COC and PP Materials for Primary Packaging -

Safety Risks Posed by Compounded Drugs Stored in Non-Suitable Container Closure Systems

Agenda

01 Introduction.

02 Key functions of container closure systems

03 Container closure safety concerns for polypropylene syringes (PP).

04 Supply chain situation.

05 Guidelines.

06 Questions and Answers.

01

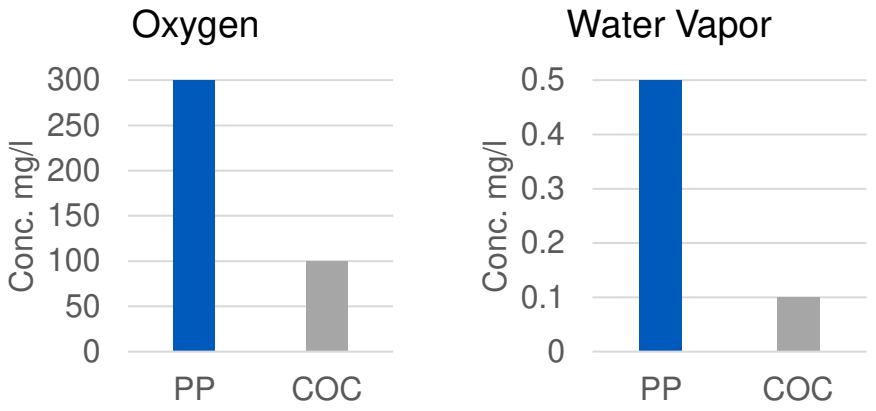
Introduction

Starting with some data & facts.

Internal

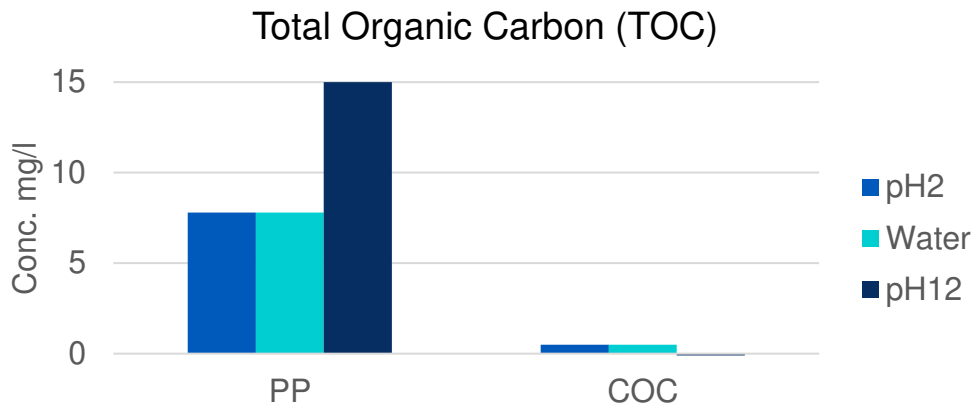
Single-use PP disposable syringes can pose a safety risk due to low barrier properties and high amount of extractables for drug storage over time.

Barrier Properties



See: TOPAS (2019)

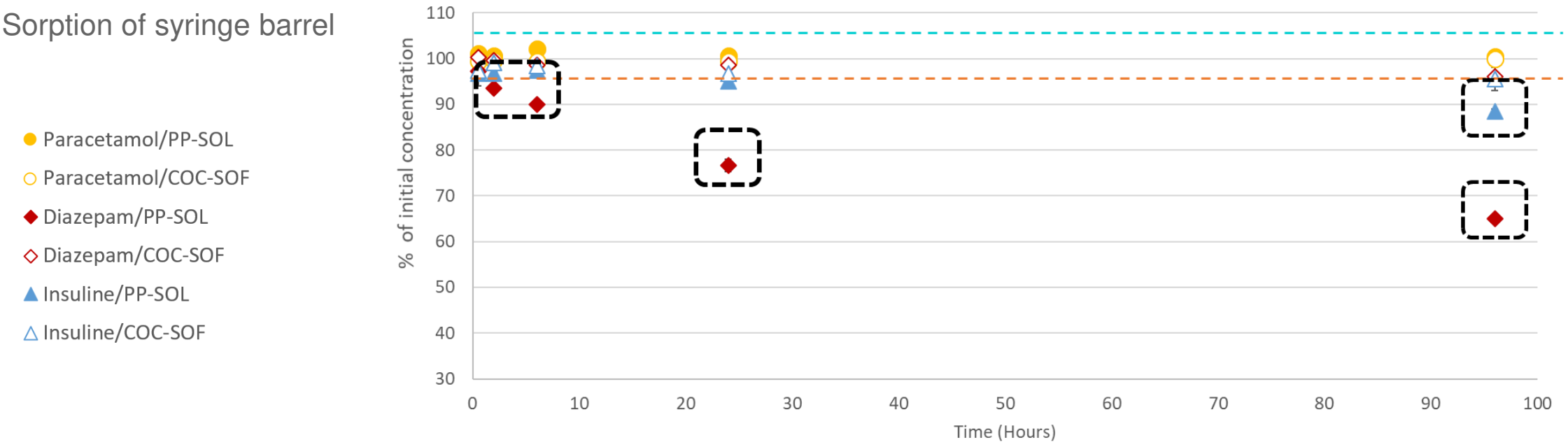
Extractables profile



See: Parenteral Medications (2019)

Different sorption phenomena between syringes made of polypropylene and COC: Sorption for insulin and diazepam with PP syringes → Strong particle formation

- Sorption of syringe barrel



Paracetamol:
No API loss

Diazepam:
COC-SOF : No API loss,
PP-SOL : ↘ 34.9 ± 0.5 % in 96 h

Insulin:
COC-SOF : No API loss,
PP-SOL : ↘ 11.6 ± 1.35 % in 96 h

→ Significant sorption for insulin and diazepam with PP syringes

See: Pharmaceutical Research, 08.11.2023, Comparative study of sorption phenomena between three medications and syringes made of COC and PP.

Single-use PP disposable syringes pose a significant safety risk due to drug stability issues resulting from change in pH over time.

- Pre-filled syringe shelf life/stability
  - 3 years (unfilled)
  - 2-4 years (filled)

- Example PP stability study[2]

  Study findings…
  - Noteable increase in pH 24h and beyond
  - PGE_1 stability is only maintained for 48hr (even when shielded from light)
  - Additional loss of PGE_1 was attributed to surface adsorption
- Risk for patient is incorrect dose and adulteration of drug product

Table 3

Stability of 1.5 and 15 µg/mL PGE_1 in 10% dextrose injection solution stored in UPL and LS2 polypropylene syringes at 30°C

PGE_1 concentration	Time	Percentage PGE_1 remaining				
		Syringe type				
		UPL		LS2		
		Mean	IC95%	Mean	IC95%	p Value
1.5 µg/mL	T_0	100.0		100.0		
	24 hours	95.7	(90.5 to 100.9)	95.9	(89.5 to 102.3)	0.92
	48 hours	96.1	(92.4 to 99.8)	91.4	(87.7 to 95.1)	0.07
	72 hours	90.9	(88.9 to 92.9)	90.0	(85.8 to 94.2)	0.46
	168 hours	85.8	(83.0 to 88.6)	84.1	(78.7 to 89.5)	0.25
15 µg/mL	T_0	100.0		100.0		
	24 hours	95.5	(91.3 to 99.7)	99.0	(93.9 to 104.1)	0.25
	48 hours	94.9	(90.8 to 99.0)	96.7	(92.2 to 101.2)	0.60
	72 hours	92.8	(87.7 to 97.9)	91.9	(85.4 to 98.4)	0.75
	168 hours	87.6	(83.5 to 91.7)	86.1	(80.7 to 91.5)	0.35

LS, light-shielded; PGE_1, prostaglandin E_1; UPL, unprotected from light.

[2]https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6319414/

Regulatory Considerations for Syringes in Drug Container Closure Systems (CCS)

The use of single-use PP disposable syringes presents a significant safety risk to the public because its suitability for use with a drug has never been reviewed or approved by FDA for long-term storage.

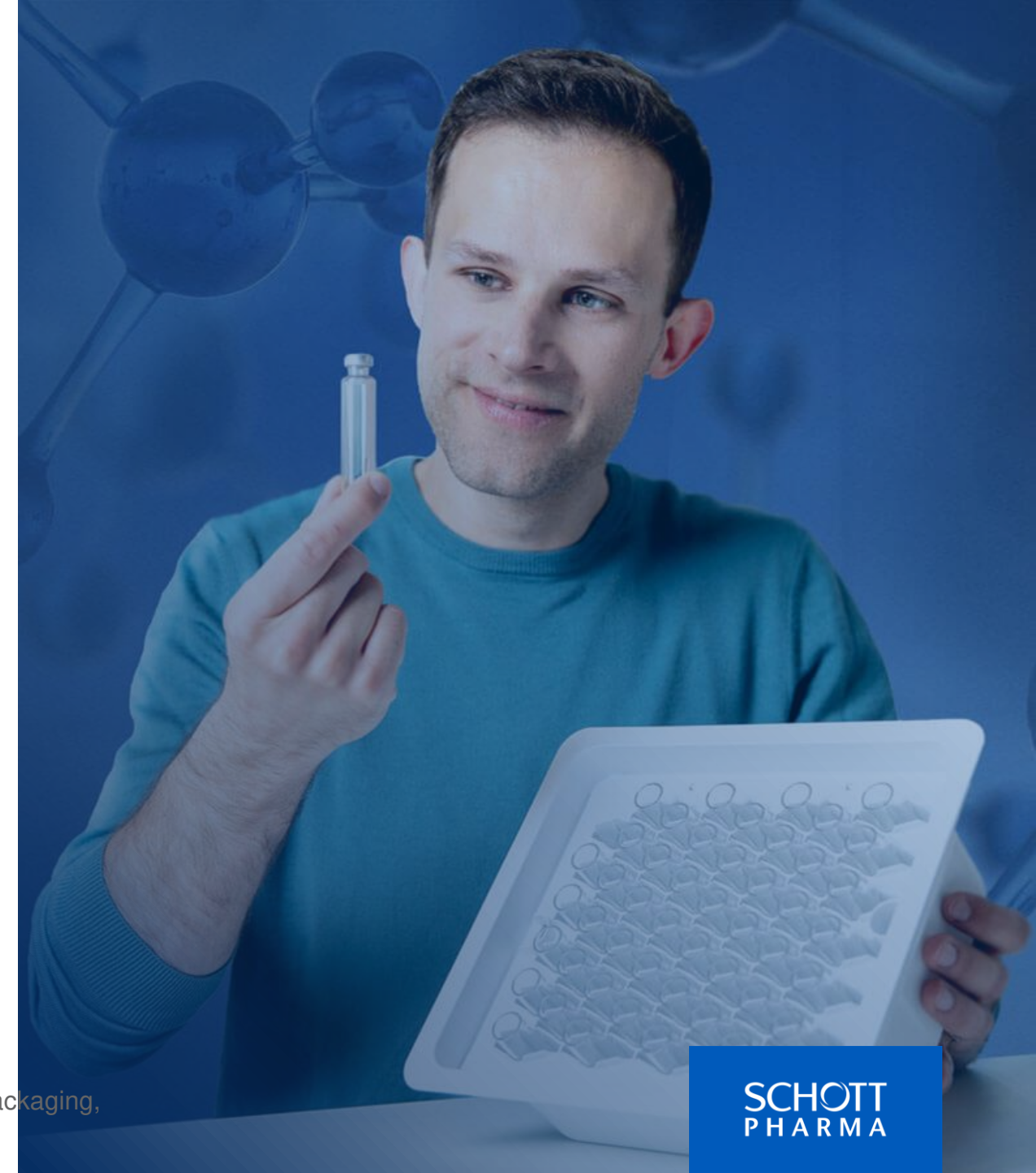
- FDA clears single-use PP disposable syringes for general-purpose fluid aspiration and injection only (21 CFR § 880.5860).
- PP Syringes are not generally cleared for use as drug container closure systems.
- Syringes are considered CCS and require FDA approval if:
  - Used as prefilled syringes for drug delivery (21 CFR § 3.2(e)).
  - Constituent parts or materials are used in a CCS for an approved drug (21 CFR § 4.4).
- Approved CCS must protect and be compatible with the drug and its route of administration.

(1):Container Closure Systems for Packaging Human Drugs and Biologics: Chemistry, Manufacturing, and Controls Documentation (May 1999) (“CCS CMC Guidance”)

02

Key functions

of container closure systems



Key functions of container closure systems

- Container closure **systems must offer adequate protection against external factors** that could lead to drug product deterioration or contamination during storage and use.

- Drug product containers and closures **must not react with, add to, or absorb substances** that would alter the drug's safety, identity, strength, quality, or purity beyond established requirements.

- Drug product containers and closures **should be clean, and in some cases, sterilized** and processed to remove pyrogenic properties to ensure they are suitable for their intended use.

PP disposable vs. COC pre-fillable syringe

80-90% transparency[1]

High speed, automated inspection is not possible

High adsorption and extractable/leachable profile

Poor oxygen and moisture barrier properties

Not an FDA-approved drug storage container

91% transparency

Enablement of high speed, automated inspection

Inert surface with low extractable/leachable profile

Strong barrier for oxygen and moisture

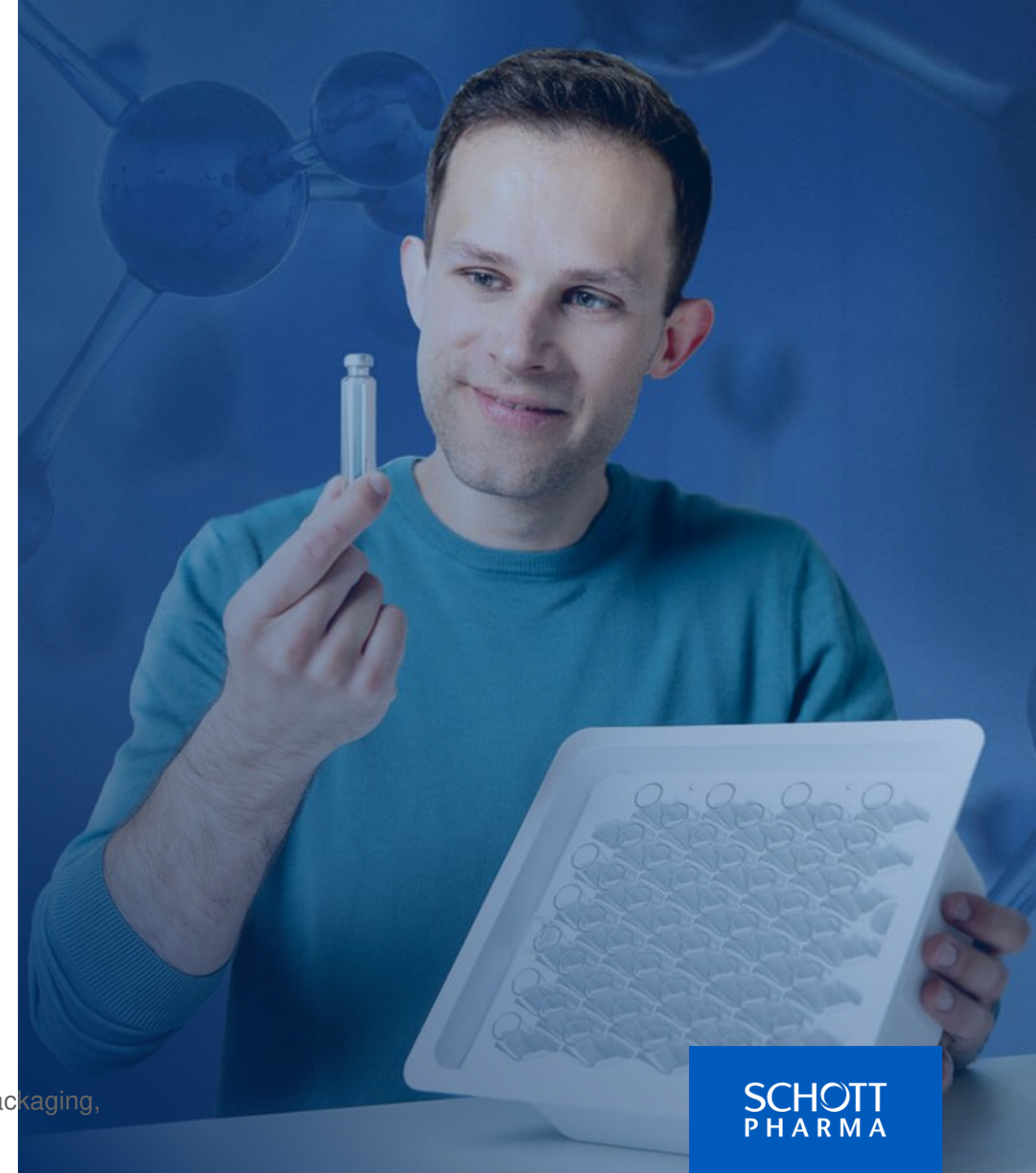
> 19 US FDA approvals to date (since 2006)

[1]https://omnexus.specialchem.com/polymer-properties/properties/transparency?id=336

03

Significant Safety Risks

Container closure safety concerns for polypropylene syringes



Critical Considerations in Syringe Containers for Drug Stability Concerns

There is uncertainty of whether the unapproved syringe or its composition will adversely affect the drug itself.

- Single-use syringes may not be suitable containers for pre-filled drug products, particularly for large-scale commercialization and long-term use.

- Stability testing is a mandatory component of the drug approval process.

- The interaction between the drug and its container can strongly impact drug stability.
  - For example, when stored in single-use PP disposable syringes, lorazepam has a stability of 48 hours, sufentanil 28 days, and fentanyl up to 100 days under optimal storage conditions (2).
  - These durations are notably shorter than the traditional stability periods when stored in their corresponding approved drug container closure systems.

(2):*Strengths and Weakness of Pre-Filled Syringes For Injections in Hospitals*, NEXT, Issue 02 / 2021.

Critical Considerations for Potency Concerns

- Drugs stored in pre-filled single-use PP disposable syringes lose potency over a significantly shorter time in comparison to the storage in approved drug CCS (3,4).

- Drugs can lose potency by interaction with:
  - component parts of the device like rubber
  - Increasing oxygen levels in the drug solution
  - water vapor barrier properties

- Several examples for loss of potency for the following drugs are present: fentanyl, rocuronium, neostigmine, morphine, midazolam, methadone, atropine, hydromorphone, cisatracurium, and remifentanil. (5, 6)

(3):*Stability of thiopental sodium and propofol in polypropylene syringes at 23 and 4 ºC, American Journal of Health-System Pharmacy,* Volume 53, Issue 13, 1 July 1996, Pages 1576–1579.
(4): *Compatibility and Stability of Dexamethasone Sodium Phosphate and Ketamine Hydrochloride Subcutaneous Infusions in Polypropylene Syringes, Journal of Pain and Symptom Management*, Volume 30, Issue 1, 2005, Pages 80-86
(5): *The risks behind the widespread use of siliconized syringes in the healthcare practice,* International Journal of Retina and Vitreous, Volume 7, Issue 66 2021.
(6): https://www.bd.com/documents/alerts/hypodermic/FDA-medwatch-report.pdf.

Critical Considerations for Leaching and Contamination Concerns

- Pre-filled PP disposable syringes **can lead to leaching** of particulates into the drugs, especially if not used immediately for delivery (high amount of total organic content, see introduction)

- Incompatibilities between pre-filled syringes and drug products include the safety of syringe-based leachable that accumulate in drug products and the ability of leachable to **interact with the drug product's ingredients** as such interactions can affect safety, efficacy, stability and physical viability. (7)

- Special case, Silicone leaching:
  - Silicone coats the plunger in disposable device syringes as typical PP syringe
  - Leaching into protein-based drugs has been observed
  - This observed leaching gave rise to language in a **September 2004 FDA guidance document** noting that a "potential source of contamination is the siliconization of rubber stoppers." (8)

(7):*Extractables and leachable considerations for pre-filled syringes*" Expert Opin. Drug Deliv. (June 2014).
(8): *Guidance for Industry, Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice* (September 2004).

04

Supply chain situation

Global prefilled syringes market is growing rapidly

- The global prefilled syringes market (glass and polymer) size was valued at US$ 7,742.9 Million in 2022, and is anticipated to reach US$ 20,167.8 Million by 2032 (9)
- Strong capacity expansions during the last years in the prefillable syringe market observed:
  - BD to Invest $1.2 Billion in Pre-Fillable Syringe Manufacturing Capacity Over Next Four Years (10)
  - Capital Investment of 2 Billion Yen in Terumo Yamaguchi D&D for Pre-filled Syringes (11)
  - SCHOTT Doubles Production Capacity for Polymer Syringes (12) and expands prefillable glass syringe production in Hungary (13)
  - Stevanato Group has taken steps to mitigate supply chain issues for prefillable syringes and is working closely with suppliers and customers, increasing capacity in its plants and continuing to expand operations. A new plant in Indiana is expected to start production in 2023, and a new plant in China is planned.

(9) Fact 603MR, Oct-2022, Prefilled Syringes Market Size & Trends Analysis By 2032
(10) BD (Becton, Dickinson and Company), 02 Dec, 2020, 17:30 IST
(11) Terumo Corporation (TSE: 4543), TOKYO, JAPAN - September 20, 2019
(12) https://www.pharmaceutical-technology.com/contractors/pharmaceutical-healthcare-packaging/schott-packaging/pressreleases/pressproduction-capacity-polymer-syringes/, November 11, 2023, 10:27 IST
(13) https://www.manufacturingchemist.com/news/article_page/Schott_expands_prefillable_syringe_production_in_Hungary/199404, November 11, 2023, 10:27 IST
(14) https://www.pharmtech.com/view/pre-filled-syringes-show-strong-growth, November 11, 2023, 10:32 IST

05

Guidelines

for FDA-approved container closure systems

Amendment of Guideline

Suggestions for FDA-Approved container closure systems and ways to reduce supply chain disruptions that could lead to drug shortages

- Present situation:
  - FDA guidance lacks sufficient precision related to requirements for CCS used with compounded drug.
  - FDA guidance does not explicitly state that the usage of approved drug storage containers is required.
  - This lack of precision has allowed for the use of non-approved alternatives, such as PP disposable syringes, to be used as CCS for compounded drugs creating known safety hazards.
  - Large-scale commercial compounding of existing approved drugs in unsafe prefilled disposable syringes, which itself is not permitted under the law.

- Corrective action necessary to mitigate the significant safety concerns posed using pre-filled PP syringes and other disposable containers that are not approved for the storage of compounded drugs.

- Such revisions would bring the Guidance into alignment with that of the cGMPs and other Agency guidance documents.

Executive Summary

- Storing compounded drugs in single-use PP disposable syringes for extended periods has become common practice, leading to a high risk for patients.

- Single-use disposable syringes are officially declared as medical devices designed for general-purpose fluid aspiration and injection.

- The use of single-use PP disposable syringes presents a significant safety risk because its suitability for storage over time is not controlled and guaranteed.
  - In this presentation we examine properties which differ significantly between CoC syringes approved for use with drug product and unapproved PP syringes and their potential impact on the drug product (DP)
    - Extractables & Leachable, Drug Product adsorption, Barrier properties and pH

In conclusion we believe a more detailed review of the requirements should be conducted and the guidance updated to reflect its' findings.

06

Questions & Answers

Internal

Thank You

Questions and answers?

ADKA KONGRESS

„COC und PP – Materialien für Primärpackmittel im Vergleich“

Bewerten Sie den Vortrag!
Einfach QR-Code scannen:

SCHOTT PHARMA