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Use of CSTD in Health Care Setting: Value Proposition and Constraints

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Agenda

1 CSTD: Definition and Value Proposition

2 Market Survey Results

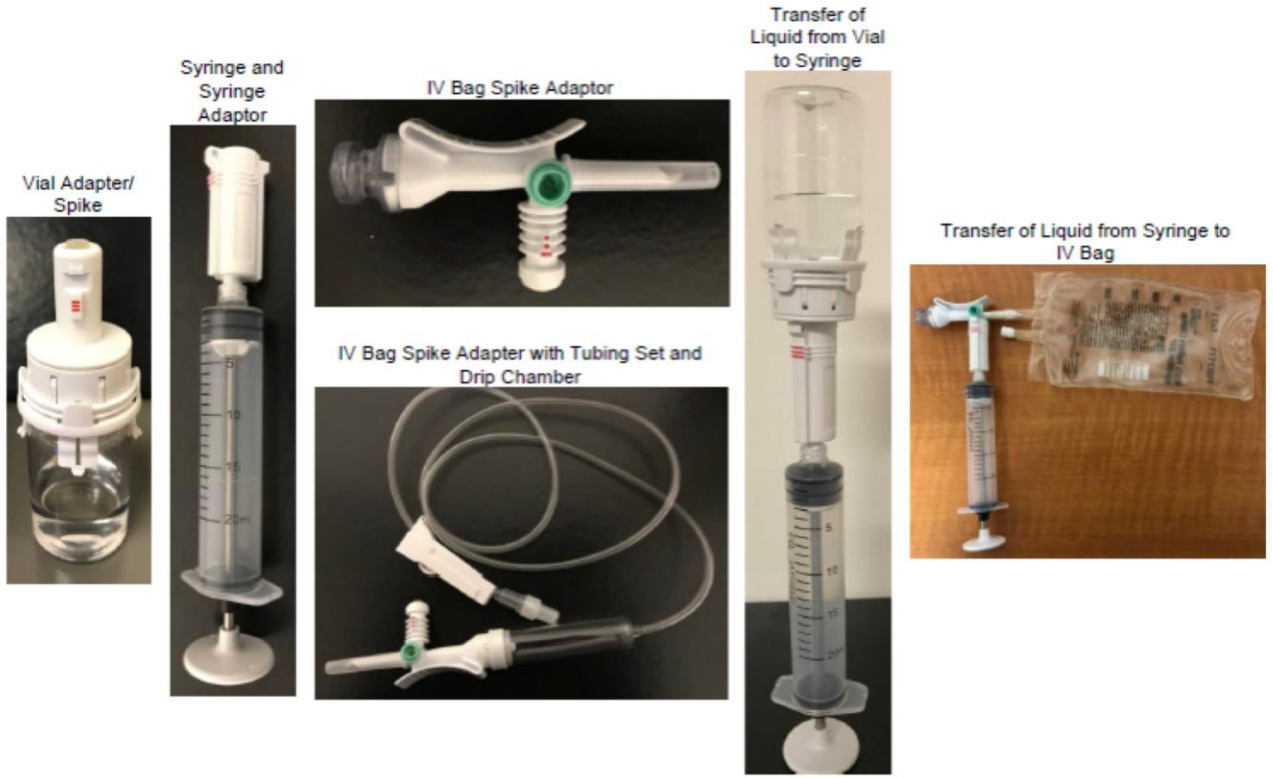
3 Constraints: Drug Product Perspective

4 Need for collaboration

Definition of Closed System Transfer Device per USP<800> & NIOSH

"CSTD is a drug-transfer device that mechanically prohibits the transfer of environmental contaminants into the system and the escape of hazardous drug or vapor concentrations outside the system."

FDA Regulation: Class II Product Code ONB, Intravascular administration set (21 CFR 880.5440)



CSTD Value proposition

- Minimizes individual and environmental exposure to drug vapor aerosols and spills
- Prevents microbial ingress
- Protects healthcare workers, patients and pharmacists associated with hazardous drug preparation, transport and delivery
- Eliminates needle-stick injuries

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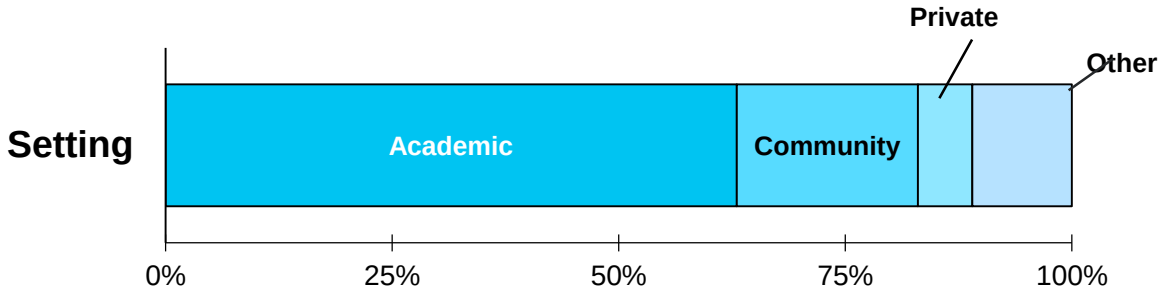
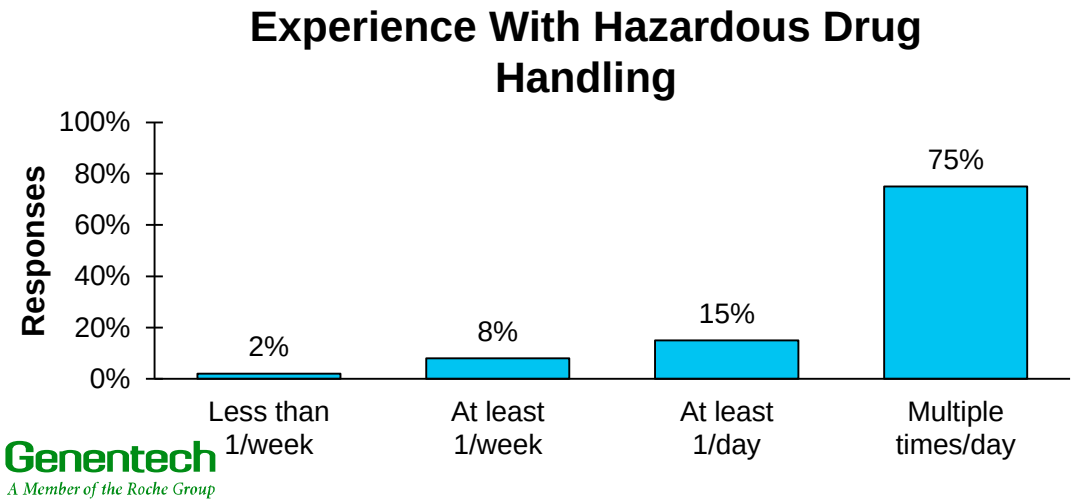
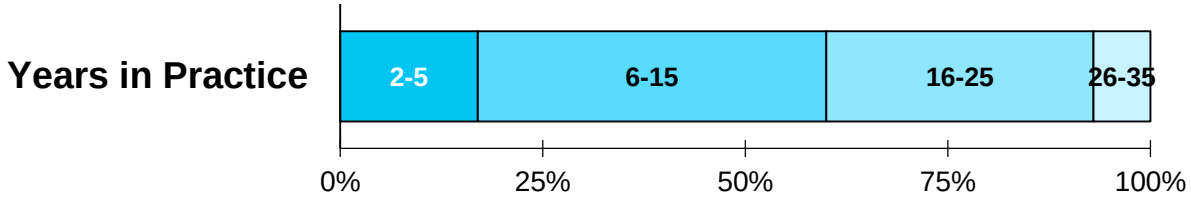
Genentech sponsored a survey across hospital pharmacists and oncology nurses with significant experience with CSTDs



Country Demographics: US, some EU countries and Australia

Total Survey Respondents (N = 130, majority US)





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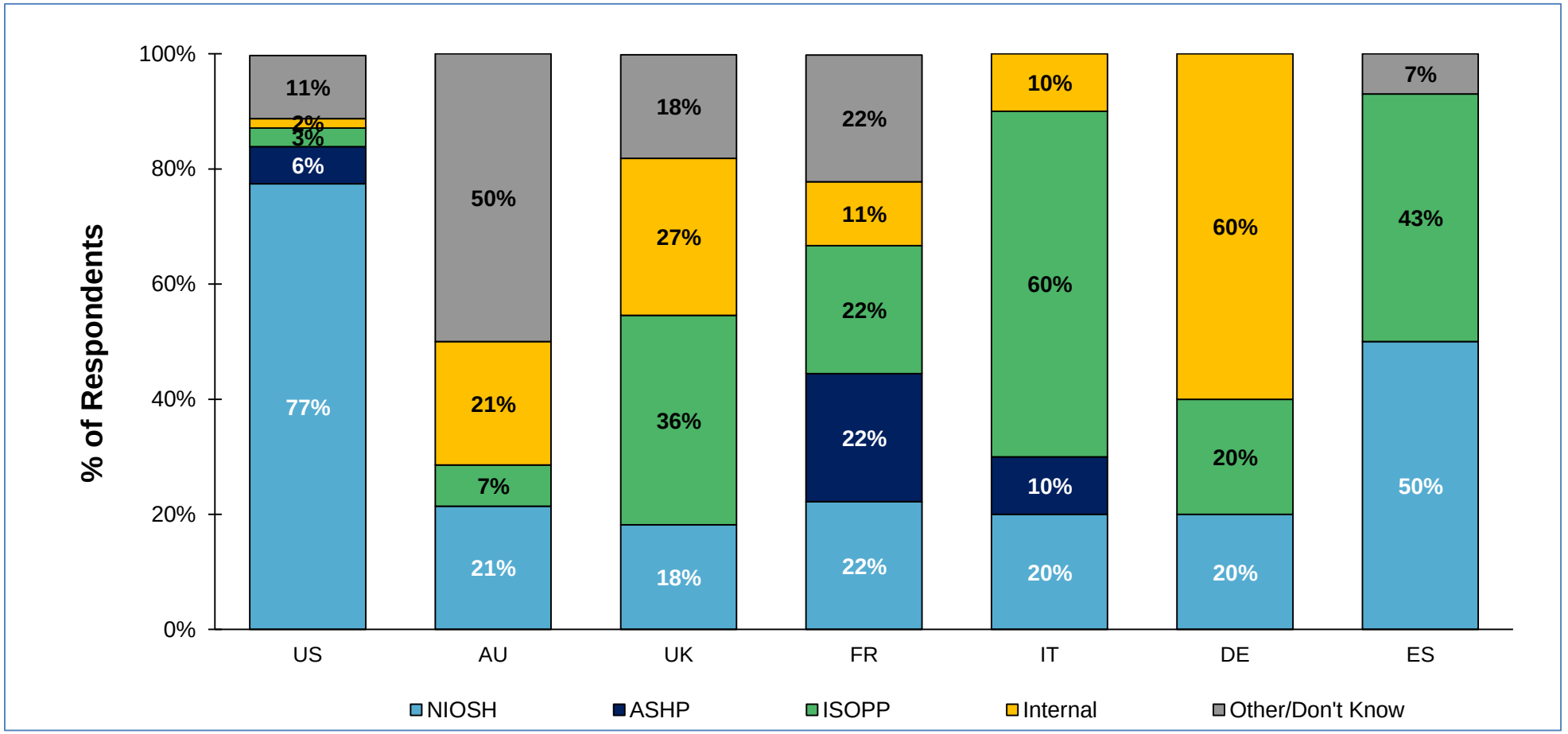
Most US hospitals use NIOSH list to classify HDs, ex-US countries have less alignment on a standard classification

How does your organization classify drugs as "hazardous"?

	Country
US	United States
AU	Australia
UK	United Kingdom
FR	France
IT	Italy
DE	Germany
ES	Spain

ISOPP: International Symposium on Oncology Pharmacy Practice

ASHP: American Society of Health-System Pharmacists



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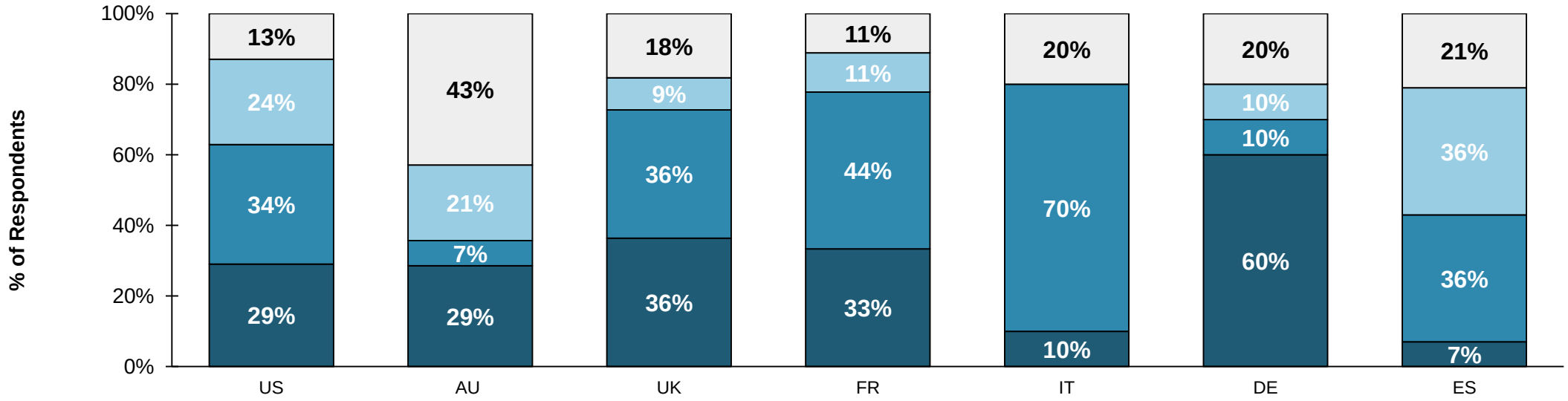
USP <800> is likely to result in an increased use of CSTDs

Will the USP <800> guidance change the practice in your organization in terms of using CSTDs?



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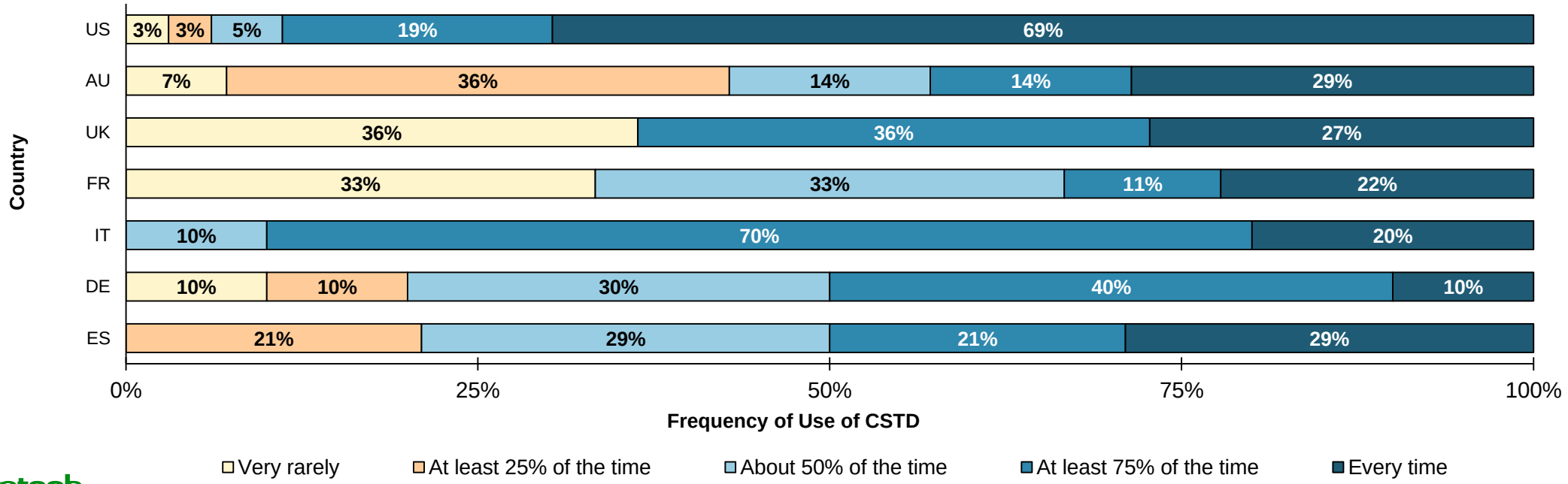
Ex-US countries use CSTDs less frequently due to lack of regulation, cost

How frequently are you using a Closed SystemTransfer Device (CSTD) when preparing or administering a hazardous drug?



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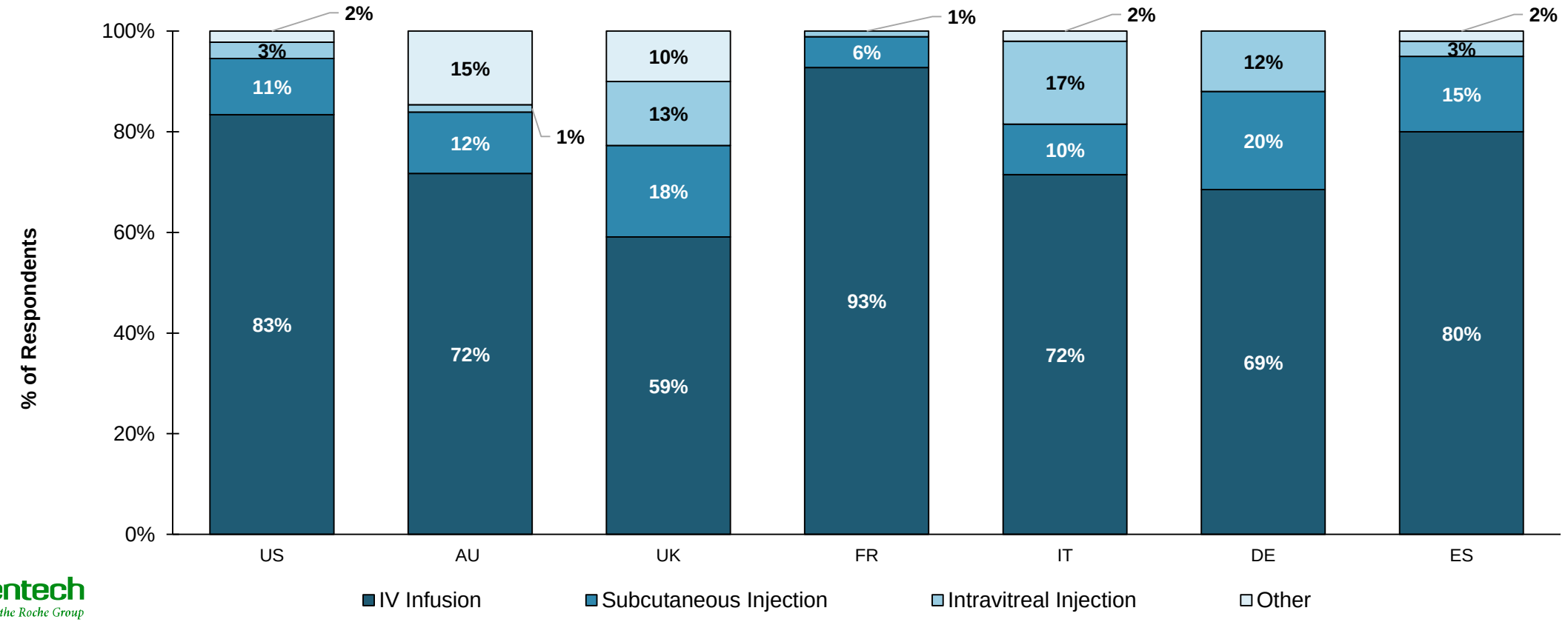
CSTDs are used for hazardous oncology drugs, inclusive of both chemotherapy agents and biologics

For which types of hazardous drugs do you currently use a CSTD?

	US	AU	UK	FR	IT	DE	ES
All hazardous oncology drugs (chemotherapy + biologics)	74%	50%	55%	67%	50%	90%	57%
Only hazardous chemotherapy drugs (not biologics)	47%	43%	45%	44%	10%	50%	57%
All hazardous biologics	45%	36%	45%	33%	50%	20%	50%
Hazardous antiviral drugs	18%	14%	45%	11%	0%	60%	21%
Hazardous antibiotic drugs	6%	7%	**27%**	11%	0%	**30%**	7%
Hazardous hormones	0%	7%	27%	0%	0%	0%	7%
Other	2%	14%	18%	11%	10%	0%	7%

CSTDs are used primarily for IV infusion

For drugs that require a CSTD (closed system transfer device), what is the approximate percentage breakdown between the routes of administration?



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About 50% of respondents report they will reach out to *device* manufacturer for compatibility

Definition of Compatibility: Interviewees indicated that compatibility is defined in two different ways: 1) The ability to mechanically attach the CSTD to the drug vial and 2) The potential changes to the drug quality due to the pressurization and potential aerosolization of the drug. Certain CSTDs might even retain a small amount of drug volume in the chamber, which can impact drug dose and potentially efficacy if not accounted for.

Before using a certain CSTD (closed system transfer device), does your institution verify that it is compatible with the drug?

	Check Device Mfg Specs	Ask for Compatibility Data from Device Mfg
US	27%	13%
AU	36%	14%
UK	55%	9%
FR	0%	33%
IT	20%	40%
DE	10%	50%
ES	36%	14%

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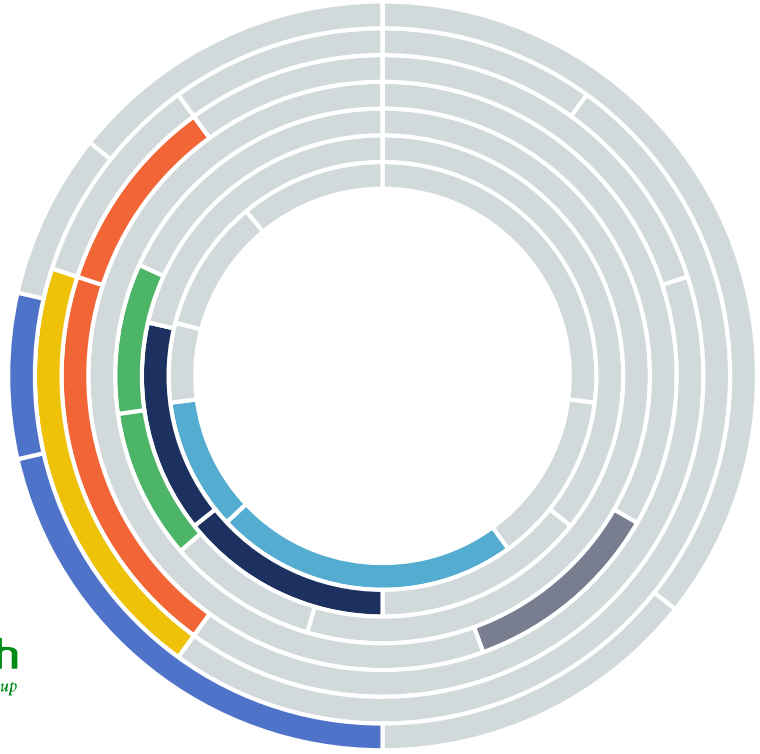
About 25% of respondents report they will reach out to *drug* manufacturer for compatibility

Before using a certain CSTD (closed system transfer device), does your institution verify that it is compatible with the drug



	Check Drug Mfg Specs	Ask for Compatibility Data from Drug Mfg
US	23%	10%
AU	14%	14%
UK	9%	9%
FR	11%	0%
IT	20%	10%
DE	0%	20%
ES	21%	7%

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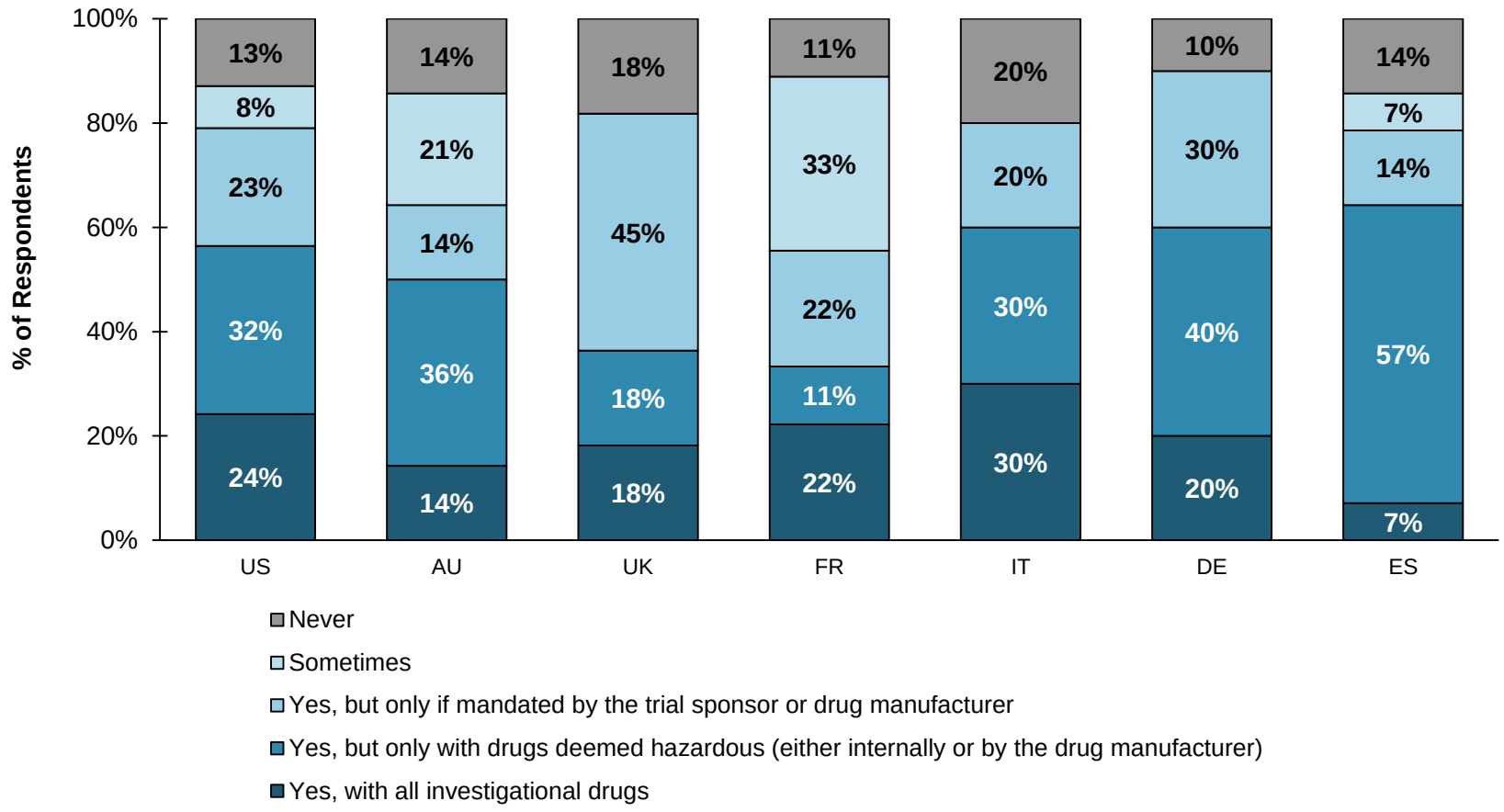
CSTDs are used to varying degree in Clinical Trials

Do you use a CSTD (closed system transfer device) for investigational drugs in clinical trials?



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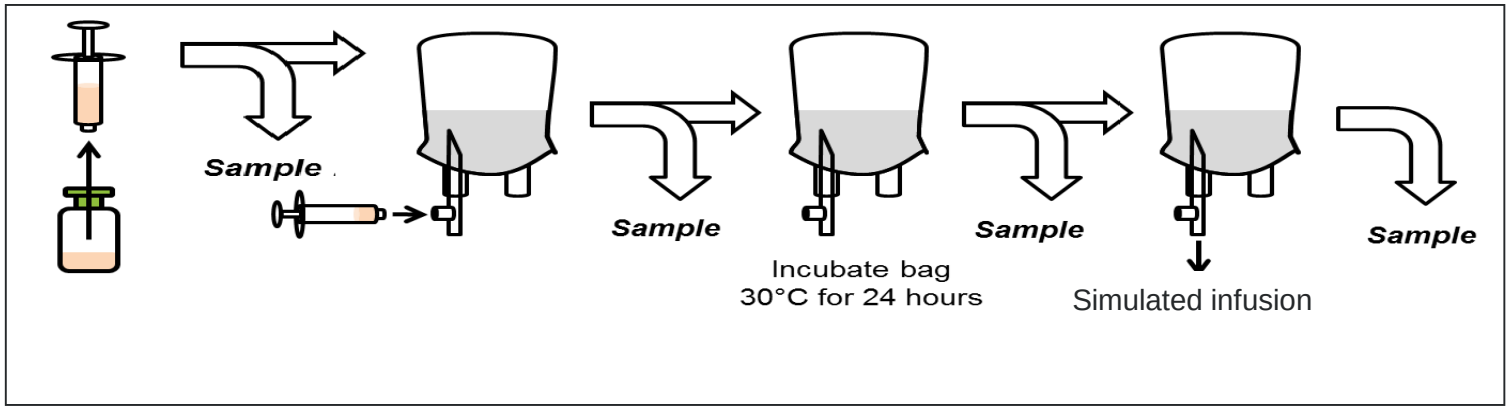
Genentech Evaluated Commercial CSTDs for drug compatibility

Study 1. Extrinsic particles (n=80 vials per CSTD)

- Study Control: samples withdrawn with syringes and SS needles

Study 2. In-use physicochemical compatibility of a mAb with CSTDs and impact to product quality

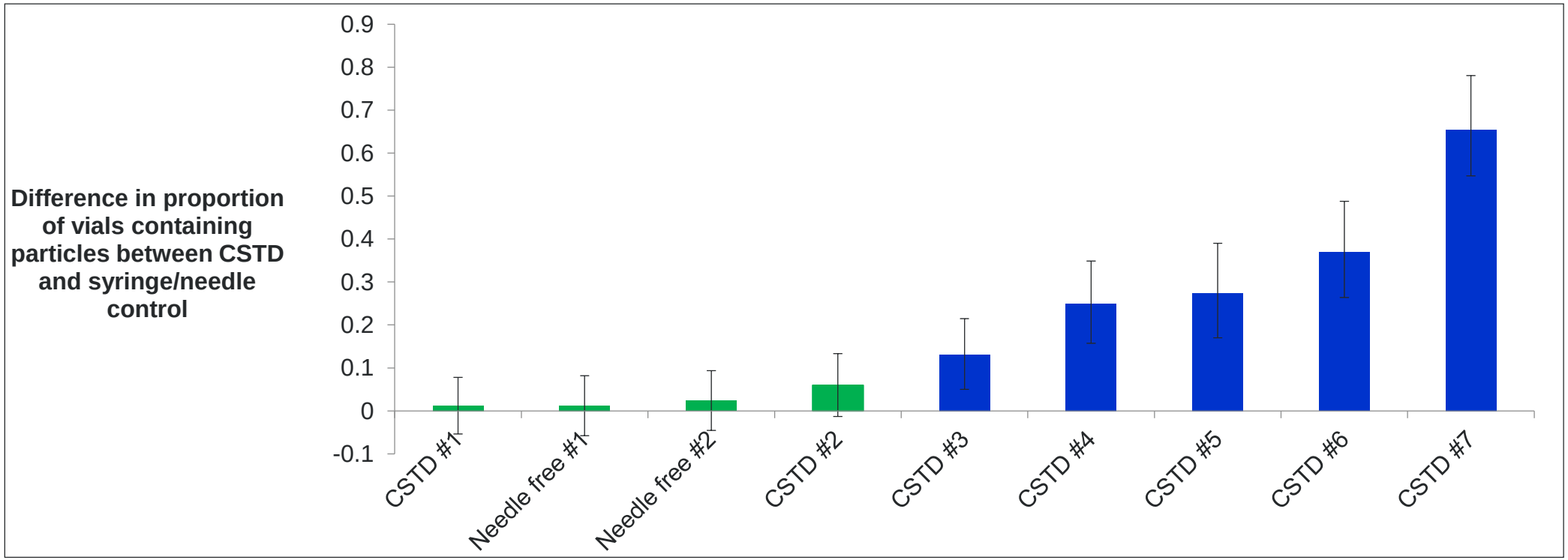
- Study Controls
  - mAb samples prepared with syringes and SS needles
  - Buffer filled vials as a control for evaluation of visible/sub-visible particles



Study 3. Extractable volume (n=5 vials per CSTD)

- Study Control: samples withdrawn with syringes and SS needles

Study 1 shows that CSTDs may Introduce Extrinsic Visible Particles



- Five CSTDs (3-7) were found to have a statistically significant higher number of vials containing extrinsic visible particles as compared to the syringe/needle control

  - Proportion is calculated as number of vials with corresponding CSTD containing a least 1 visible particle/total number of vials tested (n = 80).
  - Error bars represent 95% confidence interval. Green bars indicate data comparable to syringe/needle controls; Blue bars indicate statistically significant higher rate of vials containing visible particles when compared to syringe/needle control

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Extrinsic Particles included elastomer, polymers and silicone

Rubber stopper particles

- The usage of some CSTDs resulted in rubber particles in solution; potential for stopper coring/fragmentation

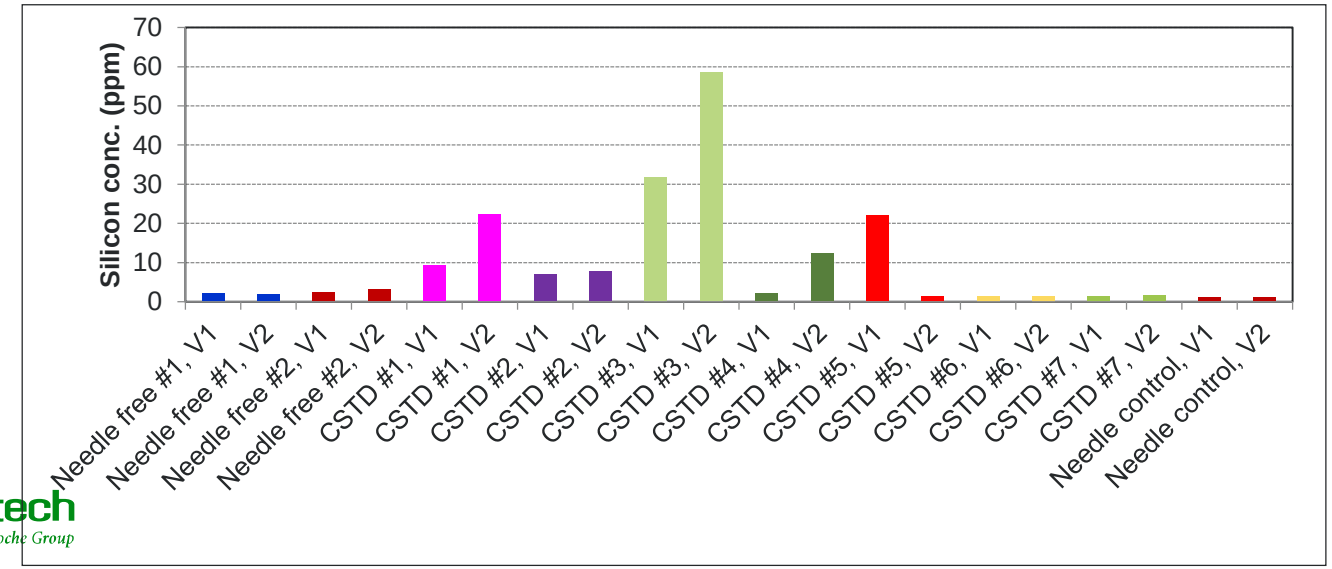
CSTD related material of construction

- e.g. silicone (polymer plastic) and polyethylene

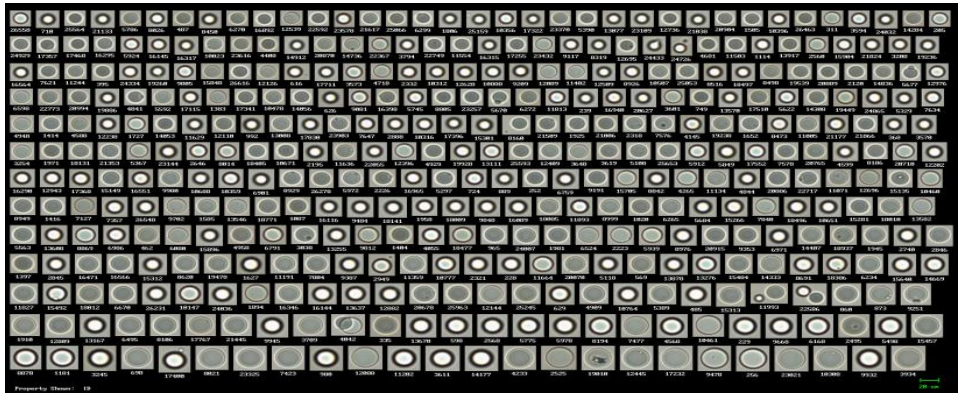
Different lubricants used in the manufacturing of CSTDs

- e.g. silicone oil related lubricants

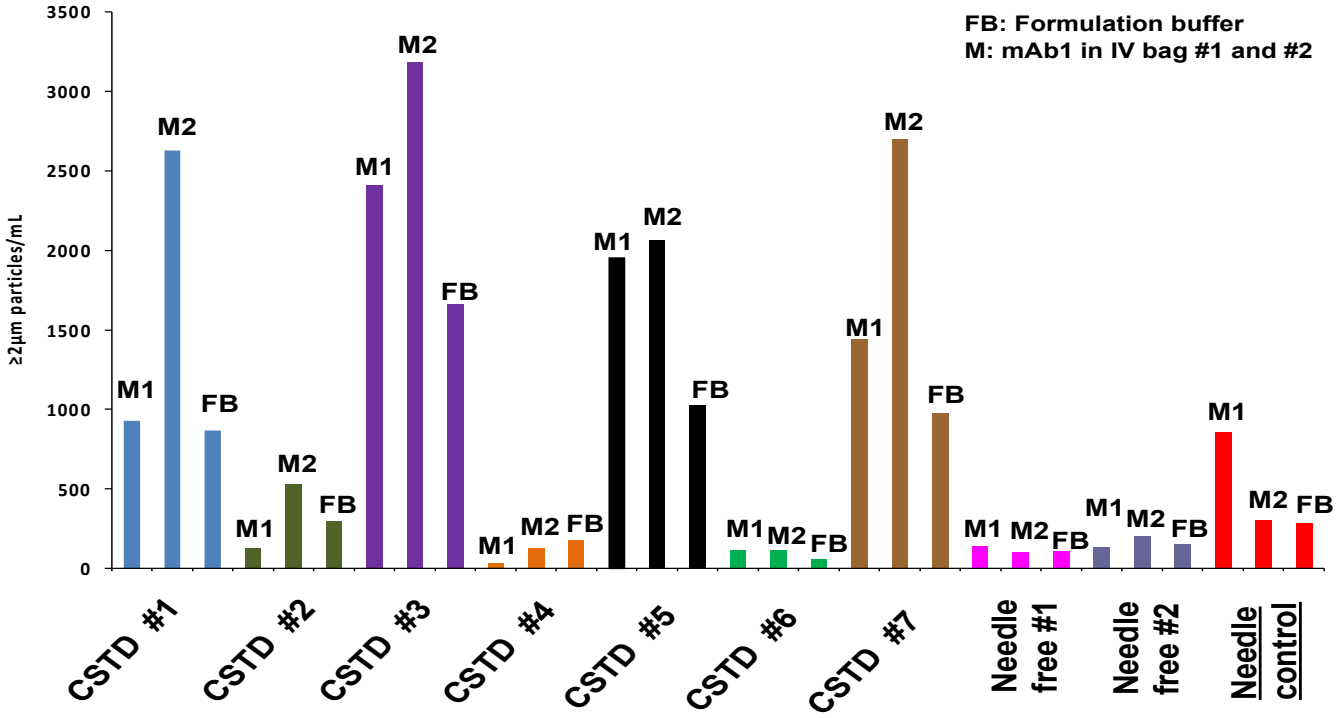
Silicon quantification by ICP-OES



MicroFlow (MFI) imaging of a vial spiked with a CSTD

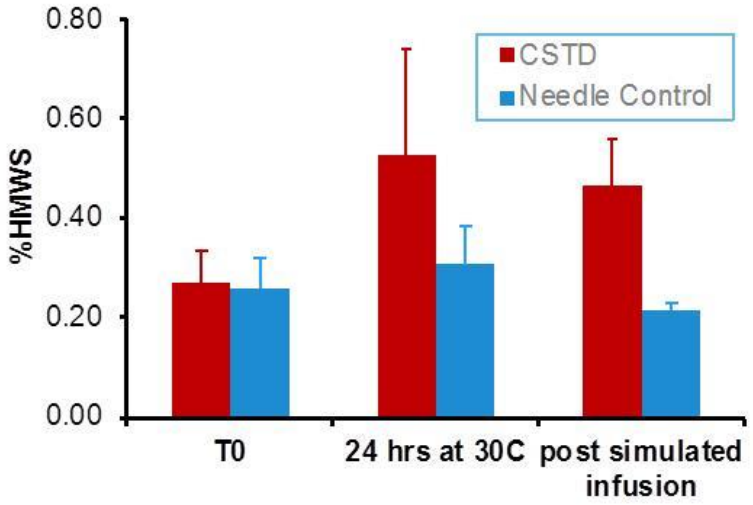


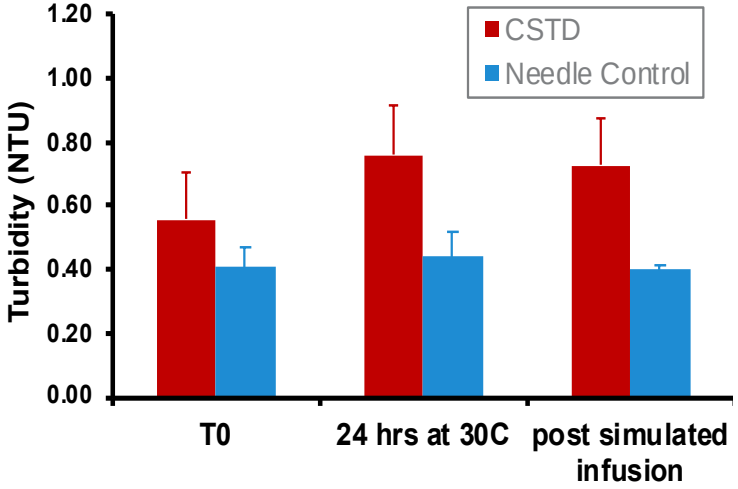
Study 2 shows increased number of Sub-visible Particles



- Increase in number of subvisible particles (≥2µm/mL) were observed in buffer and mAb formulations after dilution into 0.9% sodium chloride IV bags, storage for 24 hours at 30°C, followed by simulated infusion using some CSTDs
- CSTD to CSTD variability in SVP levels

Proteinaceous Visible Particles and Higher Amounts of Soluble HMWs in mAb Drug Product after dilution in IV Bags with one CSTD





IV bags prepared by CSTD	T0 (post dilution)	T24 (post incubation at 30°C	Post simulated infusion (after 24 hours storage at 30°C) without in line filter
Number of IV bags with visible proteinaceous particles	9 out of 10	8 out of 10	4 out of 10

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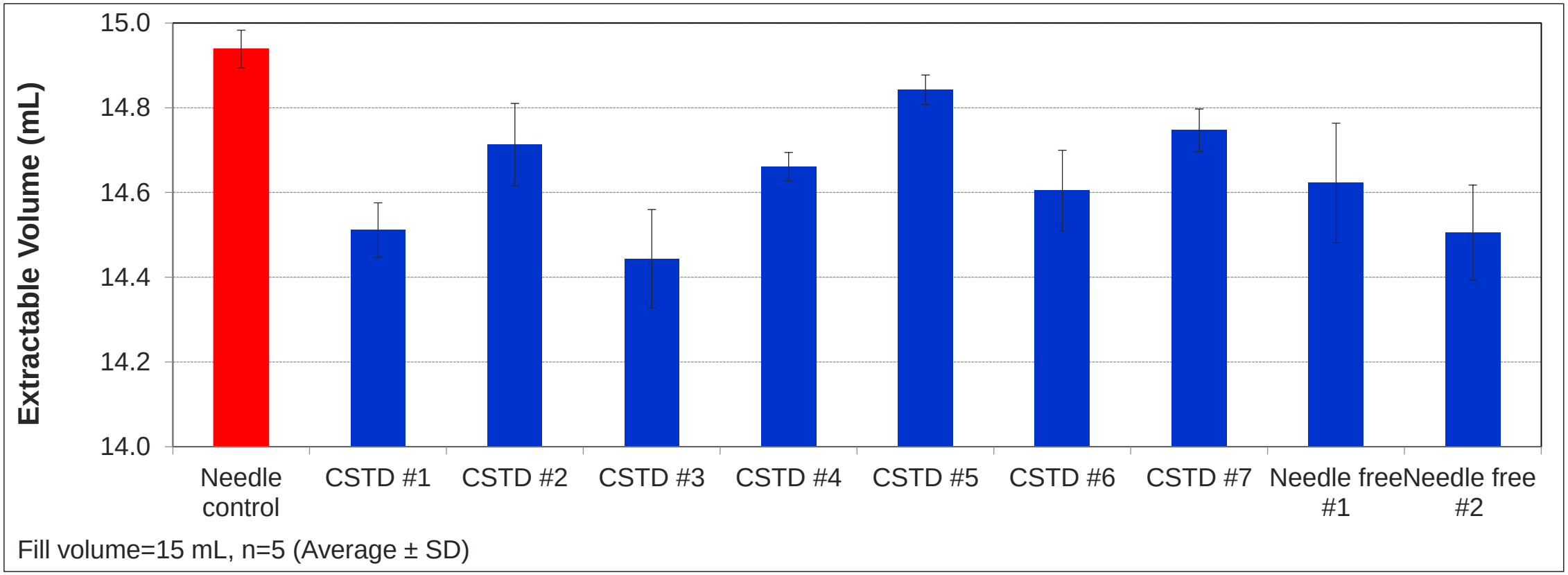
Note: No visible particles were observed in control samples (syringe/needle)

Study 3 shows that CSTDs can Result in Lower "Extractable Volume" Compared to "Syringe/Needle Control"



Fill volume=15 mL, n=5 (Average ± SD)

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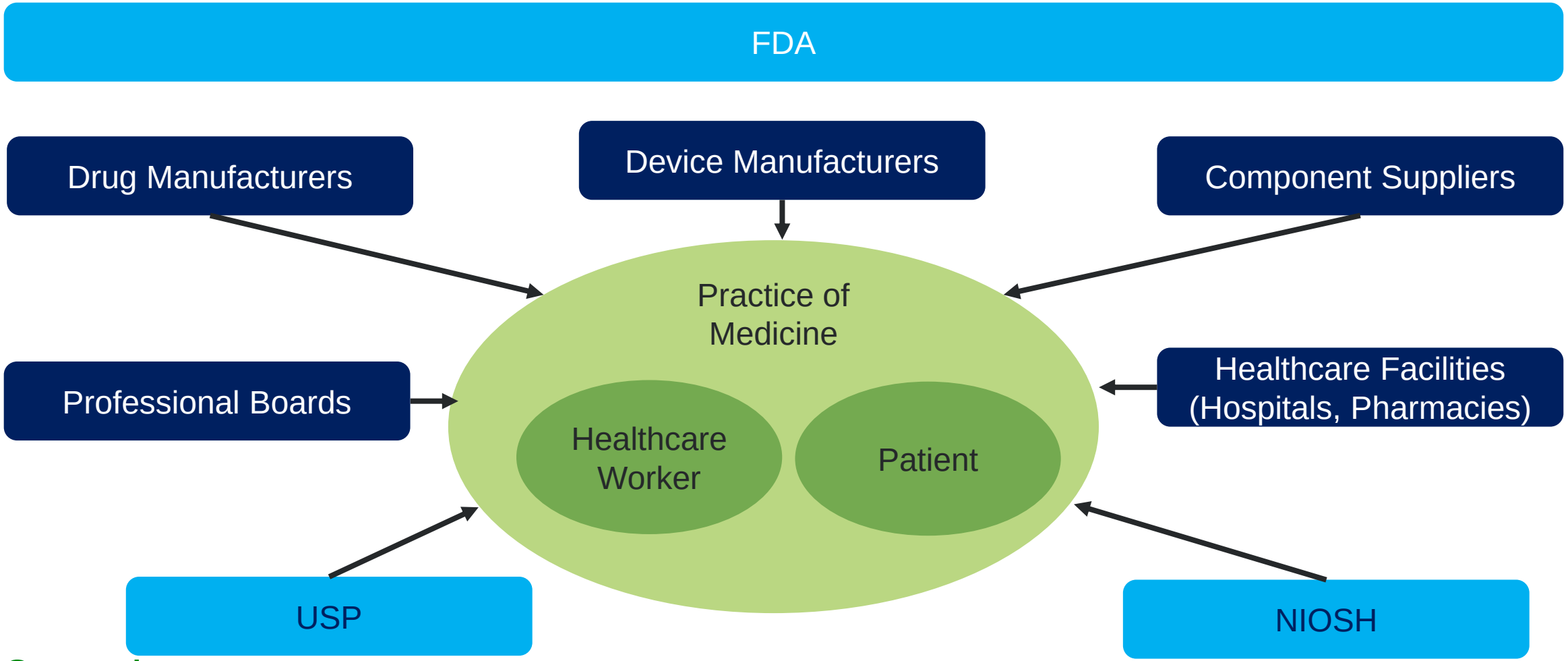
Product Quality and Patient Safety Risks can Become More Prevalent after USP<800> is Made Official

Issue	Concern
Recommendations to apply USP<800> beyond compounding to include reconstitution and administration of FDA-approved drug products	Inconsistent with scope of USP<797>
Recommendations for routine use of CSTDs for certain categories of molecules (e.g., all antineoplastics) beyond those specifically identified on the NIOSH Hazardous Drug List	Inconsistent with NIOSH Hazardous Drug List
Standards for routine use of CSTDs with therapeutic protein products regardless of whether the specific drug handling scenario poses an occupational risk to healthcare workers	Compulsory risk mitigation where an unacceptable risk has been assumed rather than demonstrated

Collaboration between Stakeholders Required to Address the Issue



Opportunities for Future Engagement

- Collaborate with USP and professional societies to clarify scope and applicability of USP<800> to compounded products
- Collaborate with NIOSH regarding the scope of the NIOSH List as it relates to antineoplastic monoclonal antibodies
- Consider issuing a public statement encouraging healthcare workers to review FDA-approved drug labels prior to using CSTDs
- Issue updated guidance and support development of technical standard to drive consistency in CSTD design and development

Key Takeaway

- CSTDs can be a critical tool to protect the patients and HealthCare professionals from Hazardous Drugs
- Survey of HealthCare professionals indicates inconsistency in the way CSTDs are used
- It is critical to evaluate the compatibility of the CSTD with a drug to ensure the rewards exceed the risk
- Collaboration between stakeholders at multiple levels is required to come up with an optimal solution

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