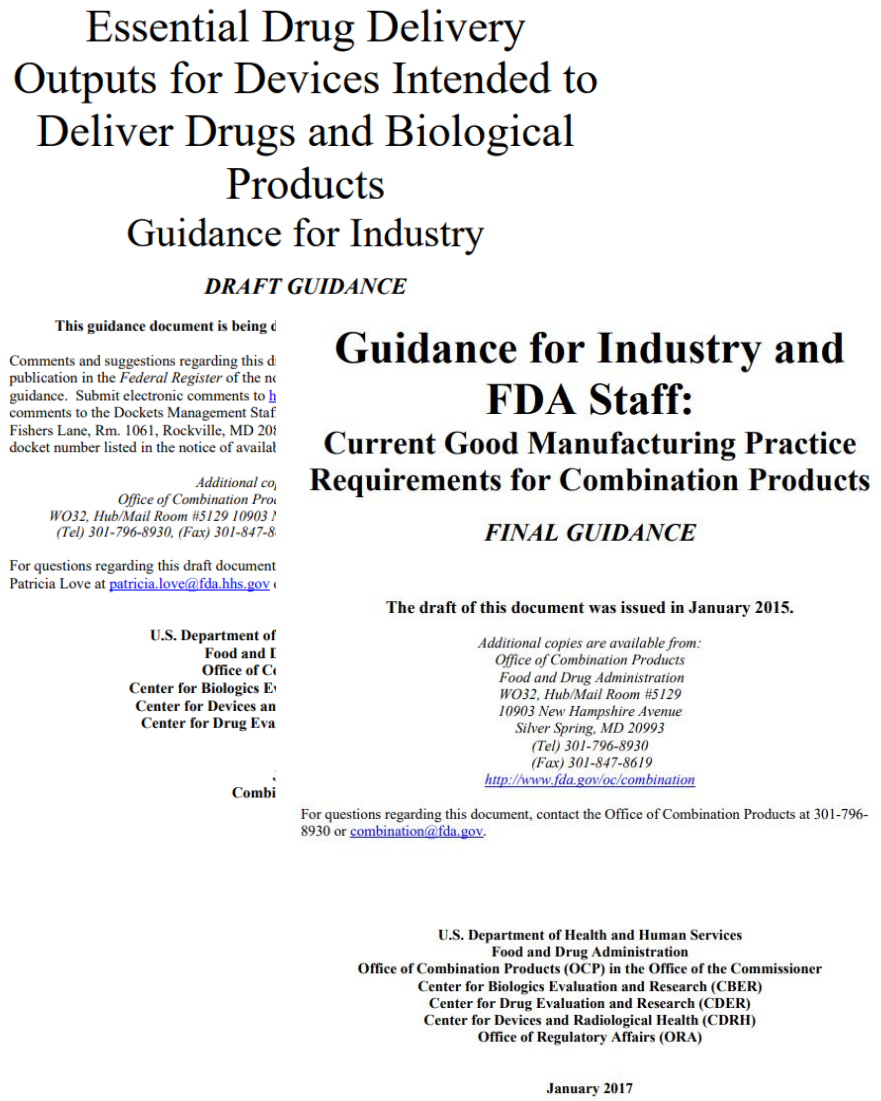
Autoinjectors – Standards and Regulation

- US FDA: Autoinjectors are Combination products, not 2ndary packaging
- To comply with 21 CFR Part 820 (quality system), and cGMP
- MDR 2017/745: to fulfil General Safety and Performance Requirements (GSPR), listed in MDR Annex 1
- ISO 11608-5: Needle based injection systems
- EDDO from FDA: Design outputs necessary to ensure drug delivery function



Essential Drug Delivery Outputs for Devices Intended to Deliver Drugs and Biological Products

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being

Comments and suggestions regarding this d
publication in the *Federal Register* of the n
guidance. Submit electronic comments to h
comments to the Dockets Management Staf
Fishers Lane, Rm. 1061, Rockville, MD 20
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Additional co
Office of Combination Pro
WO32, Hub/Mail Room #5129 10903
(Tel) 301-796-8930, (Fax) 301-847-8

For questions regarding this draft document
Patricia Love at patricia.love@fda.hhs.gov

U.S. Department of
Food and
Office of C
Center for Biologics E
Center for Devices an
Center for Drug Eva

Combi

Guidance for Industry and FDA Staff:

Current Good Manufacturing Practice Requirements for Combination Products

FINAL GUIDANCE

The draft of this document was issued in January 2015.

Additional copies are available from:
Office of Combination Products
Food and Drug Administration
WO32, Hub/Mail Room #5129
10903 New Hampshire Avenue
Silver Spring, MD 20993
(Tel) 301-796-8930
(Fax) 301-847-8619
http://www.fda.gov/oc/combination

For questions regarding this document, contact the Office of Combination Products at 301-796-8930 or combination@fda.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Office of Combination Products (OCP) in the Office of the Commissioner
Center for Biologics Evaluation and Research (CBER)
Center for Drug Evaluation and Research (CDER)
Center for Devices and Radiological Health (CDRH)
Office of Regulatory Affairs (ORA)

January 2017

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Example Procedures - Exercise

Guidance for Industry and FDA Staff:
Current Good Manufacturing Practice Requirements for Combination Products

Design Input/User Needs	*Design Output*
Required minimum/maximum dose delivery for drug	Drawing/specification for syringe dimensions, markings, etc.
Drug viscosity and desired/required delivery rate	Drawing/specification for needle bore, glide force, etc.
Expected use condition (e.g., expected user experience/education level)	Content and reading level for the prefilled syringe's labeling
Maximum and minimum allowable temperature for prefilled syringe	Packaging/labeling specifications for the prefilled syringe
No degradation of drug or syringe over the expected shelf-life as a result of contact with one another	Specifications for drug-contacting syringe materials
Expected shipping method and appropriate storage conditions	Design drawings/specifications for primary and secondary packaging, labeling for acceptable storage conditions
Drug delivery method (e.g., needle or needleless delivery)	Drawing/specification for needle and/or other associated syringe components

Flick over the Guidance:

Current Good Manufacturing Practice Requirements for Combination Products | FDA

What chapters are applicable and important for PFS?

Essential Drug Delivery Outputs for Devices Intended to Deliver Drugs and Biological Products

Design outputs	Drug delivery design outputs	System level	Device dependent	EDDO (yes or no) and rationale
Dose accuracy				Yes. The automated dose delivery is necessary to ensure appropriate drug delivery.
Extended needle length				Yes. It ensures the needle is at the right depth and is dependent on the device.
Activation force				Yes. It initiates drug delivery and is dependent on the device not the user.
Injection time				Yes. It ensures the drug is delivered to the intended space within the appropriate time and is dependent on the device not the user.
Audible feedback/clicks				Yes. It signals that the injection is complete and is dependent on the device.
Visual feedback				Yes. It signals that the injection is complete and is dependent on the device.
Cap removal force				Yes. Cap removal needs to be completed before the injection can be administered and it is dependent on the device.

Flick over the Guidance:

Essential Drug Delivery Outputs for Devices Intended to Deliver Drugs and Biological Products | FDA

What chapters are applicable and important for auto-injectors?

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Summary - Autoinjectors

Self administration

Syringe or cartridge based

Essential Performance Requirements