



Development and Regulatory Aspects of Primary Packaging

Horst Koller - HK Packaging Consulting GmbH

PDA Training Course; Development and Manufacturing of PFS

09-10 November 2017; Vienna Austria



AGENDA

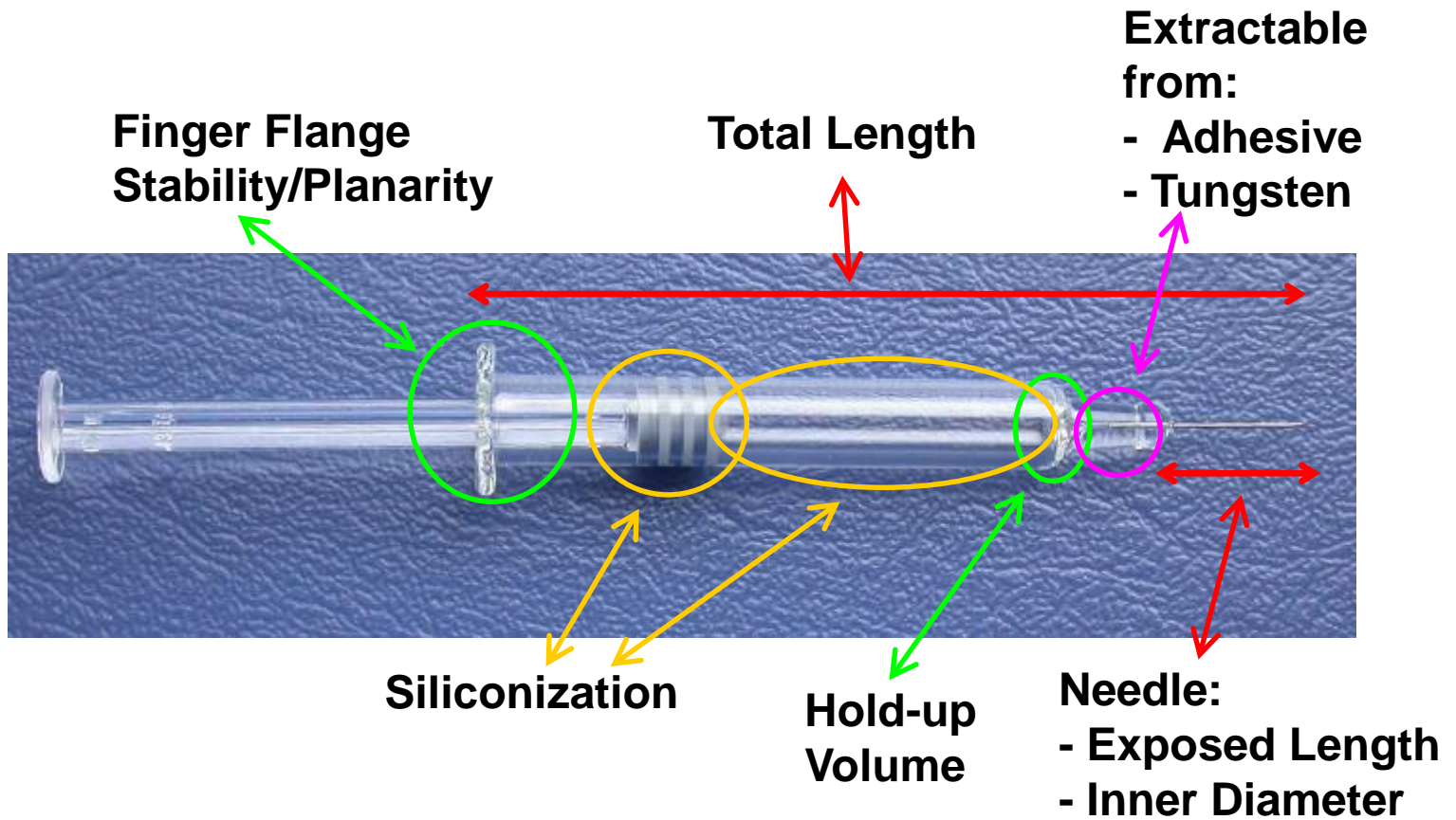
The Relevant Guidelines

- **Agencies, Committees (tasks and responsibilities)**
- **Syringe related Standards (ISO)**
- **Syringe related Monographs (USP, EP, JP,..)**

Vial – Syringe Life Cycle Management Considerations



What to think about.....





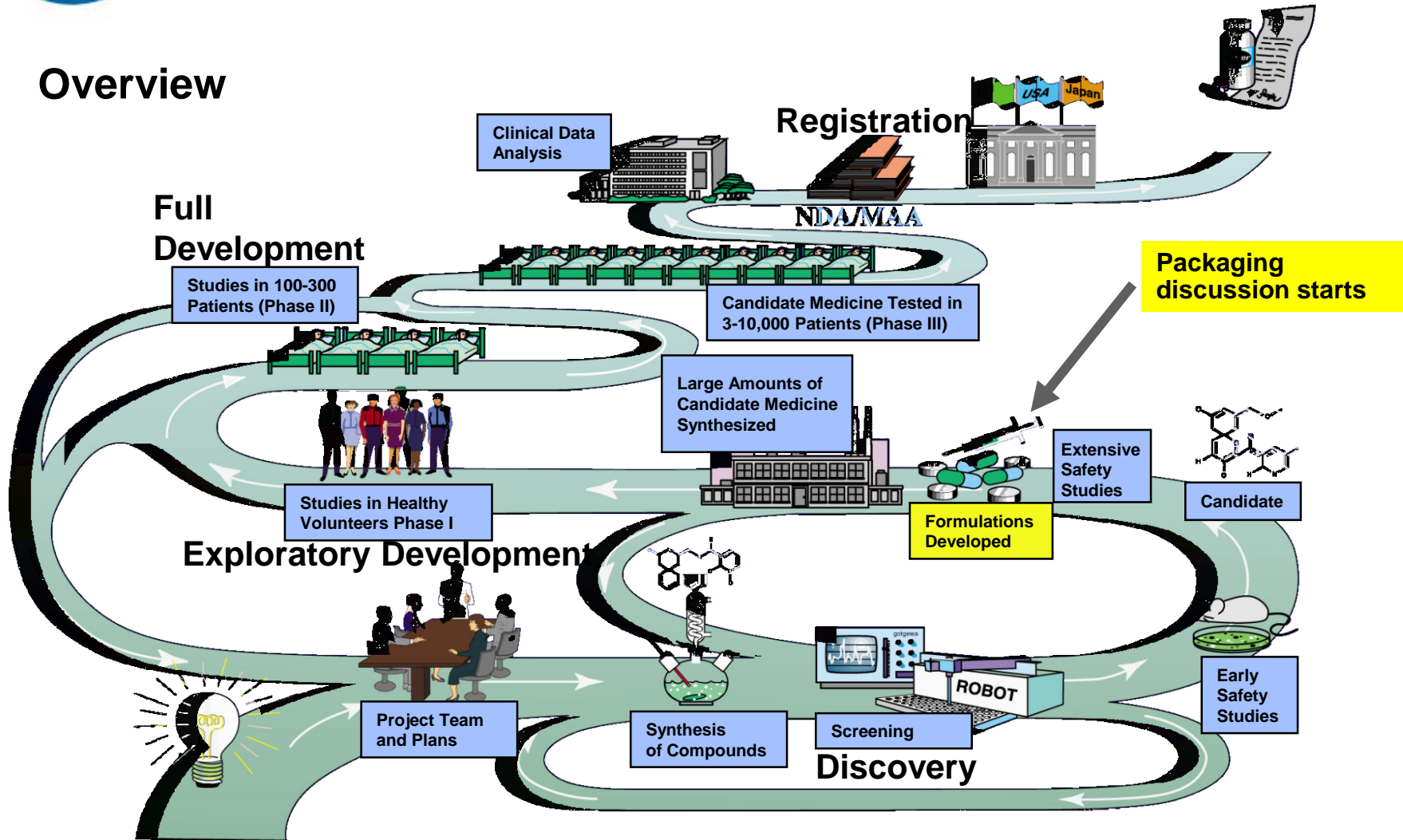
And many things more.....

Material (Permeability, E&L)
Sterilization (ETO, Gamma, X-ray, Steam)
Silicone Amount
TipCap Rubber Formulation
Stopper / Piston Rubber Formulation
Needle Type and Diameter
Fill Volume
Needle Shield Type
Needle Shield Formulation
Nest Configuration (160 / 100)
Piston Rod
Breakloose and Sliding Force Specification
Drug Compatibility
Container Closure Integrity
Shelf Life
Etc.....



A long way from the idea to submission

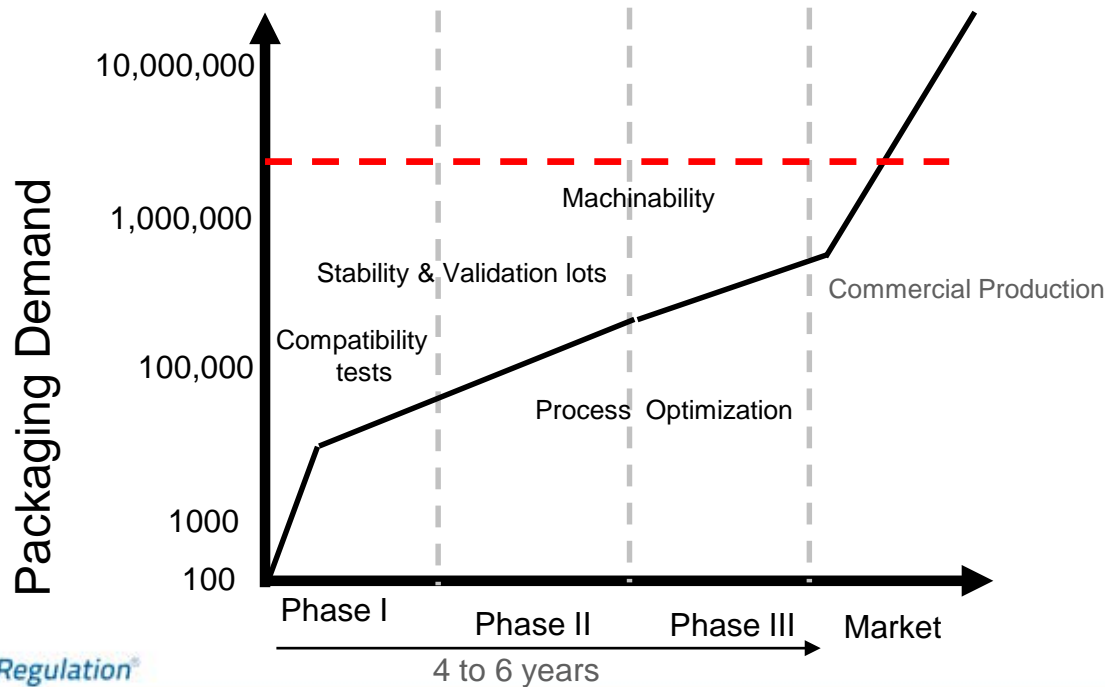
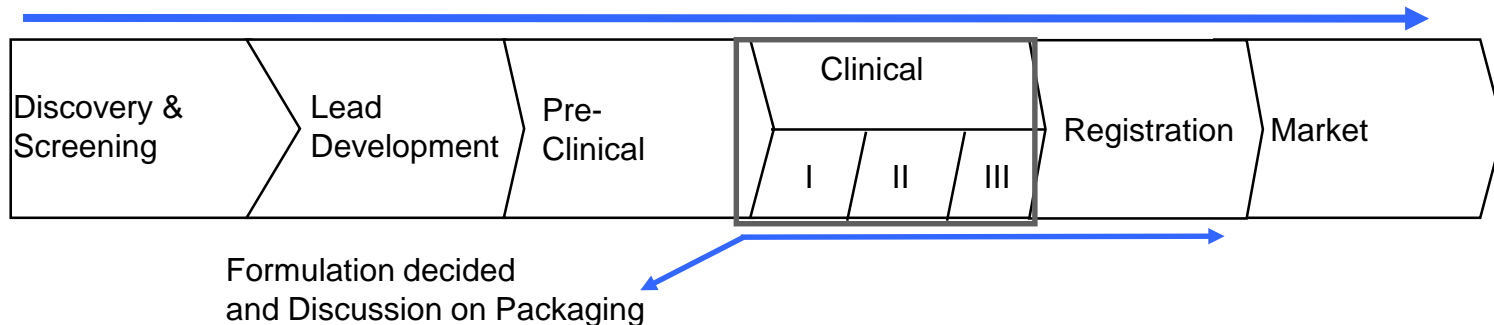
Overview





Example of a development timeline

Development time & cost per drug: 8 - 10 years and ~ 600 Mio \$ to 1 Bn \$





Agencies and Committees



European Directorate for the Quality of Medicines & HealthCare

EUROPEAN PHARMACOPOEIA COMMISSION

International Organization for Standardization
 Organisation internationale de normalisation
 Международная организация по стандартизации [1]



International Organization for Standardization
 English language logo of the ISO



List of members

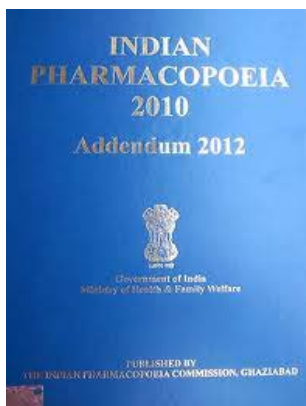
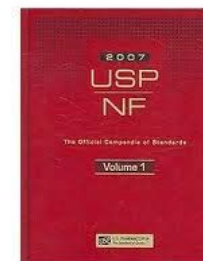
Formation	23 February 1947
Type	NGO
Purpose/focus	International standardization
Headquarters	Geneva, Switzerland
Membership	162 members [2]
Official languages	English, French and Russian
Website	www.iso.org



Food and Drug Administration



Agency overview



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH





Area / Responsibilities / Tasks

Area	Name	Roles and Responsibility	Information
Europe	EMA	Evaluation of medicines and devices	http://www.ema.europa.eu/ema/
Switzerland	Swiss Medic	Evaluation of medicines and devices	http://www.swissmedic.ch/index.html?lang=de
Germany	BfArM	Evaluation of medicines and devices	http://www.bfarm.de/DE/Home/home_node.html
USA	FDA	Evaluation of medicines and devices	http://www.fda.gov/default.htm
Canada	Health Canada	Evaluation of medicines and devices	http://www.hc-sc.gc.ca/index-eng.php

Non limitative list



Syringe Related Standards

Type	No.	Name	PFS Relevant Content
ISO	7886-1	Sterile hypodermic syringes for single use – part 1: syringes for manual use	Residual volume; side load, graduations, axial compression, piston vacuum
ISO	7886-2	Sterile hypodermic syringes for single use – part 1: syringes for use with power driven syringe pumps	Dose accuracy, dose consistency
ISO	11040-4	Prefilled syringes – part 4: glass barrels for injectables and sterilized subassembled syringes ready for filling	Cone and flange breakage, particulate matter, endotoxin, closure tightness, closure removal, siliconization performance, dimensions
ISO	11040-6	Prefilled syringes – part 6: plastic barrels for injectables	Dimensions, materials (bulk)
ISO	11040-7	Prefilled syringes – part 7: Packaging systems for sterilized subassembled syringes ready for filling	Tubs, nests materials , dimensio ⁿ , bag configurations, glass and polymer syringes
ISO	11040-8	Prefilled syringes – part 8: Requirements and test methods for finished prefilled syringes	System, physical and pharmaceutical characterization



Syringe Related Standards

Type	No.	Name	PFS Relevant Content
ISO	11040-5	Prefilled syringes – part 5: plunger stopper for injectables	Shapes and dimensions, requirements (non coated)
ISO	8537	Sterile single use syringes with or without needle, for insulin	
ISO	11608-1	Needle based injection system for medical use – requirement and test methods part 1: needle based injection system	Requirements for pens, autoinjectors, on-body delivery systems
ISO	11608-2	Needle based injection system for medical use – requirement and test methods part 2: needles	Pen needles, others
ISO	11608-3	Needle based injection system for medical use – requirement and test methods part 3: containers	Tests for combined system
ISO	7864	Sterile hypodermic needles for single use	Length, inner and outer diameter
ISO	80369-7	Small-bore connectors for liquids and gases in healthcare applications – part 7 connectors with 6% (Luer) taper for intravascular or hypodermic applications	Substitute for ISO 594 (Dimensions)
ISO	80369-20	Small-bore connectors for liquids and gases in healthcare applications – part 20 common test methods	Substitute for ISO 594 (Testing)



Syringe Related Monographs

Type	No.	Name	Information
USP	660	Containers Glass	Physical, chemical testing
USP	661.2	Plastic Packaging	Physical, chemical testing, functional
USP	671	Containers Performance Testing	General testing
EP	3.1.8	Silicone oil used as lubricant	Usually used for glass and Polymer PFS and needle siliconization
EP (planned)	3.1.16	“COP and additives for container for parenteral and ophthalmic preparations”	Chemical testing, Identification
EP (planned)	3.1.17(?)	“COC and additives for container for parenteral and ophthalmic preparations”	Chemical testing, Identification
EP	3.2.8	Sterile Single Use Plastic Syringe	Chemical testing, Identification (Silicon oil limit)
EP (planned)	3.2.10	“Prefilled Syringes” COP / COC / PP	Chemical testing, Identification
JP	7.01	Glass containers for injections	General testing
JP	7.02	Plastic container for injections	General testing



Vial to PFS Life Cycle Management Considerations

Hospitalization vs. Home Care

Ease-of-use / compliance



Product differentiation

Life Cycle Management can extend the product life time

Safety

Re-Formulation: Lyo \leftrightarrow Liquid



Pictures are the courtesy of SCHOTT Pharmaceutical Packaging / SHL Group



Prefilled syringe – an economic advantage

- Devices which meet customer demands for increased safety and convenience, can be sold more expensive⁽¹⁾
- Prefilled Syringes also help increase the saleable amounts of API which is remaining in a vial because of overfilling



(1) Financial Model for Converting from a Vial to a Pre-filled Syringe

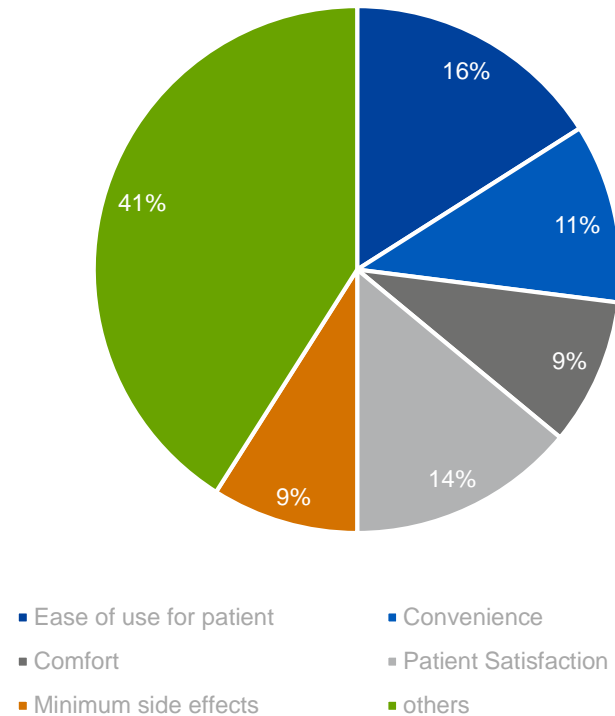


Important for the way of administration

«When administer a drug the *ease of use* for patients and the patient *satisfaction* are the most important key factors»

«When selecting a drug-delivery device for their patients, *46% of physicans* take into account wheter it easily enables self-administration»

Choice of a drug delivery type



Info taken from: Pharmaceutical Technology; Supplement Sep 2009 Issue, Author: Raul Soikes



Complexity of finished product – filled containers

Ampoule	Vial	Cartridge	PFS
Type 1 Glass	Type 1 Glass Polymer	Type 1 Glass Polymer	Type 1 Glass Polymer
	Rubber stopper	Septum	TC / NS*
		Rubber Plunger	Rubber Plunger Plunger Rod
		Baked Silicone	Silicone (Baked)
			Glue*
			Needle*
+ Hypodermic needle / syringe	+ Hypodermic needle / syringe	+ Pen + Pen Needle + Delivery Device	+ Autoinjector + Safety Device

**C
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Summary

The Development of PFS and Manufacturing is still a

C O M P L E X

Business



- SCHOTT Pharmaceutical Packaging and SHL to allow me to using their pictures