INTERNATIONAL CONSORTIUM *for*
INNOVATION & QUALITY
in PHARMACEUTICAL DEVELOPMENT

Pharmaceutical Industry Perspective on Closed System Transfer Devices (CSTDs): Balancing Overfill, Evaluating, Communicating

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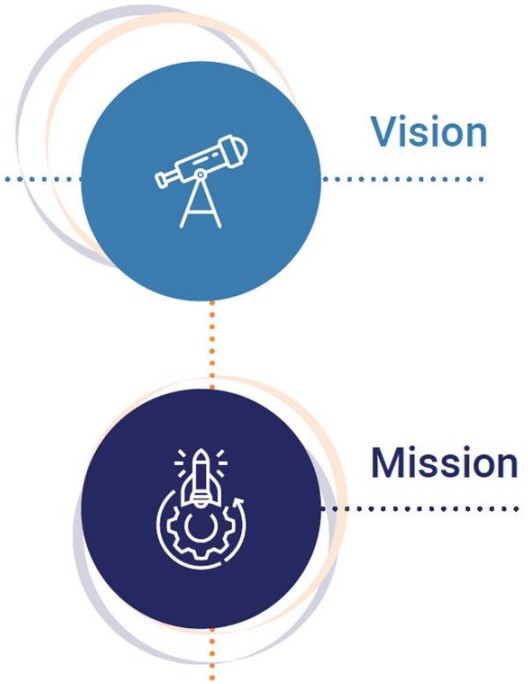
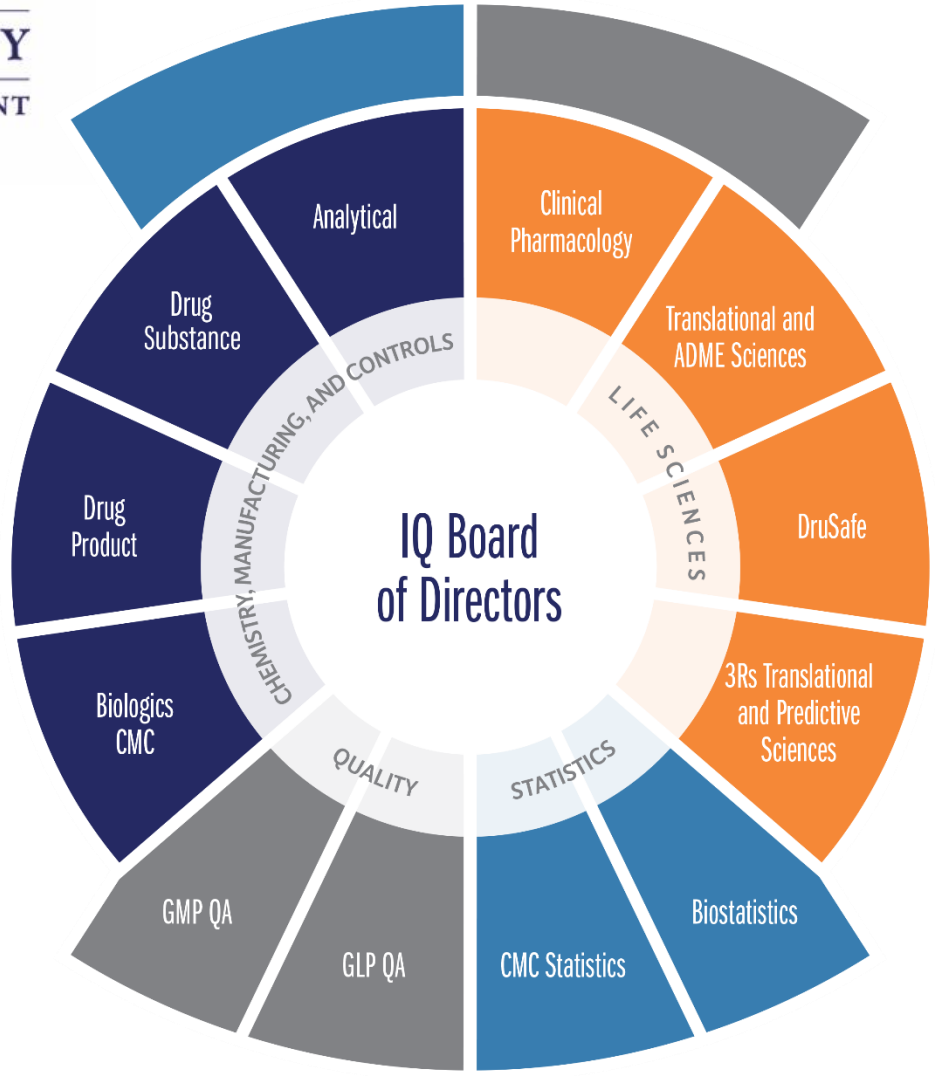
INTERNATIONAL CONSORTIUM for INNOVATION & QUALITY in PHARMACEUTICAL DEVELOPMENT

The International Consortium for Innovation and Quality in Pharmaceutical Development (IQ Consortium) was established in 2010 as a technically-focused, not-for-profit organization comprised of nearly 40 pharmaceutical and biotechnology companies.



To be the leading science-based organization advancing innovative solutions to biomedical problems and enabling pharmaceutical companies to bring quality medicines to patients.

As a technically-focused organization of pharmaceutical and biotechnology companies**, IQ advances science and technology** to augment the capability of member companies to bring transformational solutions that benefit patients, regulators and the broader R&D community.



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Introduction - CSTDs

CSTD as per CDC/NIOSH: A closed system drug-transfer device (CSTD) that mechanically prohibts:[1]

- transfer of environmental contaminants into the system
- escape of the hazardous drug or vapor

Although protection of the healthcare workers is paramount, understanding the potential impact on quality/safety[2] and efficacy in clinical studies[3] is of equal importance:

- risk of over/under dosing
- product incompatibility
- cause of particle formation

Picture from IQ Webinar presentation: Challenges of Using Closed System Transfer Devices (CSTDs) with Biological Products, 2021-03-18

[1]https://www.cdc.gov/niosh/topics/hazdrug/CSTD.html (Centers for Disease Control and prevention, National Institute for Occupational Safety and Health);
[2]Ganapathy Gopalrathnam et al. An Industry Perspective on the Challenges of Using Closed System Transfer Devices with Biologics and Communication Guidance to Healthcare Professionals, Journal of Pharmaceutical Sciences, Volume 110, Issue 6, 2021, Pages 2329-2335, ISSN 0022-3549, https://doi.org/10.1016/j.xphs.2021.02.008.
[3] Fast et al., Use of Closed System Transfer Devices (CSTDs) with Protein-Based Therapeutic Drugs - a Non-Solution for a Non-Problem?, Journal of Pharmaceutical Sciences, 2023, https://doi.org/10.1016/j.xphs.2023.11.014.

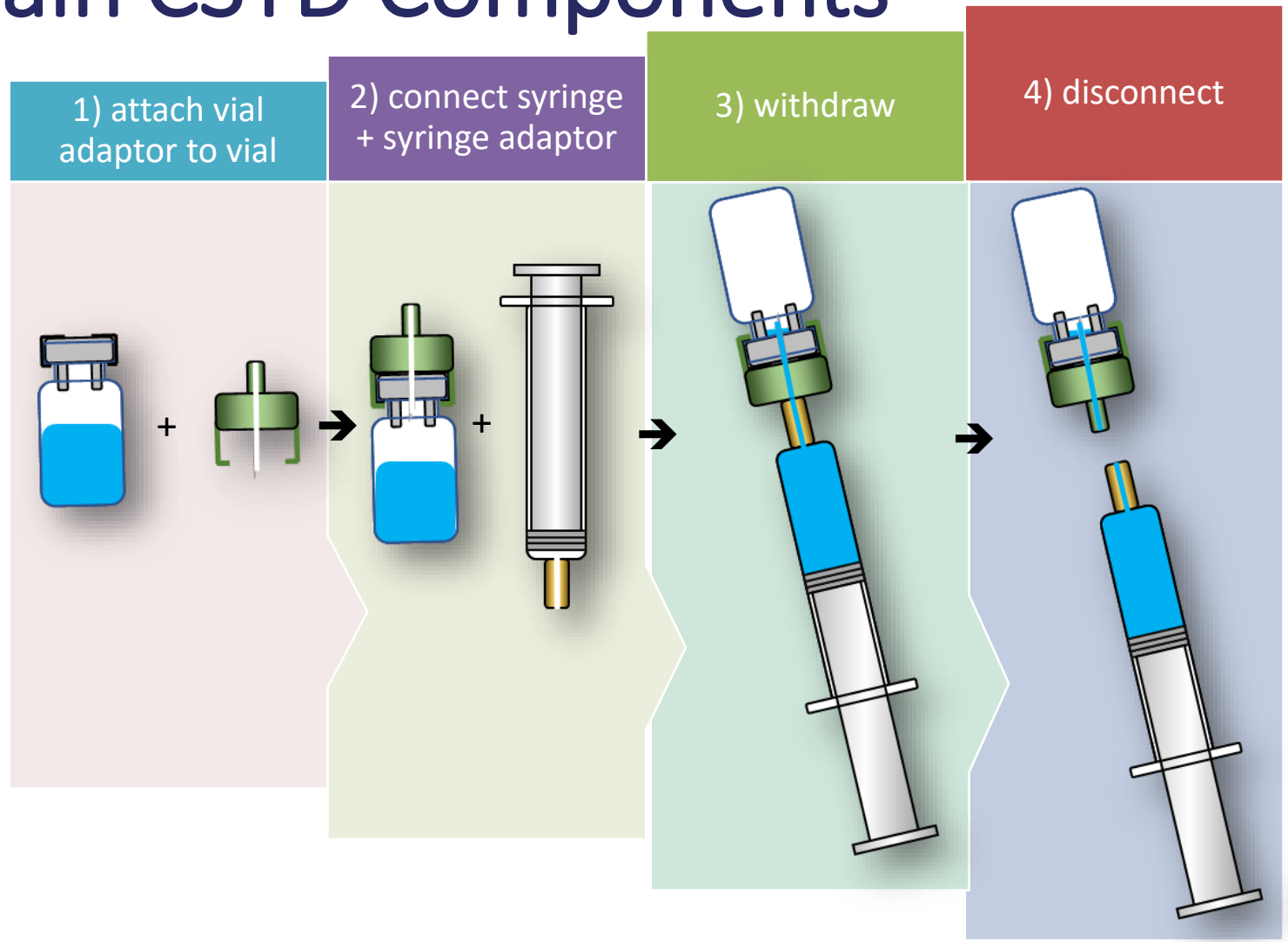
Introduction – Guiding documents

- **USP: Pharmaceutical compounding – sterile preparations <797> and nonsterile preparations <795> referencing for hazardous drugs <800> Hazardous drugs – handling in healthcare settings:**
  - CSTDs are supplemental engineering controls
- **CDC/NIOSH "Managing Hazardous Drug Exposures, Information for Healthcare Settings"**
  - CSTDs should be used for hazardous drugs as engineering control, if dosage forms allows, for compounding and administration
  - Employers can develop a facility-specific list of hazardous drugs, and that due to limited or incomplete toxicology data for investigational drugs, it is prudent to handle investigational drugs as hazardous if mechanism of action suggests that there may be a concern
- **CDC/NIOSH "Procedures for Developing the NIOSH List of Hazardous Drugs in Healthcare Settings"**
  - If a drug also exhibits a molecular property that may limit the potential for adverse health effects from exposure to the drug in healthcare workers, may be determined not a hazard
  - [footnote 17] Properties of a drug molecule that may limit adverse effects in healthcare workers are typically chemical, physical, and structural properties that affect its absorption (ability to enter the cells of the body), e.g., chemical structure, molecular weight, or mass
  - [footnote 43] very large drug molecules may be therapeutically active and potentially toxic when injected, but may be too large to be absorbed appreciably through inhalation, ingestion, dermal, or percutaneous (needle puncture) routes of exposure
- **EU Commission Document "Guidance for the safe management of hazardous medical products at work"**
  - There is differing information in literature on the effectiveness of use of closed system transfer devices (CSTDs) for reducing the risk in the preparation of HMPs (hazardous medicinal products).
  - It is the decision of the management/staff on whether CSTDs are to be used in accordance with the risk assessment performed and relevant legislation

Introduction – Main CSTD Components

Compounding:

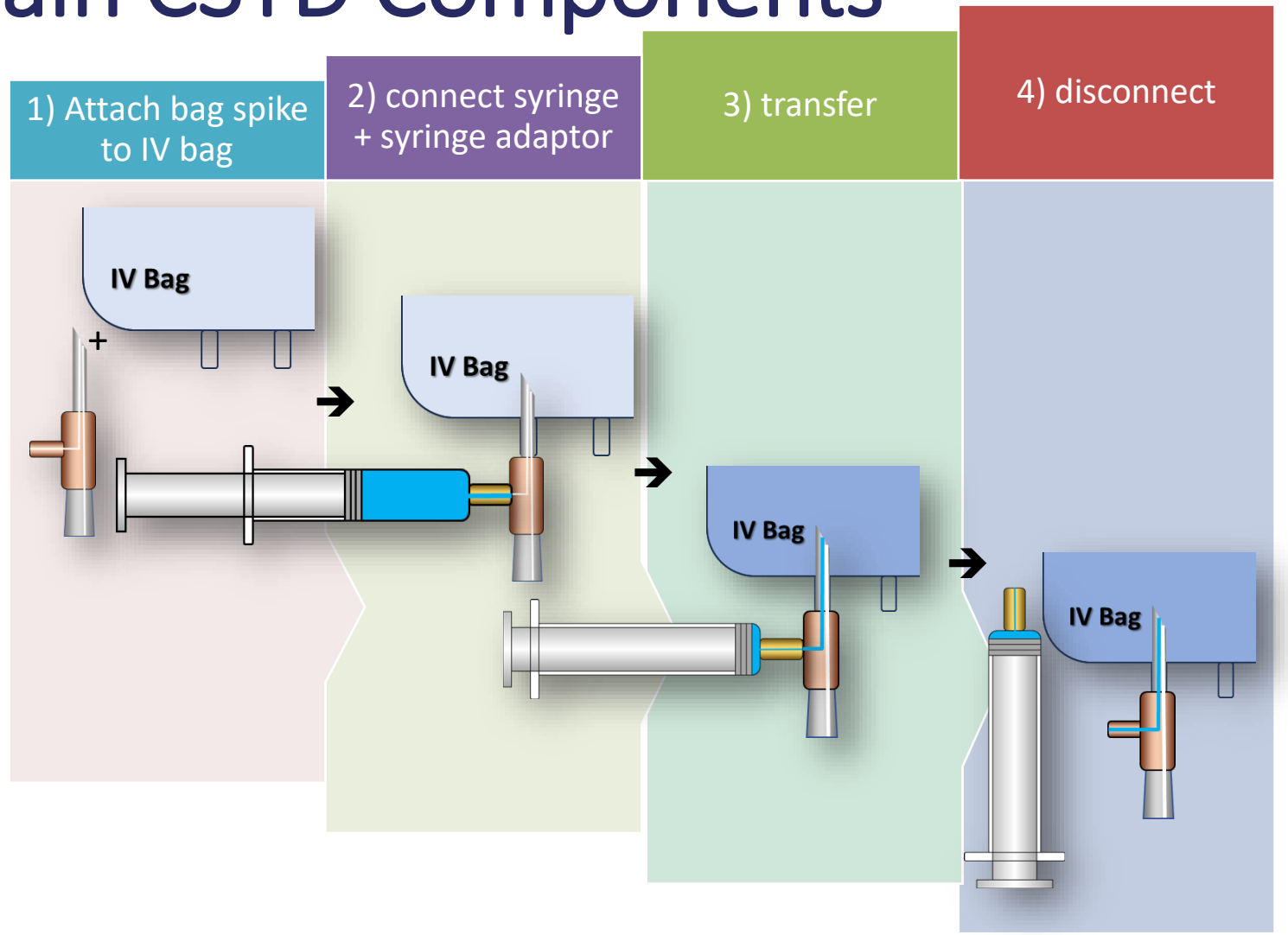
- vial adaptor (green)
- syringe + syringe adaptor (yellow)



Introduction – Main CSTD Components

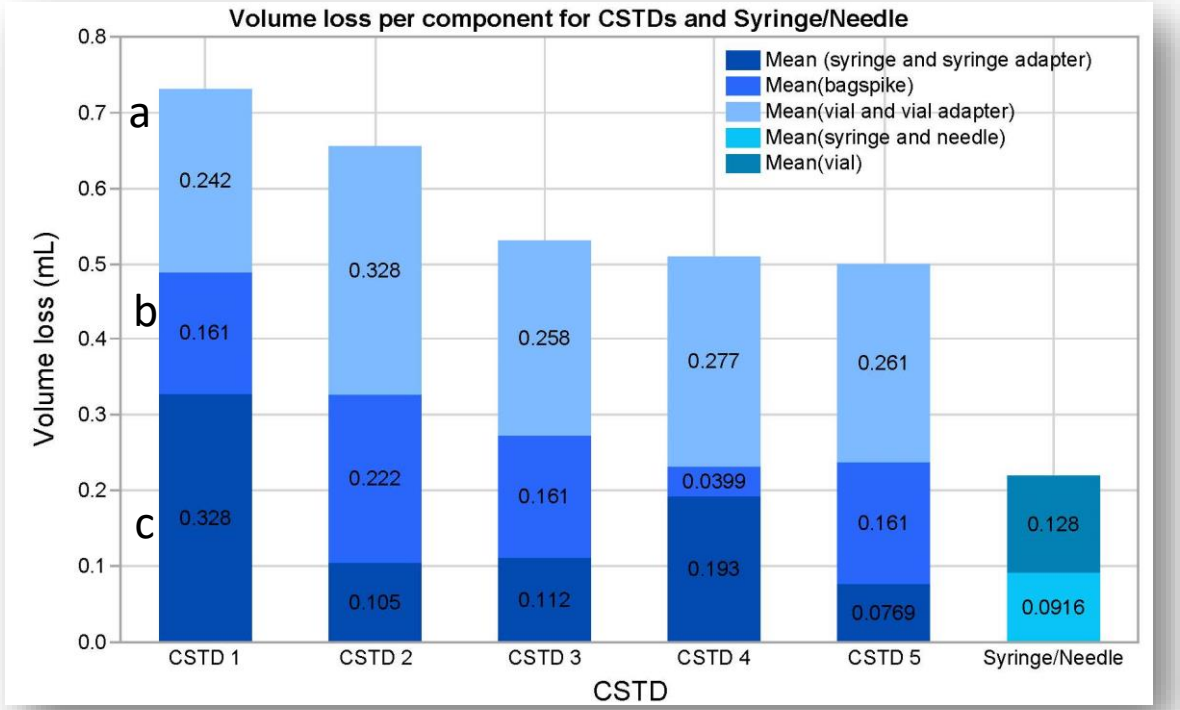
Administration:

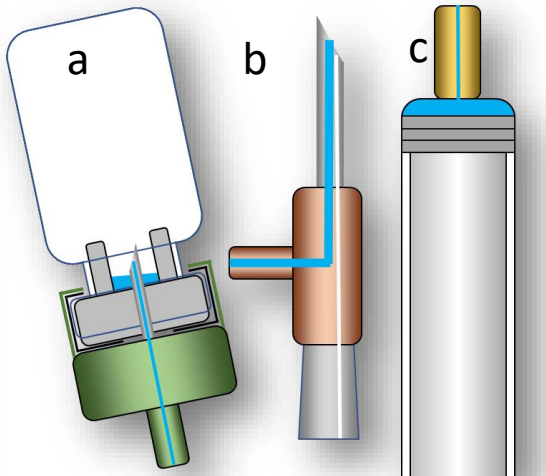
- bag spike (red)
- syringe + syringe adaptor (yellow)



Too Little – Too Much

- CSTDs have higher holdup volumes compared to needle/syringe and holdup volumes differ between CSTD brands (and product properties):[1]





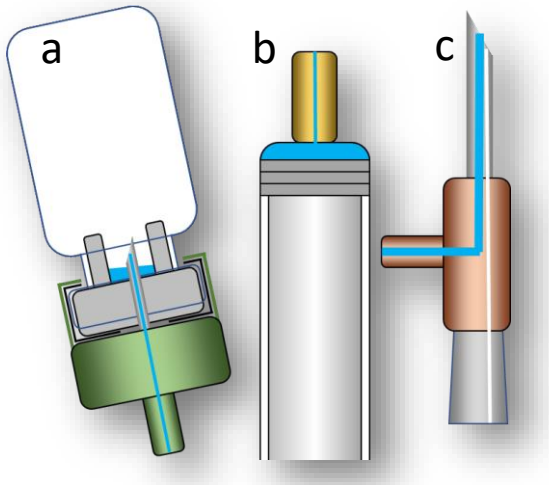
holdup volumes = blue:
a. vial + vial adaptor (green)
b. bag spike (red)
c. syringe + syringe adaptor (yellow)

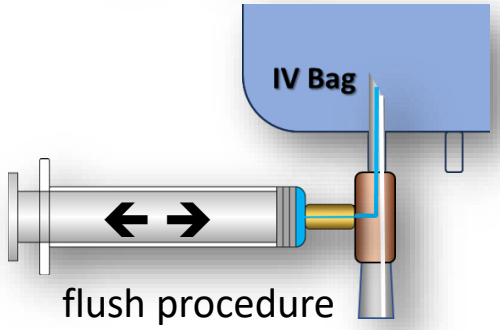
➔ Challenge for balancing overfill

[1]Lehermayr et al., Closed System Transfer Devices (CSTDs): Understanding Potential Over- and Under- Dosing of Liquid Vial Drug Products and How to Generally Mitigate, Journal of Pharmaceutical Sciences, Volume 112, Issue 9, 2023, Pages 2532-2537, ISSN 0022-3549, https://doi.org/10.1016/j.xphs.2023.04.014;
[2]Simal et al., Developing a flowchart to evaluate the use of Closed System Drug-Transfer Devices with monoclonal antibodies: Focus on the clinical trial setting. Journal of Oncology Pharmacy Practice. 2023;0(0). doi:10.1177/10781552231199412; Kulju et al., Assessment of unintended volume loss of six closed system transfer devices. *Journal of Oncology Pharmacy Practice*. 2020;26(5):1134-1140. doi:10.1177/1078155219888682;
[3]Schmelzer et al., Tolerance Interval Approach for the Determination of Overfill of Liquid Parenteral Drug Products. PDA J Pharm Sci Technol. 2023 May-Jun;77(3):181-196. doi: 10.5731/pdajpst.2022.012743. Epub 2022 Oct 14. PMID: 36241216.

Too Little – Too Much

- Overfill Options:
  - Include sufficient overfill to fulfill label claim **(a)** with all CSTDs?
  - Include sufficient overfill to compensate additional hold-up volumes of **(a)**, **(b)** and **(c)**?
  - Include sufficient overfill to fulfill the label claim with needle/syringe?
  - Use USP<1151> overfill recommendations?
- Overfill Risks
  - Compensating for **(a)** increases the risk of misuse when using needle/syringe
  - Compensating also for **(b)** and/or **(c)** additionally increases the risk of overdosing in case a CSTD flushing procedure is applied
  - Not compensating for additional CSTD hold up volumes increases the risk of underdosing when CSTDs are used
  - Applying USP<1151> can underestimate the overfill for small volumes and overestimate it for large volumes[1]
- Good news: The larger the transferred dose volume, the lower the product specific risk of over-/ underdosing (>2-5mL / dose transferred is within 95-105%[1])





[1]Lehermayr et al., Closed System Transfer Devices (CSTDs): Understanding Potential Over- and Under- Dosing of Liquid Vial Drug Products and How to Generally Mitigate, Journal of Pharmaceutical Sciences, Volume 112, Issue 9, 2023, Pages 2532-2537, ISSN 0022-3549, https://doi.org/10.1016/j.xphs.2023.04.014;
[2]Simal et al., Developing a flowchart to evaluate the use of Closed System Drug-Transfer Devices with monoclonal antibodies: Focus on the clinical trial setting. Journal of Oncology Pharmacy Practice. 2023;0(0). doi:10.1177/10781552231199412; Kulju et al., Assessment of unintended volume loss of six closed system transfer devices. *Journal of Oncology Pharmacy Practice*. 2020;26(5):1134-1140. doi:10.1177/1078155219888682;
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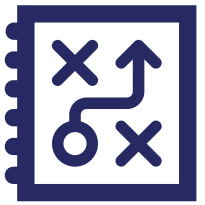
Evaluation and Risk Assessment



Pharma Companies, based on portfolio, should define a phase appropriate CSTD strategy considering the risk of the product being used with CSTDs

- hazardous classification, indication, route of administration, dosage form, type of molecule, prior knowledge and literature, clinical landscape and local/site regulations
- define mitigations (e.g. requirement of an additional flush, use of in-line filter, extra vial in clinical studies)
- perform testing where required

To enable

- Early stage clinical trials
- Final product design fulfilling the market needs

Stay aware of global landscape of CSTDs

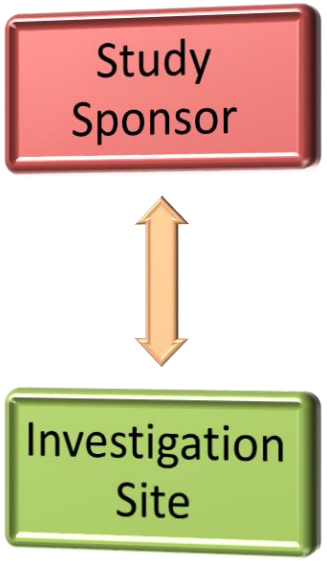
Communication for Investigational Studies

Study sponsor should proactively communicate (e.g. during pre-study surveys, via pharmacy manual):

- position on allowing / restricting usage of CSTDs
- possible mitigations to overcome hold-up volumes

Investigation site should proactively communicate:

- how hazardous products are defined[1]
- local safety procedures required for preparation and administration
- available infrastructure, possible personal protective equipment (PPE) incl. requirements for the use of CSTDs and available alternatives



[1]Simal et al. Developing a flowchart to evaluate the use of Closed System Drug-Transfer Devices with monoclonal antibodies: Focus on the clinical trial setting. Journal of Oncology Pharmacy Practice. 2023;0(0). doi:10.1177/10781552231199412

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* IQ working group co-chairs

Other Industry Collaborations

Some IQ CSTD Working Members are also participating in:

- AAMI (Association for the Advancement of Medical Instrumentation):
  - CSTD Committee that includes FDA / Pharma Industry / CSTD Manufacturers
- Realhope
  - An academic and Industry collaboration working on understanding real life stress scenarios for protein-based drug therapies and educate drug users in order to ensure patient safety. It is realized through the IMI (Innovative Medicines Initiative)
- PQRI (Product Quality Research Institute)
  - Biopharma companies and device manufacturers working towards authoring a publication based on FMEA analysis to address the risk and mitigations of vial transfer devices.
- AAPS handling group:
  - A cross industry community that discusses topics centered around in use practices for biologics drug products.

Acknowledgement

This presentation was developed with the support of the International Consortium for Innovation and Quality in Pharmaceutical Development (IQ, www.iqconsortium.org). IQ is a not-for-profit organization of pharmaceutical and biotechnology companies with a mission of advancing science and technology to augment the capability of member companies to develop transformational solutions that benefit patients, regulators and the broader research and development community.