What device engineers can tell you about Cell & Gene Therapy delivery devices and regulatory challenges

Saran Baskaran, Device Development, BioPharmaceuticals Development, R&D, AstraZeneca, Gaithersburg, US

Samir A. Shah, PhD, CMC Regulatory Affairs, Devices & Digital Therapeutics, Oncology R&D, AstraZeneca, Gaithersburg, US

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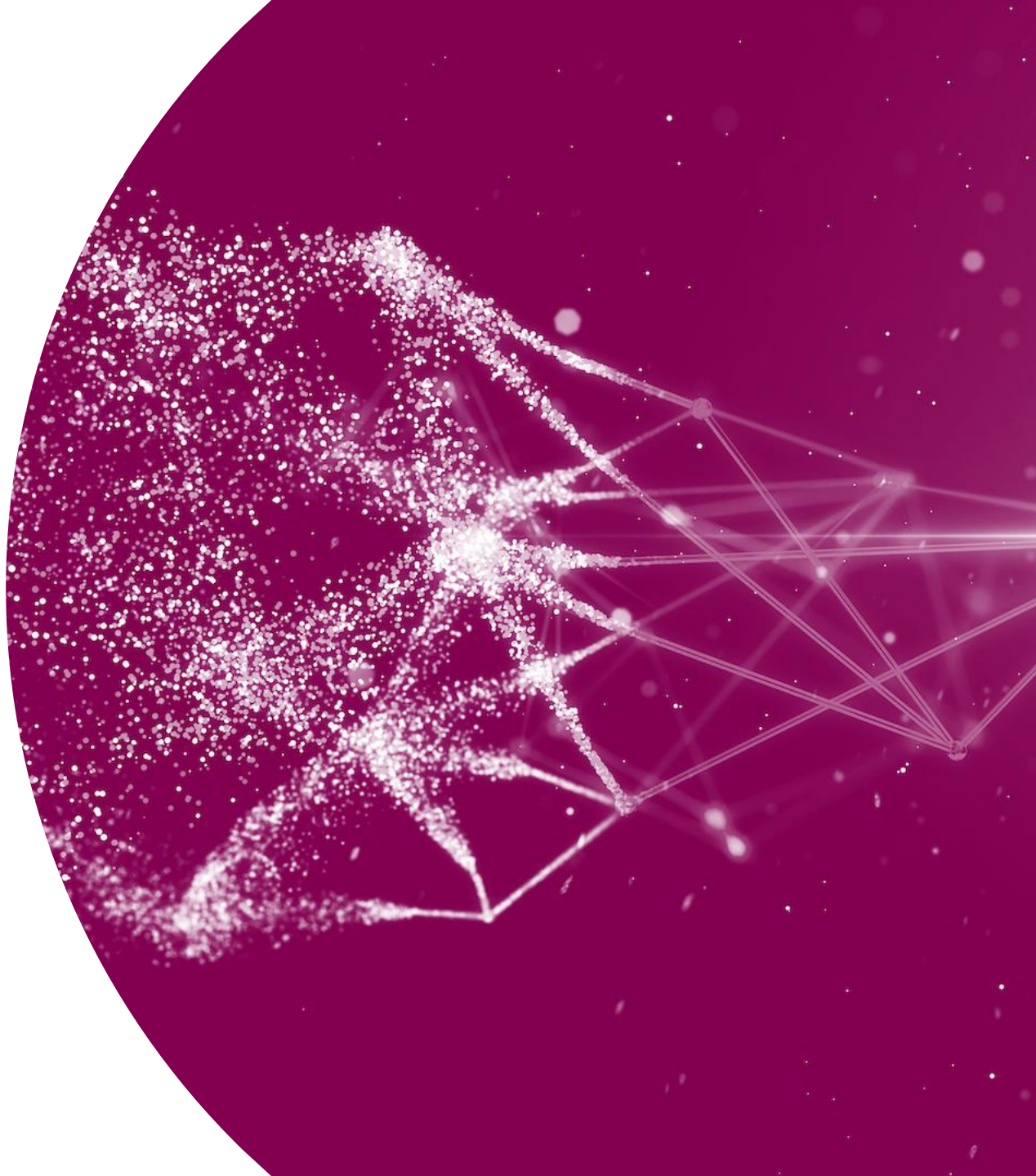


Agenda

1. Identifying a need for a device for cell & gene therapeutic (CGTP) delivery
2. Unique aspects of device development for cell & gene therapies
    1. Human Factors Considerations
    2. Drug-Device Compatibility
    3. Risk Management
3. Regulatory challenges with CGTP delivery devices

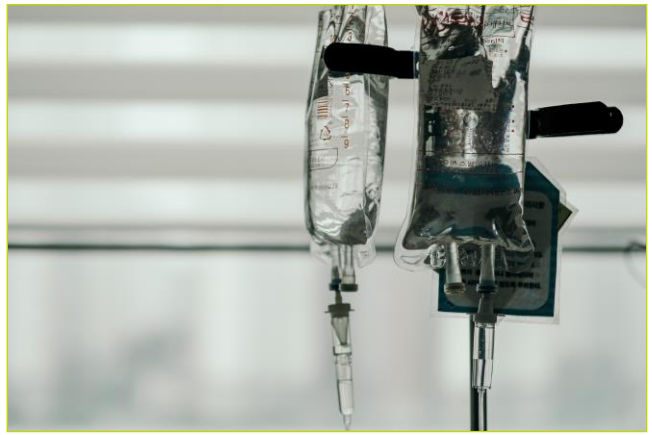
Cell and gene therapies are increasingly looking at medical devices for therapeutic delivery

- Developers for a candidate cell or gene therapy (CGTP) will seek a method of delivery that optimizes therapeutic effect
- Today, most therapies achieve therapeutic effect through **systemic delivery** (e.g., intravenous infusion)
- Therapies that require **local delivery** (e.g. direct to organ) tend to need a medical device

Image: Diana Polekhin

CGTP can be grouped into two delivery categories

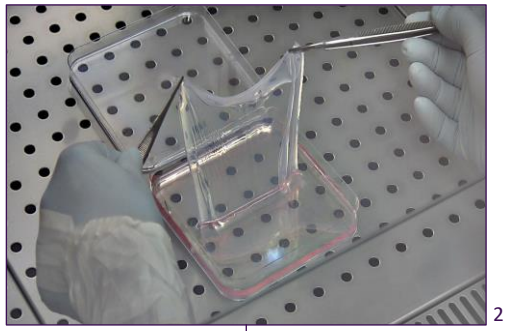
Systemic



[1]

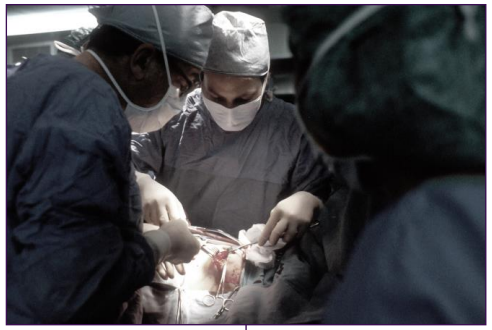
Intravenous & Intra-arterial

Local



[2]

Topical



[3]

Direct-to-organ

Intramuscular

Intranasal

Intrathecal

Intravitreal

Needle & syringe may be all that are needed to create access

[1] Image: Insung Yoon, [2] Image: Center for Regenerative Medicine, University of Modena and Reggio Emilia, [3] Image: National Cancer Institute

Existing device development framework can be leveraged to focus team effort and optimize therapeutic delivery

Manage Risk

Plan | Establish Design Inputs | Create Design Outputs | Verify | Validate

Device Need Identified

Organizational Stakeholders must be able to recognize that a Device needs to be developed

Recognize that changing an intended use often entails new or modified design inputs

Ensuring cell or gene therapy compatibility with the device may be an iterative process

Identification of a specific design vs a range of candidate designs

Image: Drew Hays, University of Northern Iowa

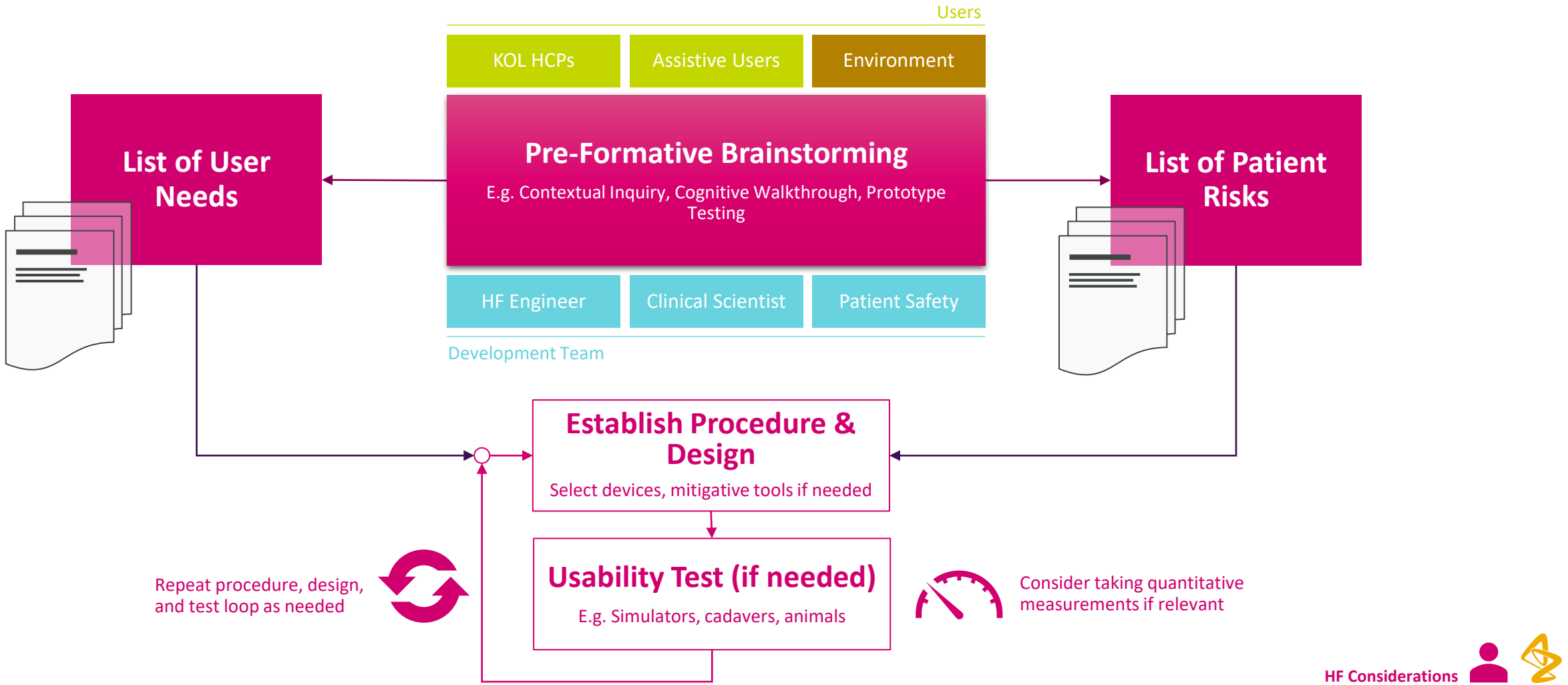
Three considerations for developing CGTP devices

Proper Identification of **User Needs** and associated **Human Factors Work**

Designing a cell/gene-therapy **compatible** delivery vehicle and **device**

Consider the **full risk picture**: surgical intervention and cell/gene therapy

The development team should employ human factors tools early with users to identify **user needs** and **patient safety risks**



Three takeaways for human factors

Work early + directly with clinical experts

- Important for novel delivery methods
- Identify user familiarity with device & scenario
- Iterate fast with a smaller group

Use brainstorming exercises to identify use-related showstoppers

- Rule out disfavored designs early

Take time to think about how best to simulate the workflow

- More realism comes at greater cost
- Use product risk profile to help decide

CGTP products have several specific design considerations

Design parameters commonly considered for **protein** therapeutics

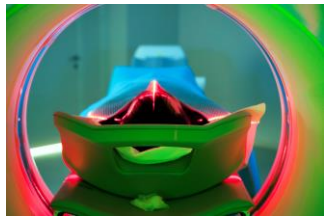
- Viscosity
- Volume
- Material Interactions
- Environmental Interactions
- Injection Site Targeting

Parameters of Interest

Design parameters that may differ for **gene/cell** therapies

- Non-homogenous fluid properties
- Time-dependent fluid properties
- Multi-site injection volumes
- Impact of varying dead volumes
- New material contact interfaces
- Variable duration of material contact
- Surface adsorption characteristics
- Dose prep/admin environment
- Dwell time at each step
- Injection site location & navigation
- Maintain injection site

Key takeaways for drug/device compatibility

Identify methods for functionality, viability and potency early		▪ Success of design parameters will be gauged on the impact the device has on the drug quality attributes
Interfaces with users and other devices: new orientations & forces		▪ Navigation/stabilization may require the use of other devices
Product loss varies with contact surfaces and dead volume		▪ Product cost may disfavor high loss designs
Deeper collaboration with device designer/manufacturer		▪ Regulatory submissions may require information known only to the device designer or manufacturer

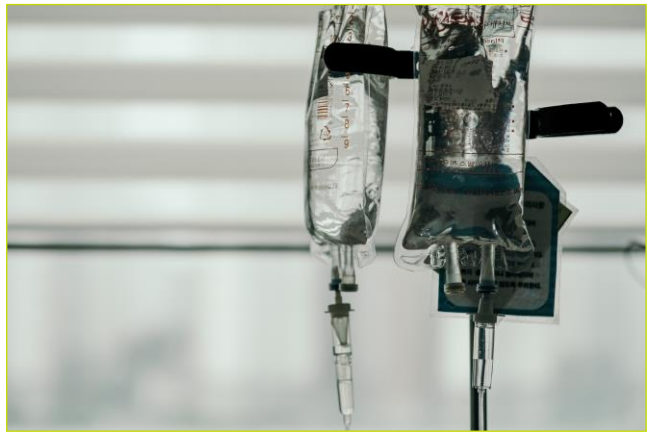
Deploy risk assessment tools early

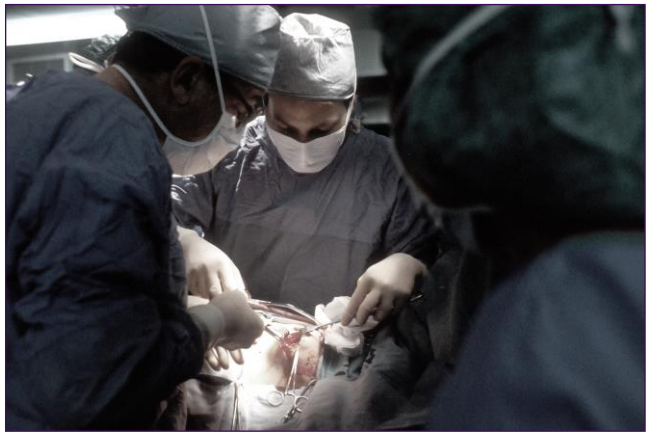
Medical Device Risk Mgmt.	Risk Guidance	Risk Assessment Tools
ISO 14971:2019	ISO/TR 24971	▪ **Preliminary Hazard Analysis** (Use Annex A) ▪ Fault Tree Analysis ▪ Failure Modes and Effects Analysis

- Direct to organ delivery may require new or existing **surgical procedures**: more clinical collaboration will be required to assess risk
- Using an **approved device** for a **new intended use** may also have risk gaps, requiring clinical and technical evaluation
- An early hazard analysis exercise will provide an overview of risks

The delivery target & delivery method affect level of risk

Systemic IV & IA < Direct tissue access with needle and syringe < Incision or vascular access required





Cell/Gene Therapy Risk

Device & Surgical Risk

Identify risk controls and keep the big picture in mind

Mitigate Risks

- Use workshops with clinical experts to find the best risk controls based on state of the art and current technology
- Some procedures will simply have more **residual risk** and require more training

Inherently safe > Protective Measures > Inform & Train

Risk-Benefit

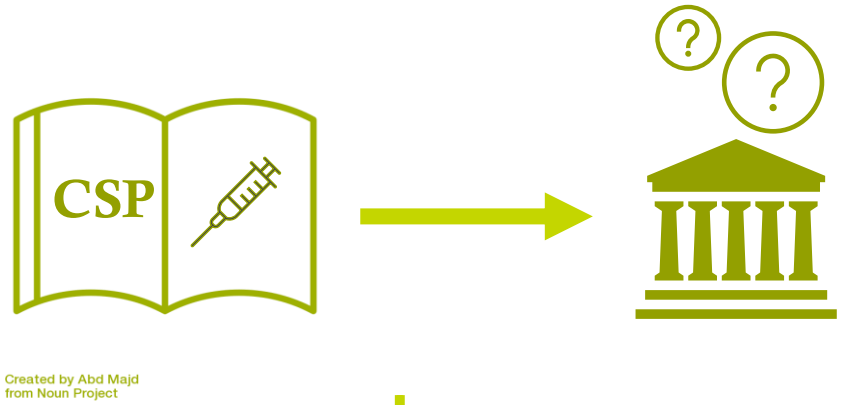
- Cell & gene therapies have the potential to achieve patient **benefits** not previously possible with traditional treatments

Regulatory Challenges with CGTP Delivery Devices

Samir A. Shah, PhD

Kathy Wang

Cell and gene therapy clinical trial protocols may list the delivery device in 3 ways that raise questions with regulators:



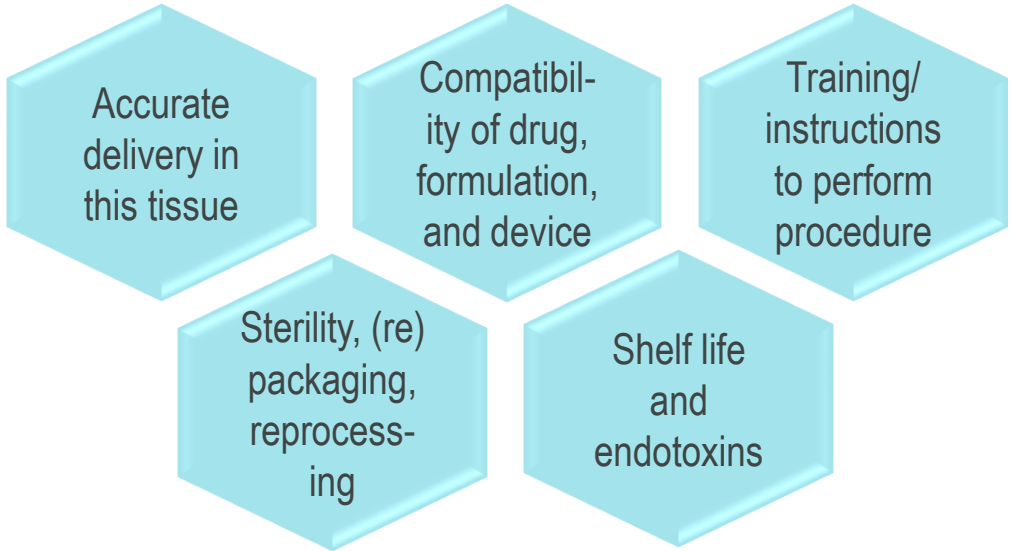
Created by Abd Majd from Noun Project

- chosen by the site
- chosen by the doctor (off-label use)
- chosen by sponsor but lacks regulatory approval* for CGTP indication

Why these scenarios are a problem

Created by Alice Design from Noun Project

Sponsor must ensure safety of the delivery device in a clinical trial <u>for this indication for use</u>, including:



An existing device approval* only means risks are mitigated when using device for the <u>approved indication for use</u>

To ensure safety when the device is used in a clinical trial for this <u>new indication for use</u>, regulators may ask for evidence that these risks have been mitigated for <u>this clinical trial use</u>

*"approval" is authorization to market the device, which could be an approval of a Premarket Application, granting of a de novo, clearance of a 510(k), or CE Mark

Who generates evidence that the device can be used safely in a clinical trial for this new indication for use?

Device manufacturer

Who has the device expertise, but may not be interested in this indication?

Drug Sponsor

Who wants to use the device in the clinical study, but doesn't have the device expertise?

Drug development

Device development

FSI

Agreement / collaboration for parallel development can de-risk study start

Drug development

Device development

FSI

Examples of evidence on device to seek authorization to use in a clinical trial for this new indication for use

- risk assessment/comparison of device's approved indications of use vs proposed clinical trial indications for use
- modifications / reprocessing / sterilization of device after acquiring from 3rd party
- device names, description, patient contacting components, principle of operation, diagrams
- proper use by the intended user in the intended use environment using the instructions/labelling
- risk analysis for the entire product
- control of device changes

- dose accuracy and compatibility of device/drug/formulation under worst case conditions (e.g. preparation, temperature, pressure, etc)
- how supplied
- biocompatibility, sterility, endotoxin, packaging, shelf life, performance data, electrical safety, electromagnetic compatibility, software

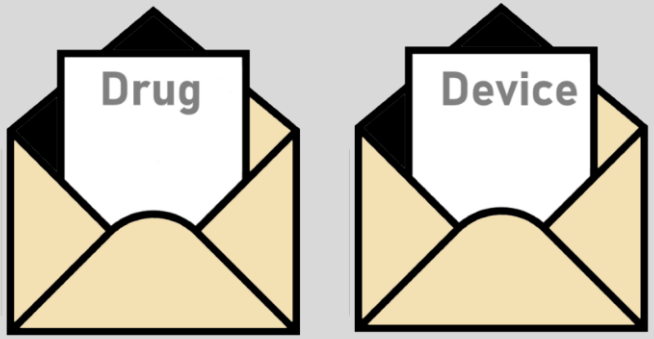
May need to generate evidence for a range of devices if there are more delivery device choices

Regulators could ask for a separate device clinical application since it is a new use of the device and new drug

Further regulatory considerations for the marketing authorization

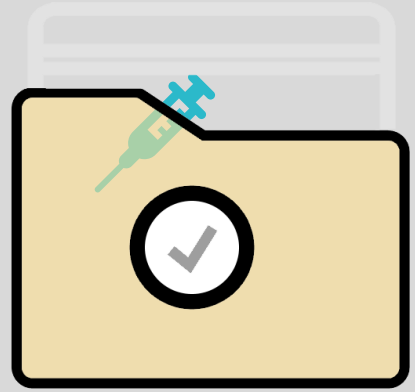
Include device in drug application?

More challenging to change the device in the future since data is specific to that device



Separate device application (510(k))?

Who submits it?
What is the exclusivity?



Where is the device clinical evidence?

Clinical protocols must be modified to include device endpoints

De-risk the regulatory path for delivery devices used to deliver new therapies

Establish an agreement / collaboration for parallel development of the delivery device

Ensure clinical study collects device endpoints for use in a device marketing application

***Regardless of approval status*, generate evidence that the device can be used for a new indications for use in a clinical trial**

For marketing applications, consider the pros/cons of a separate device application (e.g. 510(k), PMA, de novo, CE Mark)