Polymer-based pre-filled syringes designed to minimize the aggregation risk of sensitive biodrugs

Nelson Labs Virtual Symposium
Small Volume Parenteral Packaging
30-31 March 2022

TERUMO
PHARMACEUTICAL SOLUTIONS

OVERVIEW

- ✓ Corporate Introduction
- ✓ Challenges of biopharmaceuticals
- ✓ Polymer-based pre-fillable syringes as a system approach for sensitive biodrugs
- ✓ Silicone oil-free solution
- ✓ Minimizing the risks of protein oxidation
- ✓ Aspects of contact materials: extractables & leachables

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Introduction

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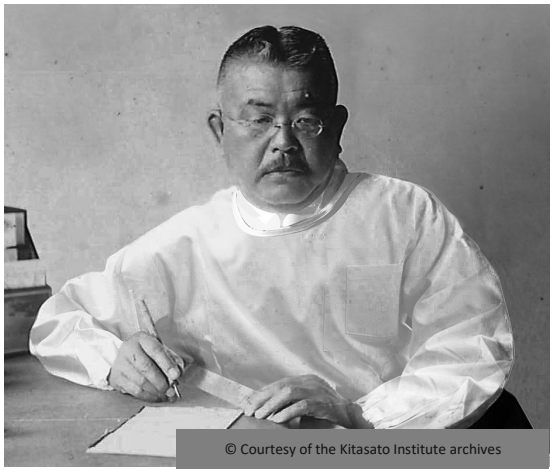
Terumo was founded by medical scientists



Dr. Shibasaburo Kitasato
(1853 – 1931)

- Terumo was founded by several medical scientists led by Dr. Shibasaburo Kitasato.
- Discovered the immune antibody against the tetanus toxin and established a serum therapy for tetanus.
- Identified a plague bacillus and paved the way for preventive medicine.

Head Office:	Shibuya-ku, Tokyo, Japan
Foundation:	September, 1921
Stock:	1st Section of Tokyo Stock Exchange
CapEx:	0.72 billion US$
Net Sales:	5.75 billion US$
Employees:	26 400

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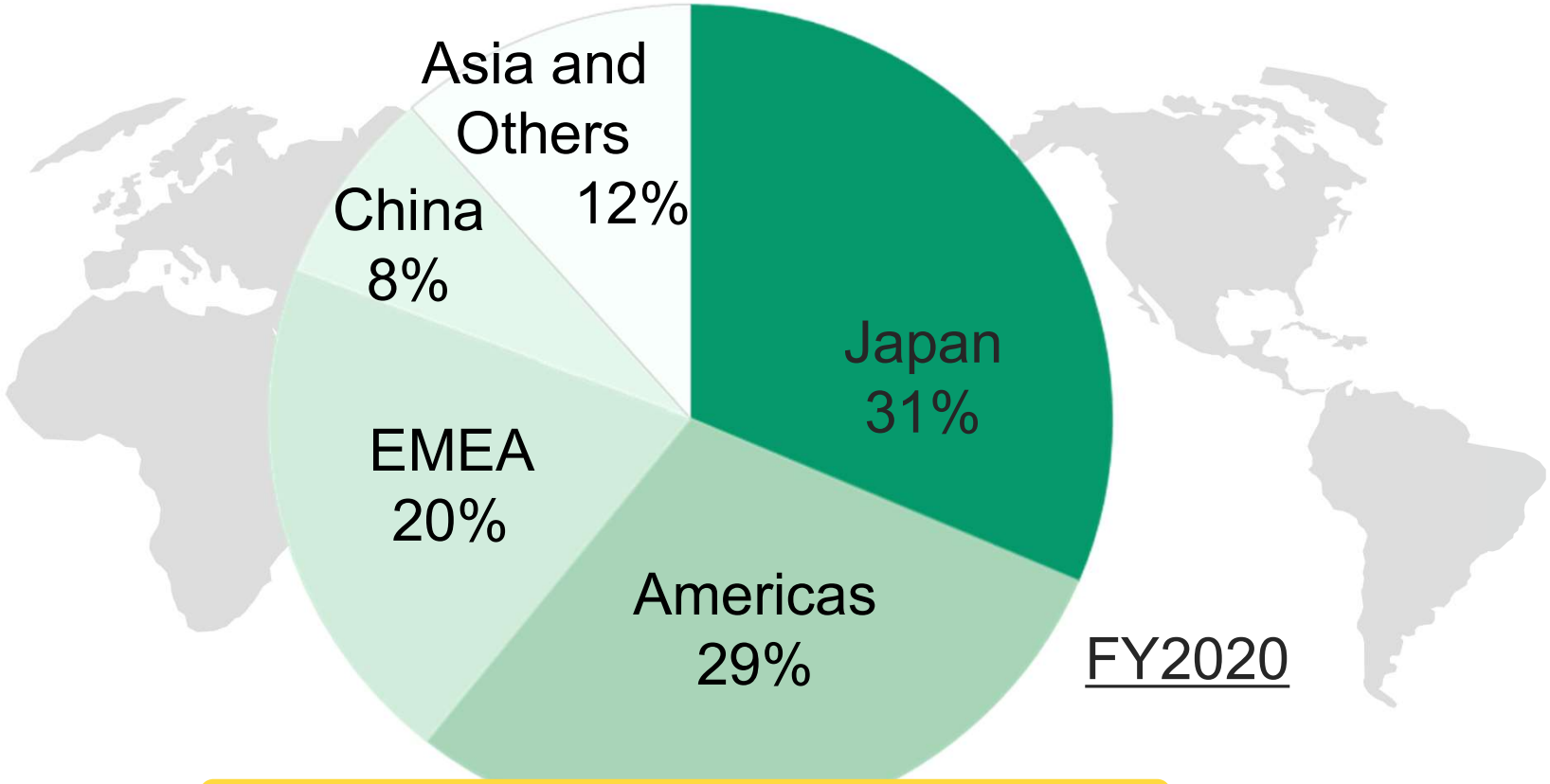
Terumo's Sales by region



Overseas Revenue Ratio: 69%

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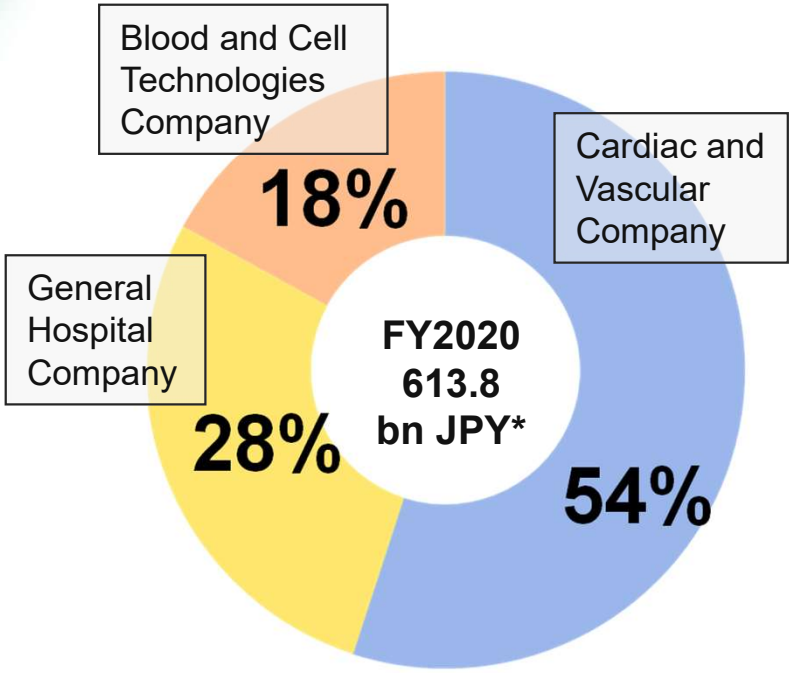
Terumo's Business

Sales by Business



*Approx $5.75 bn (1 USD =106.754 JPY)

Cardiac and Vascular Company

- Vascular Intervention
- Intervention oncology
- Cardiovascular surgery

General Hospital Company

- Hospital Systems Division
- Alliance Business
  (Collaborating with pharmaceutical manufacturers)

Blood Management Company

- Blood centers
- Therapeutic apheresis and cell collection
- Cell processing

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Challenges of biopharmaceuticals

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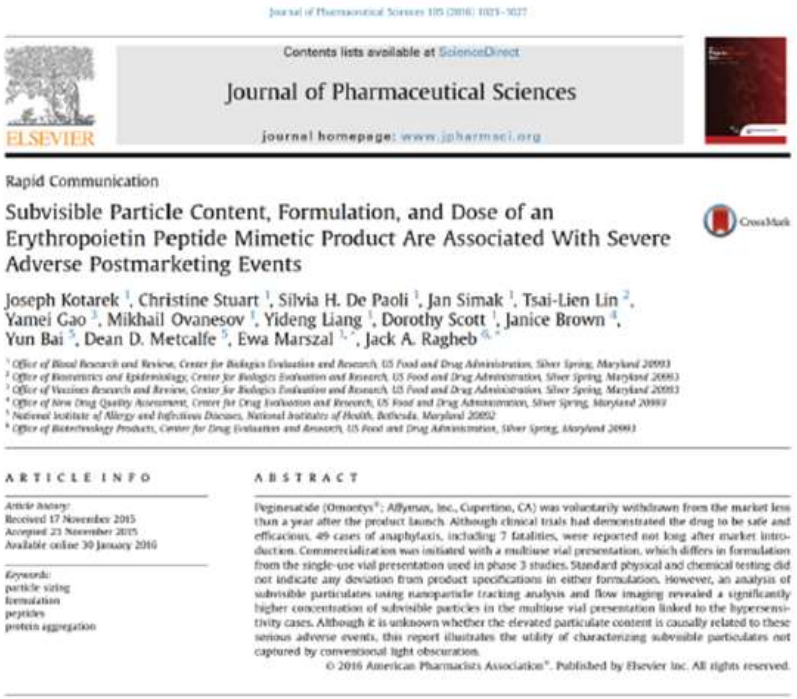
Challenges of sensitive biodrugs

Defects in quality can cause fatal incidents

- Peginesatide (Omontys®; Affymax, Inc.,) was voluntarily withdrawn from the market less than a year after launch.
- 49 cases of anaphylaxis, including 7 fatalities, were reported.
- Sub-visible particles linked to the hypersensitivity cases.



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journal homepage: www.jpharmsci.org

Rapid Communication

Subvisible Particle Content, Formulation, and Dose of an Erythropoietin Peptide Mimetic Product Are Associated With Severe Adverse Postmarketing Events

Joseph Kotarek [1], Christine Stuart [1], Silvia H. De Paoli [1], Jan Simak [1], Tsai-Lien Lin [2], Yamei Gao [3], Mikhail Ovanesov [1], Yideng Liang [1], Dorothy Scott [1], Janice Brown [4], Yun Bai [5], Dean D. Metcalfe [5], Ewa Marszal [1,*], Jack A. Ragheb [6,*]

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ABSTRACT

Peginesatide (Omontys®; Affymax, Inc., Cupertino, CA) was voluntarily withdrawn from the market less than a year after the product launch. Although clinical trials had demonstrated the drug to be safe and efficacious, 49 cases of anaphylaxis, including 7 fatalities, were reported not long after market introduction. Commercialization was initiated with a multiuse vial presentation, which differs in formulation from the single-use vial presentation used in phase 3 studies. Standard physical and chemical testing did not indicate any deviation from product specifications in either formulation. However, an analysis of subvisible particulates using nanoparticle tracking analysis and flow imaging revealed a significantly higher concentration of subvisible particles in the multiuse vial presentation linked to the hypersensitivity cases. Although it is unknown whether the elevated particulate content is causally related to these serious adverse events, this report illustrates the utility of characterizing subvisible particulates not captured by conventional light obscuration.

Joseph Kotarek, Christine Stuart, Silvia H. De Paoli, *et al*. Subvisible Particle Content, Formulation, and Dose of an Erythropoietin Peptide Mimetic Product Are Associated With Severe Adverse Postmarketing Events. *Journal of Pharmaceutical Science,* Nov 23 2005

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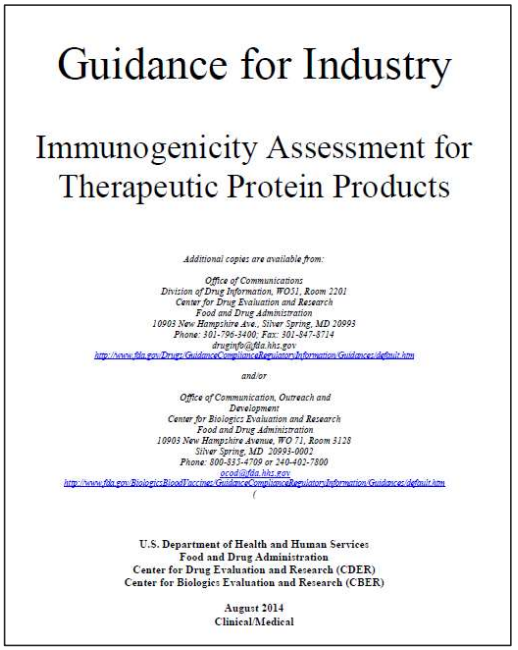
Immunogenicity is a concern

Various factors that affect immunogenicity are indicated in FDA Guidance

- Protein aggregates may elicit or enhance immune responses
- Chemical modifications, such as oxidation may elicit immune responses
- Sub-visible particles in the size range 0.1-10 microns have a strong potential to be immunogenic
- Leached materials from the container closure system may be a source of materials that enhance immunogenicity by chemically modifying the therapeutic protein product



Guidance for Industry

Immunogenicity Assessment for Therapeutic Protein Products

Additional copies are available from:

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

August 2014
Clinical/Medical

Guidance for Industry; Immunogenicity Assessment for Therapeutic Protein Products (August 2014)

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New chapters and revisions in USP

Revisions were made in response to further availability of biopharmaceuticals

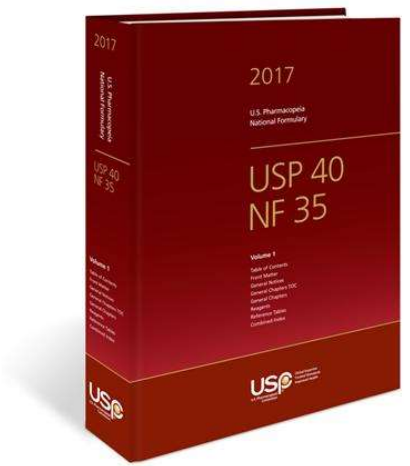
- US pharmacopeia (USP) new chapter
  - USP <1663> Extractables good practice
  - USP <1664> Assessment of leachables

- USP revisions
  - USP <661.1> and <661.2>

    Related to plastic packaging materials

- USP new informational chapter
  - USP <1787>

    Measurement of sub-visible particulate matter in therapeutic protein injections, intended to supplement USP <787>



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Factors potentially affecting biopharmaceutical PFS quality

Various causing factors = need a system approach

Factor	Issue	Caused by
Physical stress	Aggregation by silicone oil	Silicone oil
	Aggregation by tungsten	Manufacturing process
	Aggregation by glue	Manufacturing process
	Aggregation by excess physical stress	Head space
Chemical stress	Denaturation by leachables from container closure	Leachables
	Oxidation by dissolved oxygen	Dissolved oxygen
	Oxidation by remaining radicals	Irradiation
Others	Breakage	Component
	Delamination	Component
	Particles	Manufacturing process

Polymer PFS as a system approach

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A system approach with polymer-based pre-fillable syringes

Designed for sensitive biodrugs

- Polymer barrel (COP: Cyclo Olefin Polymer)
  - ➢Insert molding ➔ **Tungsten-free, Glue-free**
  - ➢High break resistance
- Prevent protein aggregation
  - ➢i-coating™ technology ➔ **Silicone oil-free**
  - ➢Low sub-visible particles
- Prevent protein oxidation
  - ➢Secondary packaging with oxygen absorber
  - ➢Steam sterilization ➔ **No radical generation**
- Low extractable syringe system
  - ➢COP, Chlorinated butyl rubber (CIIR)
  - ➢Steam sterilization ➔ Low extractable

i-coating™

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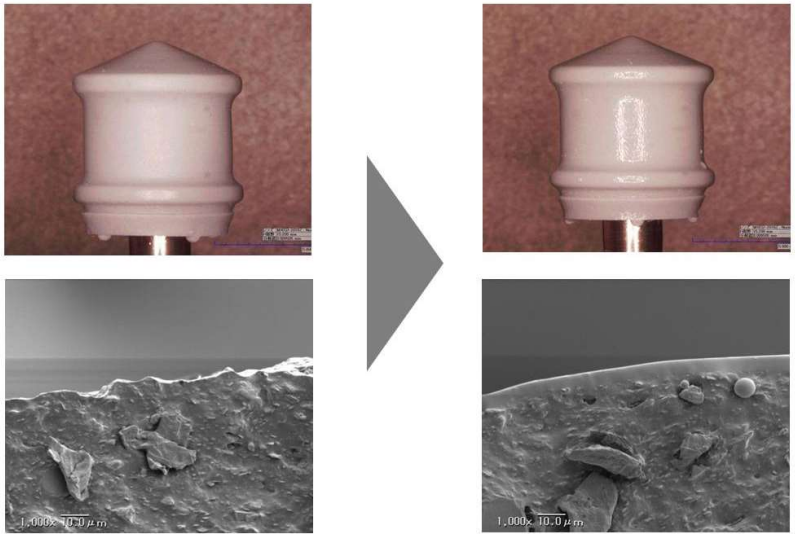
Silicone oil-free system: Stopper coating technology

i-coating™ on the plunger stopper achieves the silicone oil-free system

i-coating™ provides a smooth surface on PLAJEX™ stopper that works in combination with the dimensional tolerance of the polymer barrel to provide an enhanced container closure integrity.

Uncoated stopper

i-coating™ stopper



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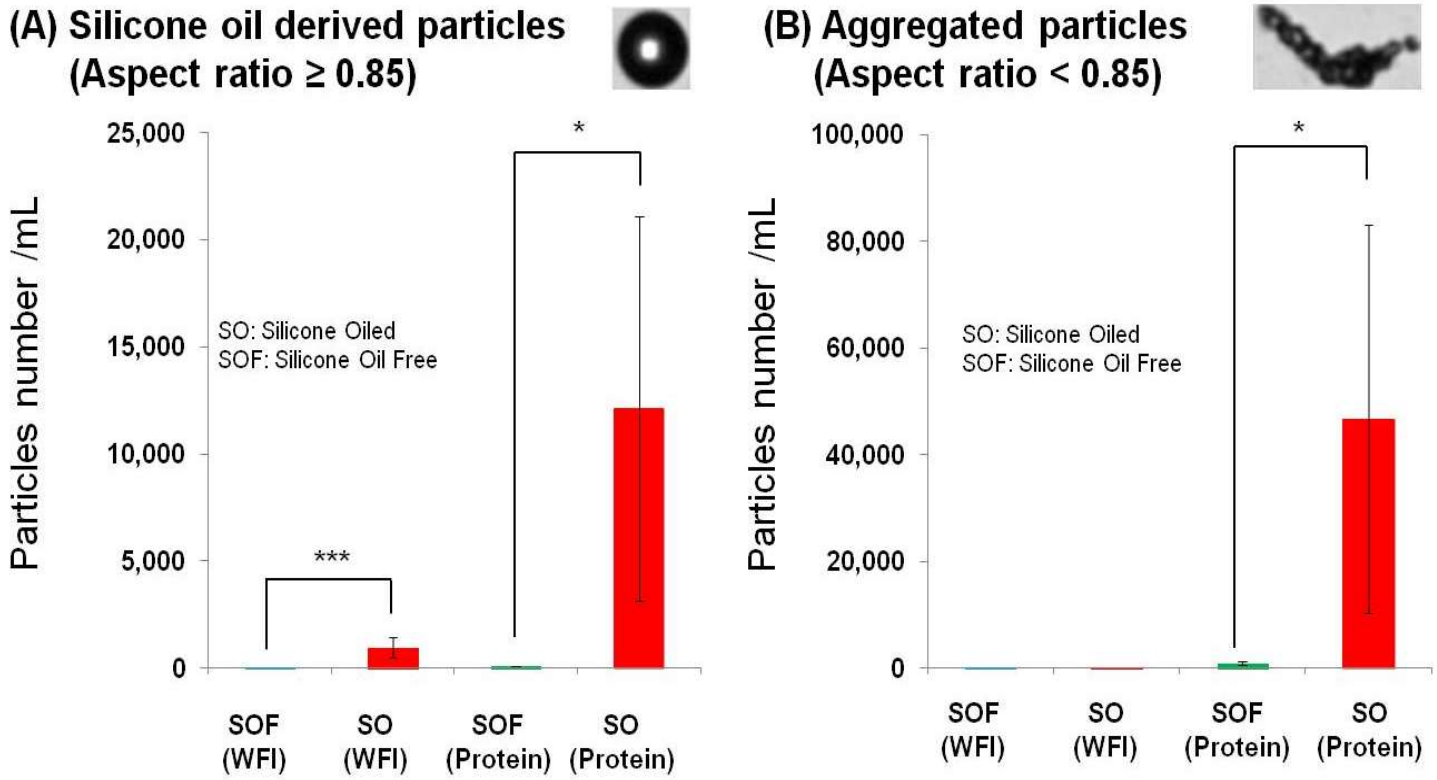
i-coating™ stopper

Silicone oil-free system shows low sub-visible particle count



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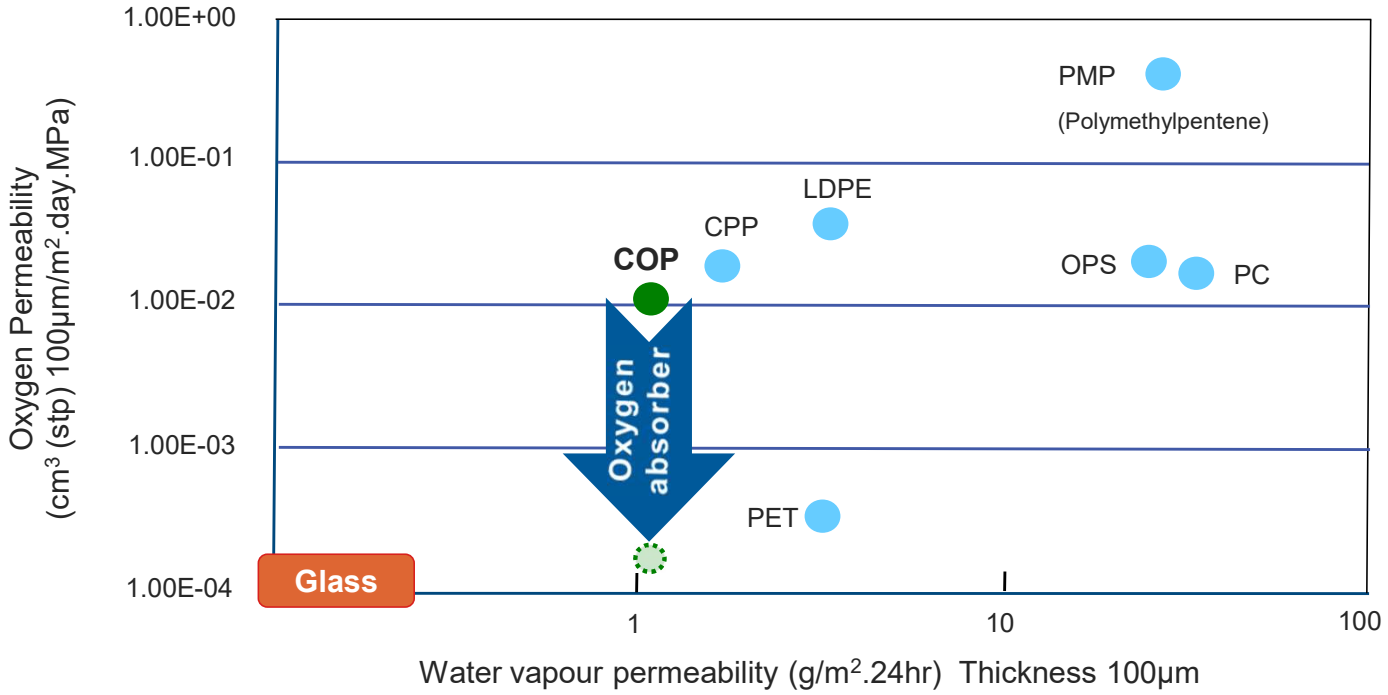
Oxygen permeability

Higher permeability of polymer can be an advantage



The value of polymer permeation and combined use of oxygen absorber with the packaging system

(a proven concept with >15 years of experience)

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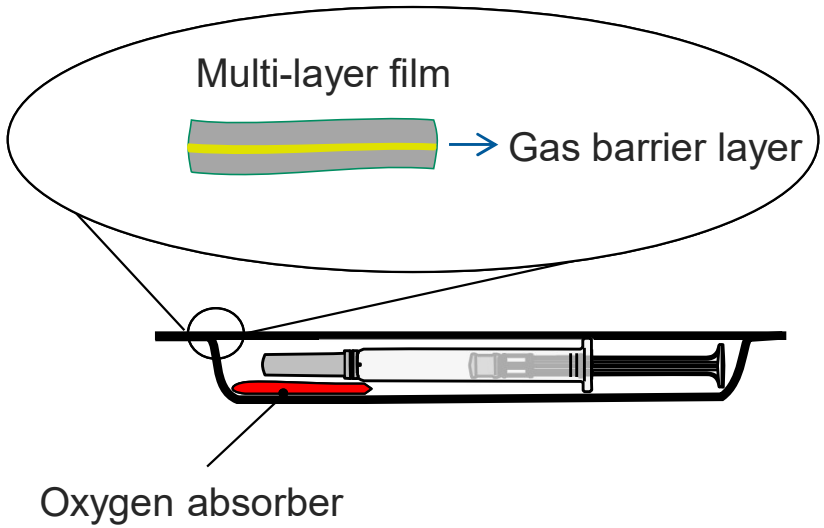
Packaging structure for elimination of dissolved oxygen

Prevent protein oxidation by dissolved oxygen

The de-oxygenated package system



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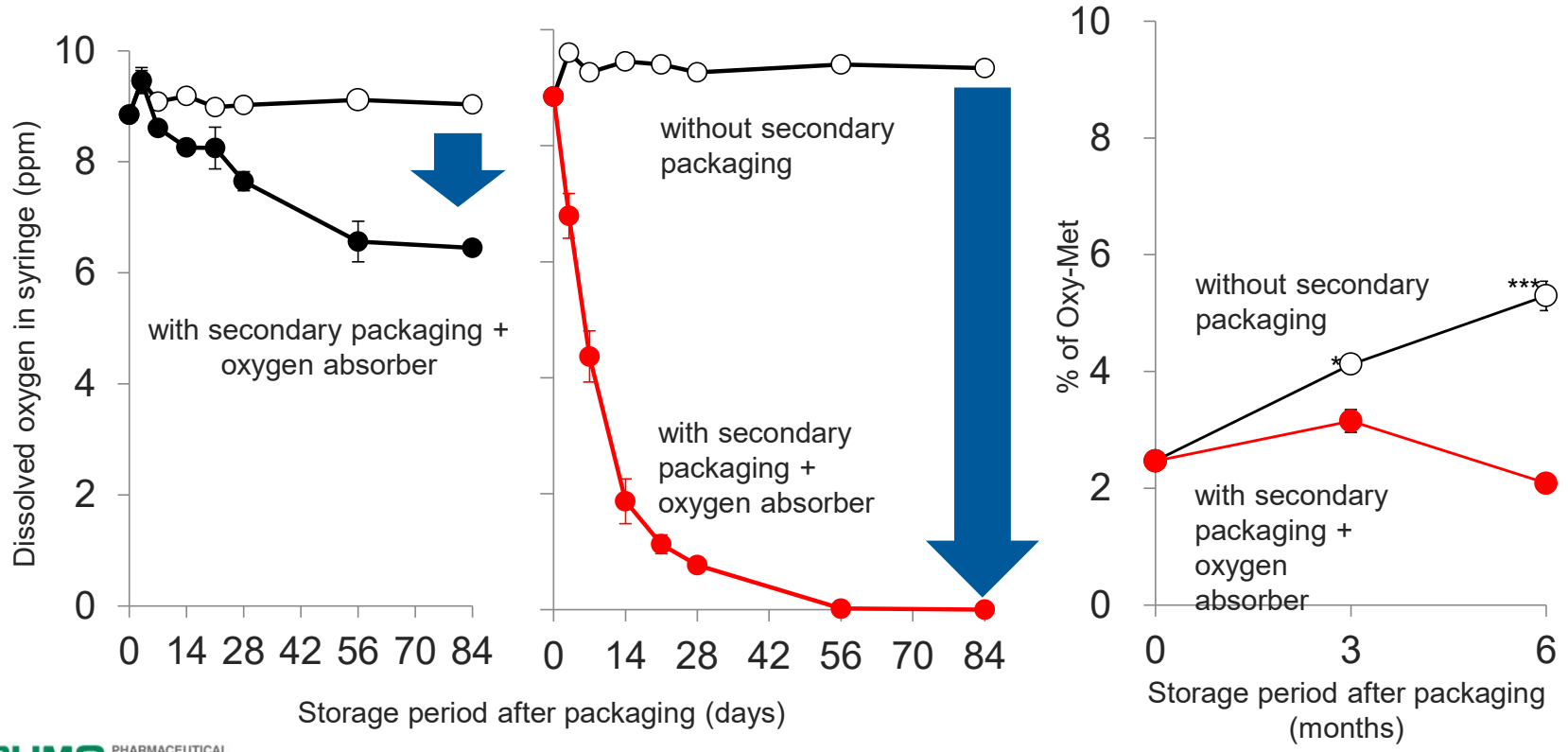
Effect of de-oxygenated packaging system

Enables elimination of the dissolved oxygen

Glass PFS

PLAJEX™

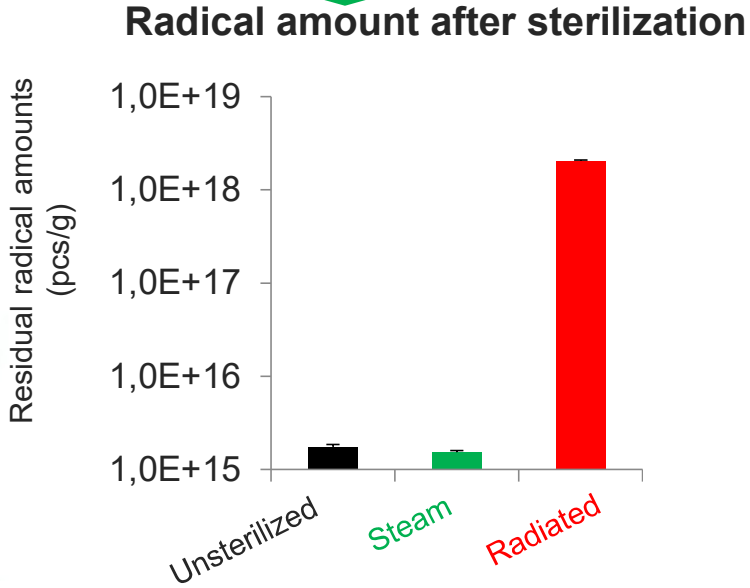
EPO stability in PLAJEX™

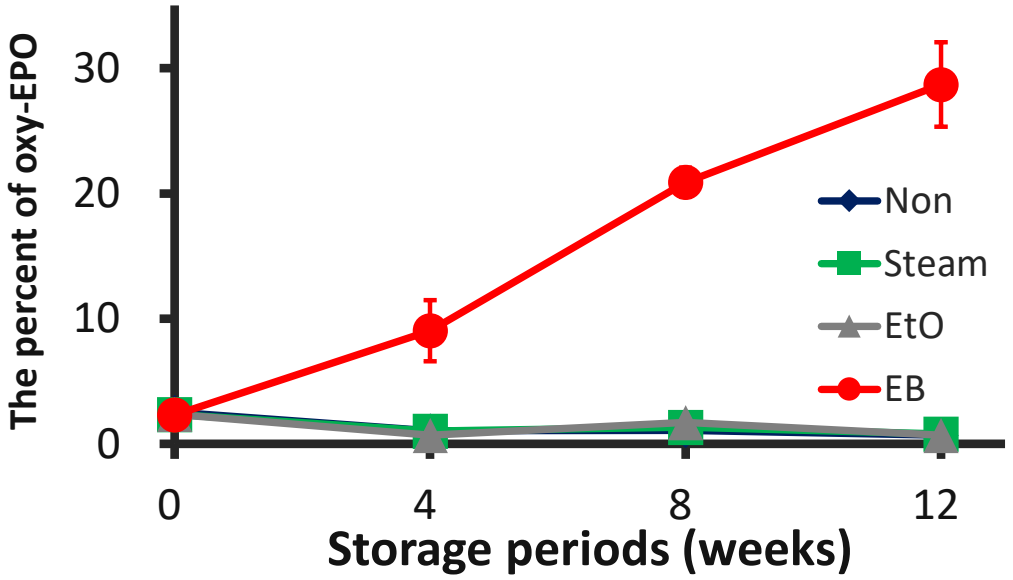


Advantage of steam sterilization

Prevent protein oxidation by radicals

Sterilization of polymer-based syringes → Filling of EPO → Storage of PFS up to 12 weeks





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Low EXTRACTABLE syringe system

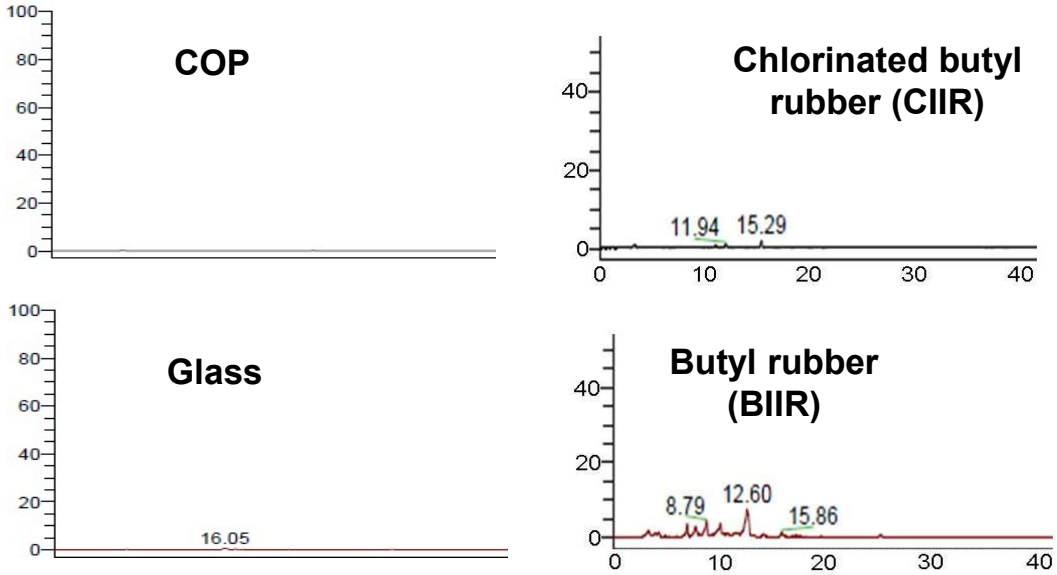
Achieved by combining material selection and applying steam sterilization

STUDY 1

Extraction condition: PLAJEX filled with WFI at 121°C for 60 min
Analysis: Organic extractable compounds by LC/MS

Material comparison

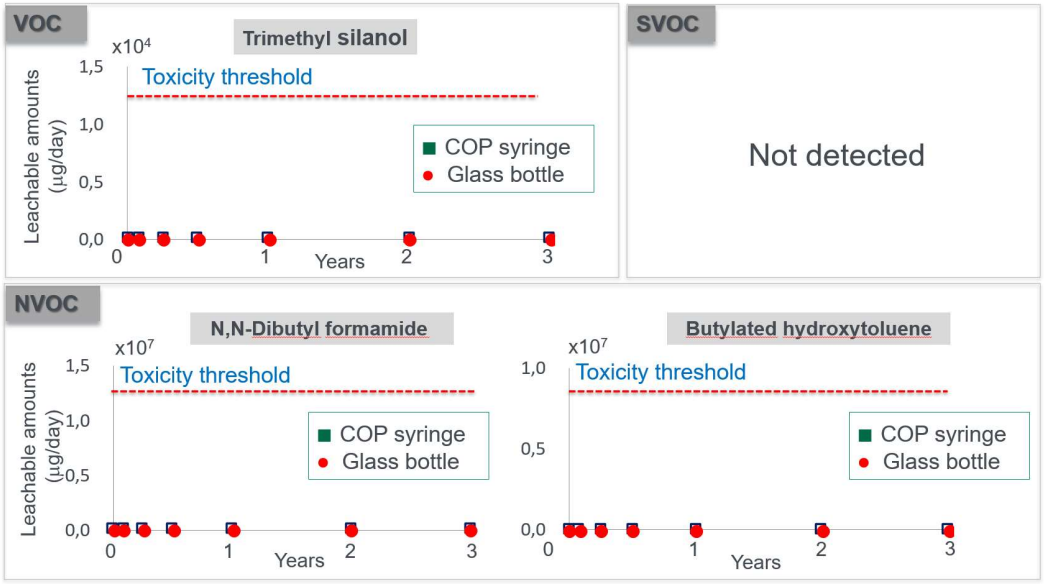
Barrel	**Stopper**
COP = Glass	**CIIR** < BIIR



Low LEACHABLE syringe system

STUDY 2

Leachable study condition: 5ml PLAJEX filled with WFI at 25°C / 60% RH for 36 months
PP label with acrylic-based glue
Analysis: Organic leachable compounds & elements



- **Detected levels of organic leachables were low and those components were not considered as a concern of toxicity.**
- **Label-related leachables could not be detected.**

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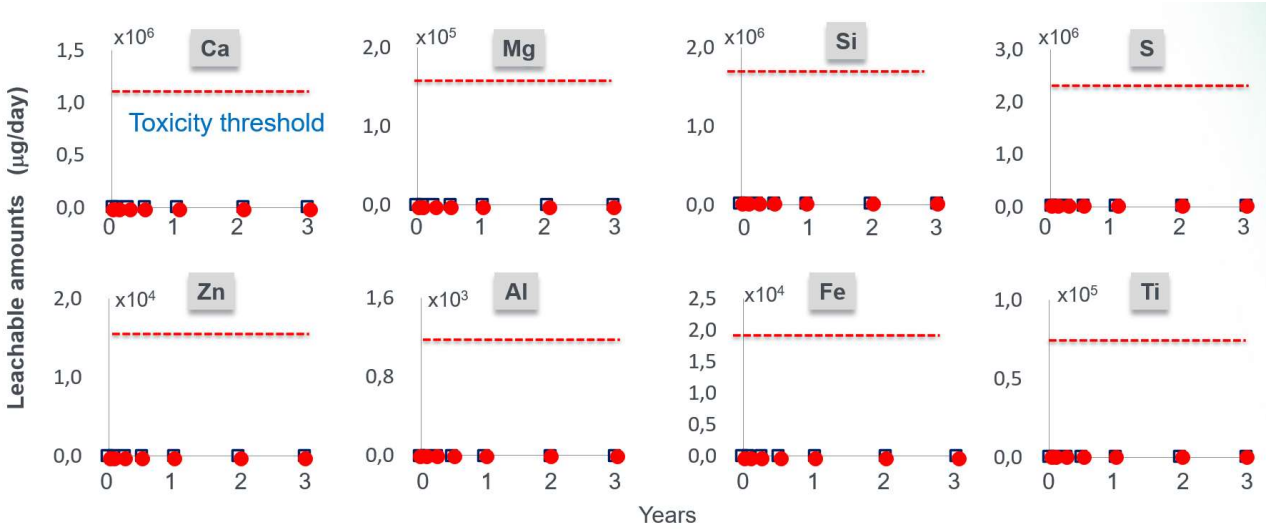
Low LEACHABLE syringe system

STUDY 2



- **Detected levels of elements leachables were low and those components were not considered as a concern of toxicity.**

- ✓ **No differential compounds were found compared with the control**
- ✓ **There were no leachables detected related to the secondary packaging and label.**
- ✓ **Leachable levels from the primary packaging were much lower than toxicity threshold.**

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Low LEACHABLE syringe system

STUDY 3

Leachable study condition: 1ml PLAJEX filled with Humira simulant at 2-8°C / darkness for 36 months
PP label with acrylic-based glue
Analysis: Organic leachable compounds, elements & acrylic acid

Analytical type	Compound	Toxicity Class	(µg/day)	Origin
VOC	Ethyl acetate	50 mg/day [1)]	2.24	Unconfirmed
SVOC	Cyclohexanone	50 µg/day [2)]	0.19	Unconfirmed
	2-Ethyl-1-haxanol	50 µg/day	0.29	Unconfirmed
	Pentadecanoic acid, dimethyl ester	50 µg/day	0.09	Unconfirmed
	2-(2-Butoxyethoxy)ethanol	50 µg/day	0.08	Unconfirmed
	Dimethyl adipate	50 µg/day	0.07	Unconfirmed
	$C_{21}H_{40}$ Rubber oligomer	50 µg/day	0.08	Rubber (Tip cap or Plunger stopper)
NVOC	4-Undecylbenzene sulfonic acid	50 µg/day	2.08	Rubber (Tip cap or Plunger stopper)
	4-Dodecylbenzene sulfonic acid	50 µg/day	4.16	
	4-Tridecylbenzene sulfonic acid	50 µg/day	7.52	
	BHT (3,5-ditert-butyl-4-hydroxytoluene)	50 µg/day	0.05	
Elements	Fe	-	0.16	All
	Mg	-	0.62	All
	Mn	-	0.02	Rubber (Tip cap or Plunger stopper)
	Si	-	1.12	Rubber (Tip cap or Plunger stopper)

*1) ICH Q3C guideline, *2) PQRI guideline

- **Leachable levels from the PLAJEX container closure system with Humira simulant were much lower than the toxicity treshold.**
- **Label-related leachables could not be detected.**

✓ **PLAJEX offers a low leachable PFS system in applying low extractable / leachable COP and CIIR materials and well-selected secondary packaging components.**

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Conclusion

PLAJEX™ with i-coating™ stopper

- **Risks for sensitive biodrugs such as aggregation and oxidation can be minimized by a system approach with polymer-based pre-fillable syringes.**

i-coating™

- Tungsten-free, Glue-free
- High break resistance
- Silicone oil-free
- Low sub-visible particles
- Secondary packaging with oxygen absorber
- Steam sterilization = Radical-free
- Low extractable materials and sterilization method

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References

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   Impact of Sterilization Method on Protein Aggregation and Particle Formation in Polymer-Based Syringes, Hideaki Kiminami *et al*, Journal of Pharmaceutical Sciences, 2016


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