Key considerations and insights for design verification test programmes and design transfer for combination products

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PDA Aseptic Processing of Biopharmaceuticals Conference 2024

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Team Consulting

Medical Device Development

- Multi-disciplinary device development from opportunity definition to product launch
- Supporting clients globally since 1986
- Based in Cambridge UK, EU & USA
- Pure healthcare focus (>50% in drug delivery)
- ISO 13485:2016 certified
- Employee trust owned, 140+ employees

Contents

- Device development process
- Understanding system performance
- Industrialisation
- Design Verification
- Design Transfer
- Production trouble-shooting

This paper applies to combination products generally but with a strong focus on pre-filled syringes and autoinjectors.

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Device development process

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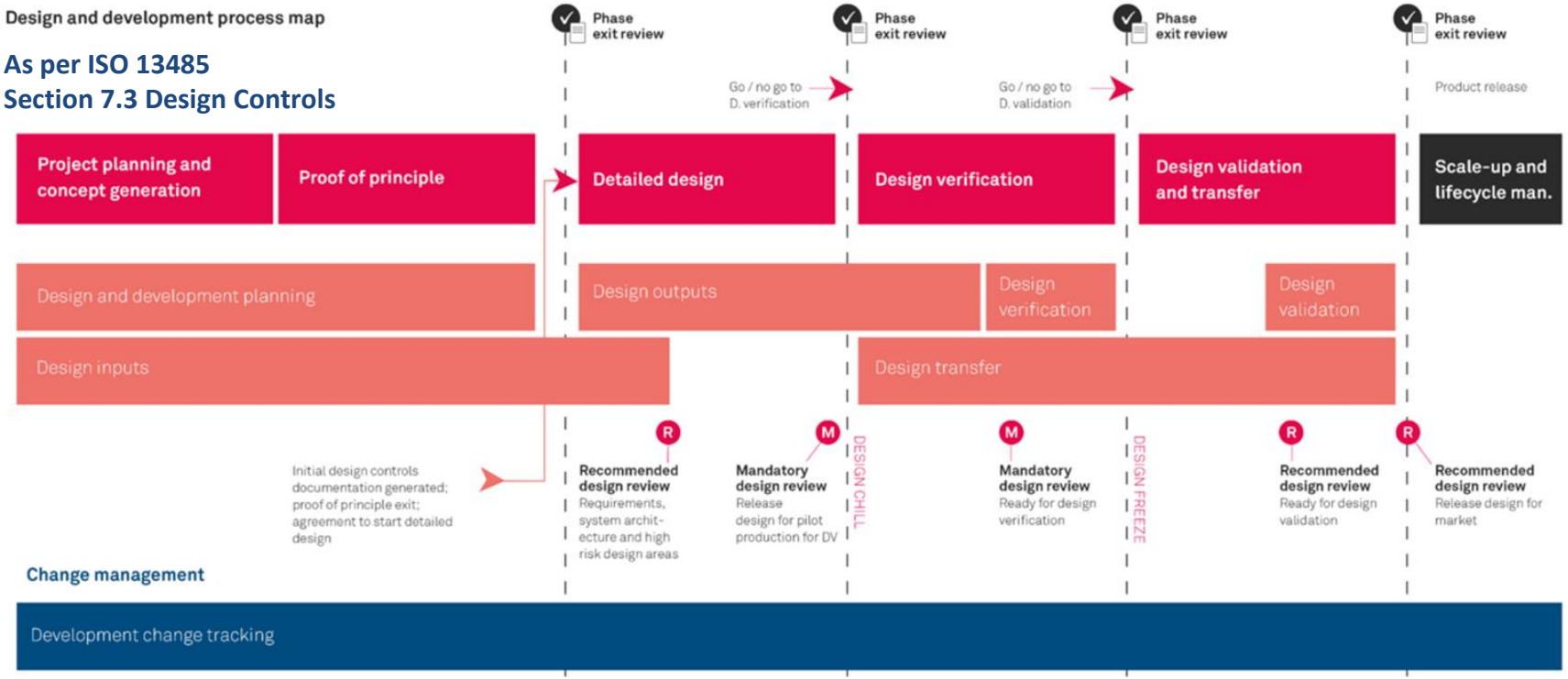
team

Design and development process map

As per ISO 13485
Section 7.3 Design Controls



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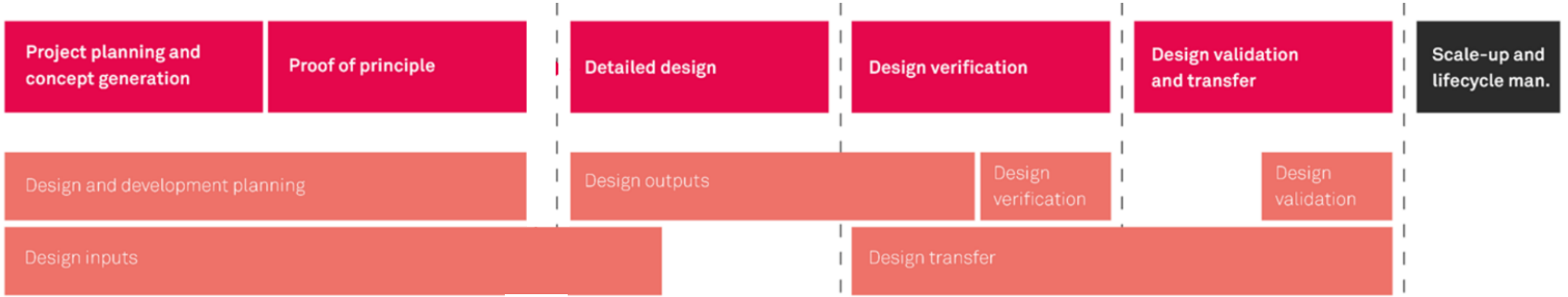

Understanding these processes is important for each new product, even if there is no significant new 'design' work e.g. if you are incorporating an existing PFS into an existing auto-injector to form a new combination.

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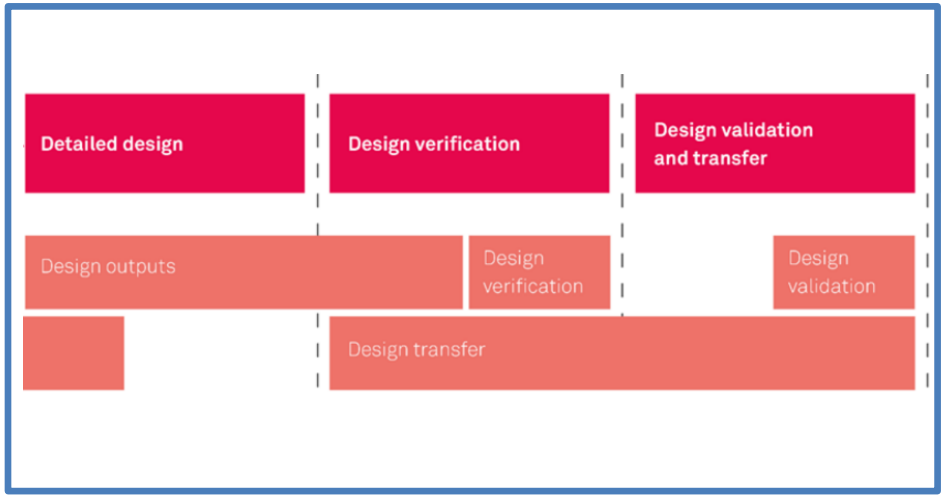
This presentation will focus on later phases:

- **Detailed design** which delivers performance and understanding
- **Design V&V** which confirms that performance meets input requirements (product and user)
- **Design Transfer** which ensures that what was verified can be manufactured reliably



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Understanding system performance

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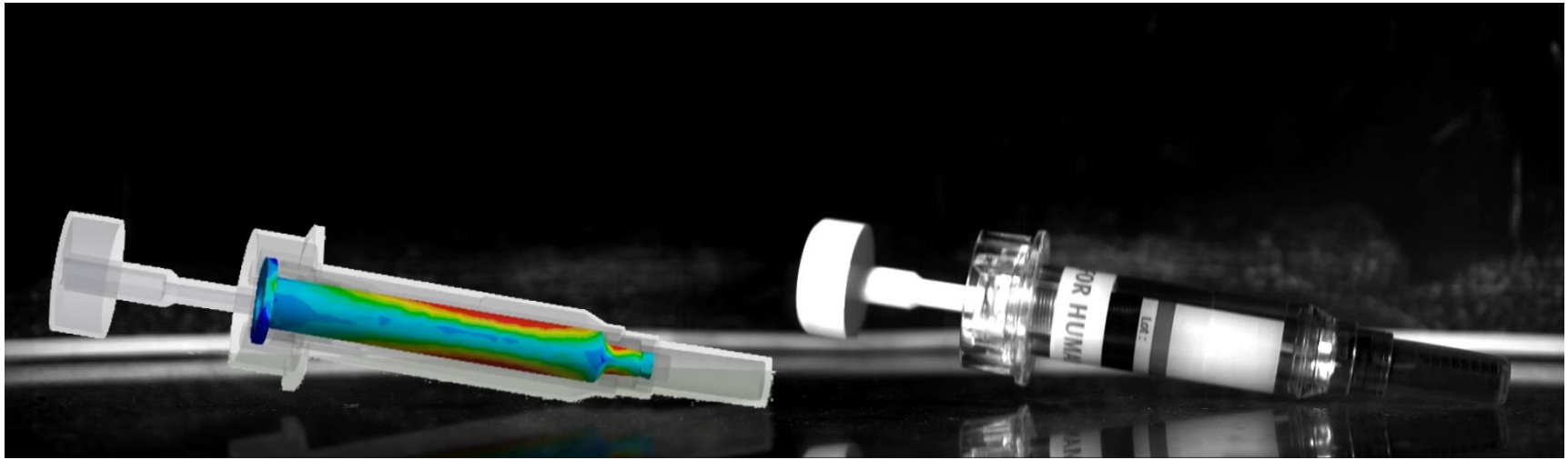
Understanding system performance

This is best achieved through a combination of **theoretical** and **empirical** methods.



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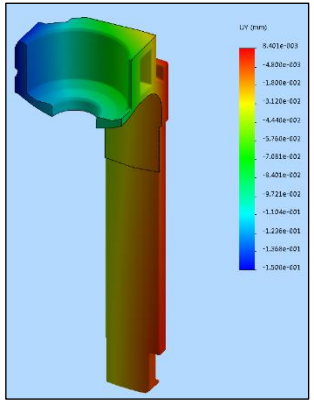
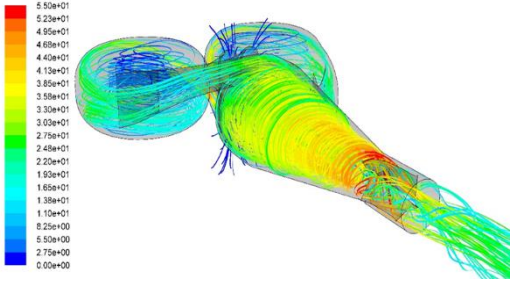
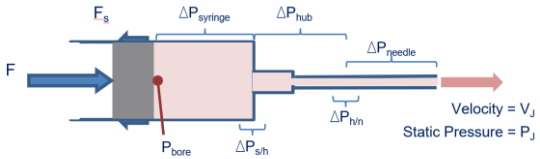
Understanding performance - Theoretically



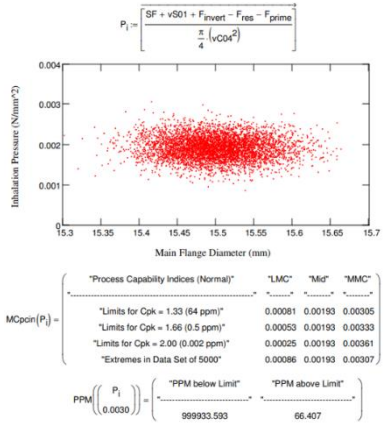
Finite Element Analysis



Computational fluid dynamics



Mathematical modelling



Sensitivity analysis

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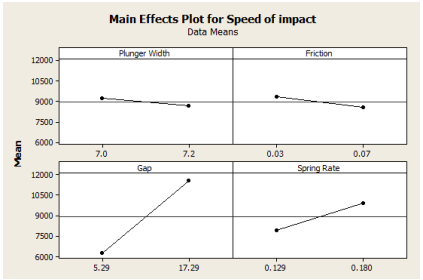
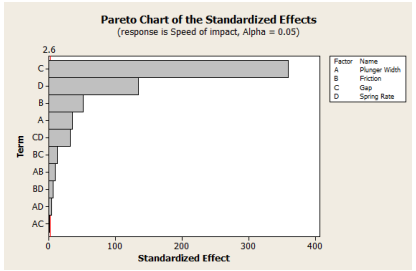
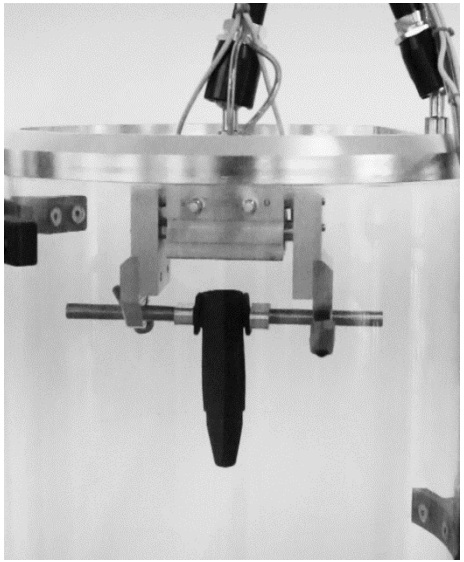
Understanding performance - Empirically

Prototype testing





Design of Experiments



Robustness and overstress testing

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Understanding performance - Outputs

- **Testing** demonstrates performance & supports characterisation
- **Analysis** and simulation identifies critical features and sensitivities
- **Engineering analyses validated by empirical data** are a very powerful combination:
  - for design development and optimisation
  - to support scale-up & design transfer
  - to inform trouble-shooting (if needed…)

This is not just a good idea! Regulatory guidance requires that you can demonstrate understanding of how your device works.

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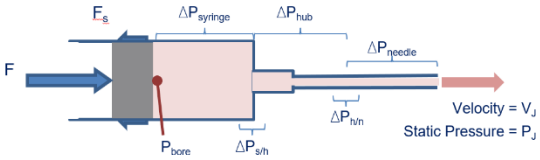
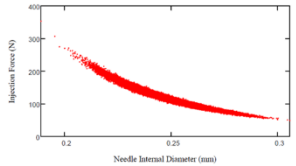
Case study – impact of drug viscosity on PFS use

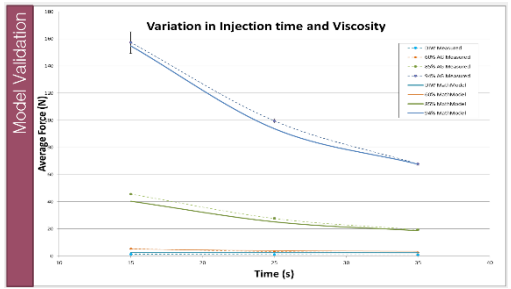
A math model was developed to identify critical characteristics of a PFS system, and the impact of increasing drug viscosity on delivery force and time.



"Process Capability Indices (Non-Normal)"	"LMC"	"Median"	"MMC"
"Limits for Assembly Cpk 1.33"	48.24	112.84	250.34
"Limits for Assembly Cpk 1.66"	32.10	112.84	284.72
"Limits for Assembly Cpk 2.00"	15.95	112.84	319.10
"Extremes in Data Set of 100000"	49.91	112.84	354.14



The math model was assessed against test data from a range of PFS (e.g. different needle diameters and lengths) and drug configurations, optimised and then validated.



The suitability of a PFS for delivery of a client's target drug could then be assessed theoretically, considering user capability and robustness of the PFS itself. Acceptability was confirmed through testing and usability studies.

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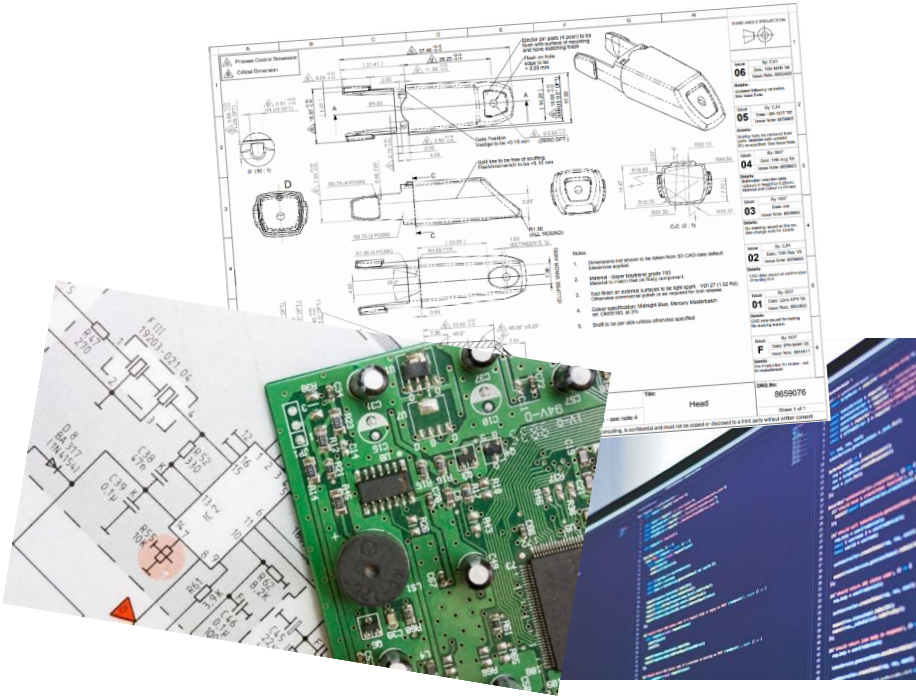
Understanding performance - Outputs

- Design specifications capture design intent and identify critical to quality attributes
- This includes sub-assemblies and final device assemblies, not just components
- Design specifications and quality plans drive control strategies including inspection and testing, and acceptance criteria
- Engineering analyses demonstrate that anticipated manufacturing variability will not adversely impact performance



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Industrialisation

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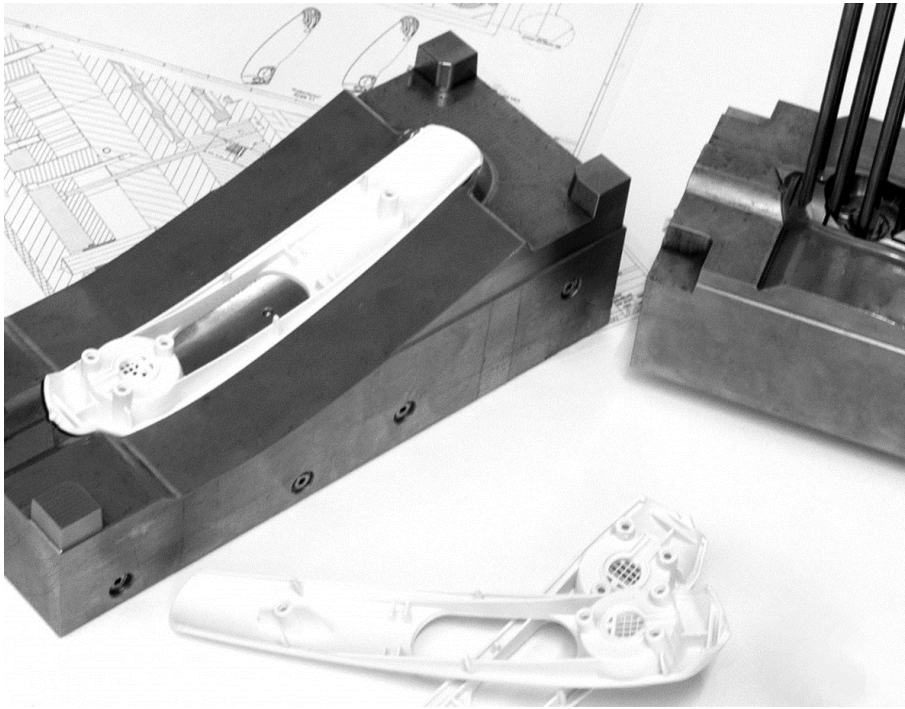
Industrialisation

This process starts during detailed design e.g.

- Tolerance analysis, which needs to be based on realistic assumptions of process capability
- Risk analysis identifies potential process induced failure modes and mitigations
- DFM/DFA must ensure that design manufacture is viable, from capable processes at the appropriate scale
- Material selection needs to consider the needs of the device performance, stability, sustainability and supply chain



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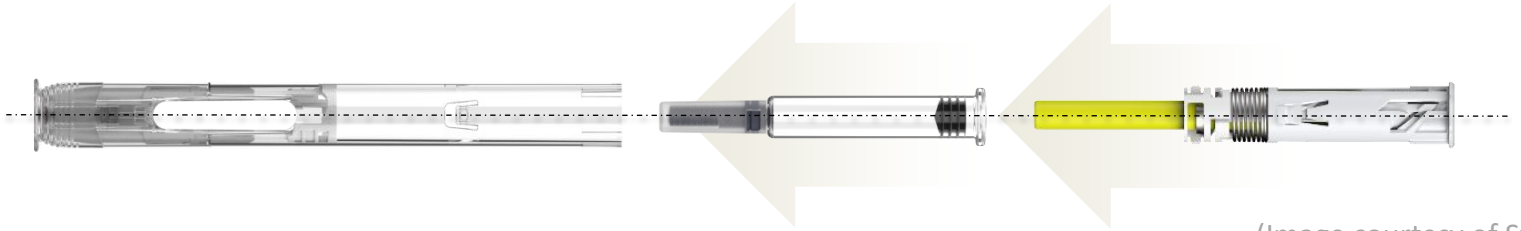
Industrialisation

- Specification of assembly, test and inspection equipment will be informed by learnings during development and risk assessments such as hazard analysis and Process FMEA e.g.
  - Tolerances required for stopper position, air bubble size, glass geometry (including flange and shoulder) and needle length
  - Accuracy of pick and place stations to ensure reliable final assembly
  - Need for process controls and 100% inline checks vs. sampling plans & inspection



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Case study – Industrialisation of Autoinjector #1

System was developed from concept and prototype stage through detailed design. Engineering analysis and testing supported de-bugging and optimisation of devices from rapid & pilot tooling.

Learnings from test & assembly fixtures fed into semi-automated systems for design verification, plus designs of fully automated systems. Understanding of critical features was communicated to CMO, tool and equipment manufacturers.

Production V&V was carried out on devices from commercial scale manufacturing systems (>10M per annum). Process validation and release inspection and testing was based on need for reliability levels consistent with emergency use devices.

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Design Verification

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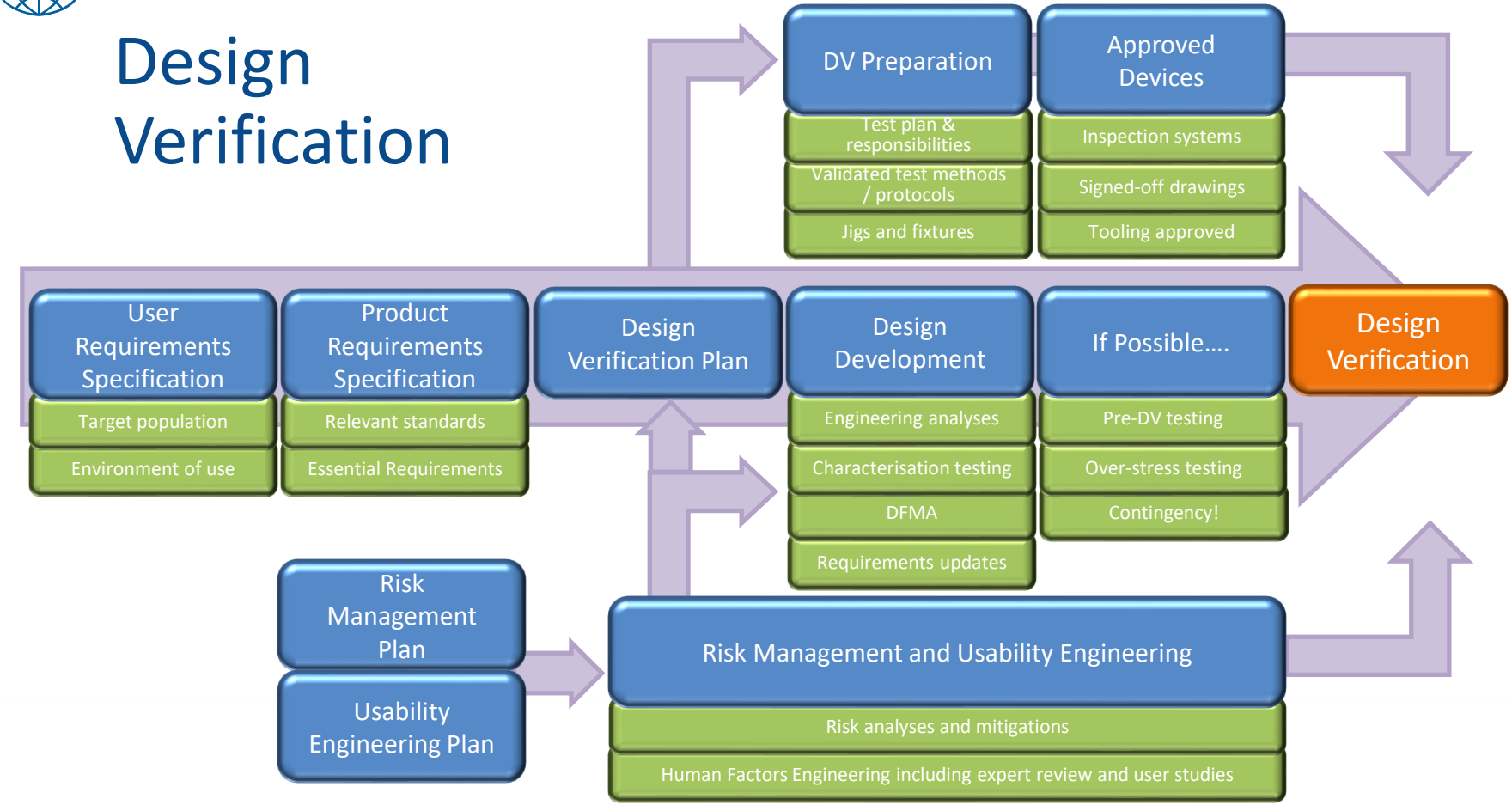
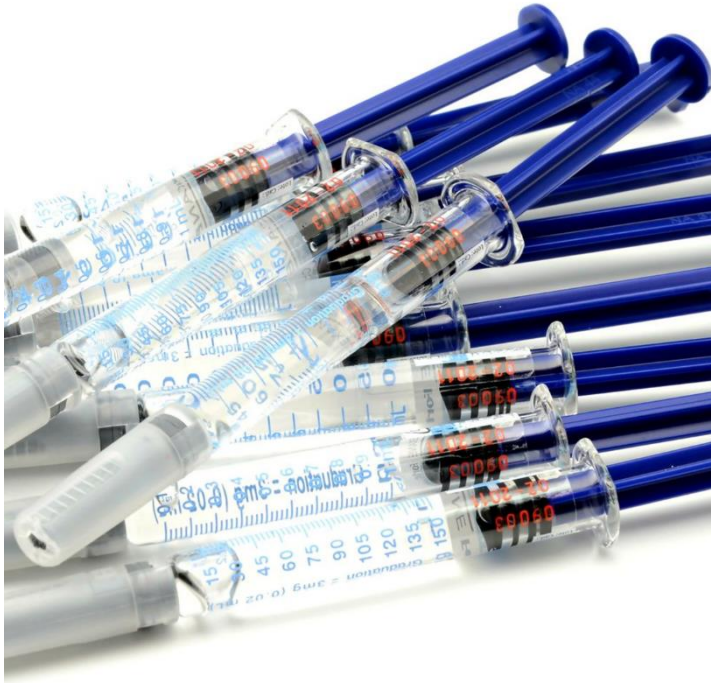
Design Verification



Case study – Design Verification of PFS systems

Design Verification Test programmes for commercial pre-filled syringe products, carried out over recent years by Team, have identified a range of issues and challenges to be aware of:

- Potential disengagement of the plunger stopper from the plunger rod during aspiration (pull-back).
- Excessive break-loose force (at the start of delivery) to overcome syringe barrel stiction. In one case the cause was identified as being due to drug/PFS material incompatibility
- Impact of packaging on drop test robustness
- For PFS with needle safety systems, passive needle guards not deploying at end of delivery stroke. This was for reasons relating either to design (which in one case allowed a single trigger finger to deploy) or test method (inappropriate test piece fixturing).



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Case study – Design Verification of Autoinjector #2

- Team recently completed DVT of a novel emergency use autoinjector, from preconditioning to testing and reporting.
- A bespoke, semi-automated instrument was developed and validated to measure four device primary functions during engineering testing and DVT: activation force, extended needle length, dose delivery time, and delivered volume.
- Some challenges overcome included ensuring product requirements were unambiguous and verifiable, managing a complex pre-conditioning framework and validating measurement systems in parallel with ongoing device development.
- Further work included generating evidence to demonstrate primary function performance met emergency use autoinjector reliability targets, as per FDA guidance (99.999%/99.99%).

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Design Transfer

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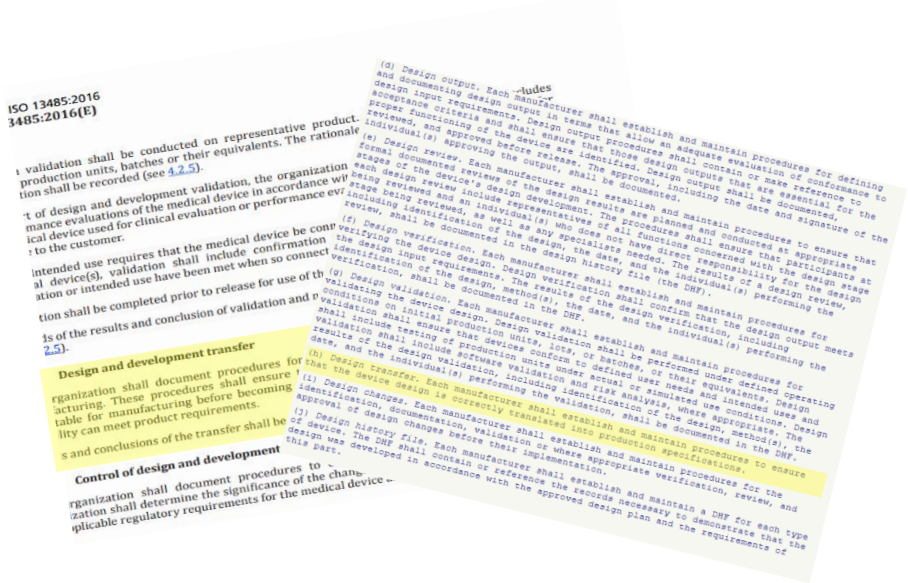
Design Transfer

Ensures that:

- The design is verified as being suitable for manufacture, including meeting cost and production volume requirements
- Design specifications are correctly translated into production specifications
- Production controls ensure capable manufacture of product which reliably meets requirements
- The understanding of the design is well documented and communicated



ISO 13485 and 21CFR820.30 include specific requirements for Design Transfer

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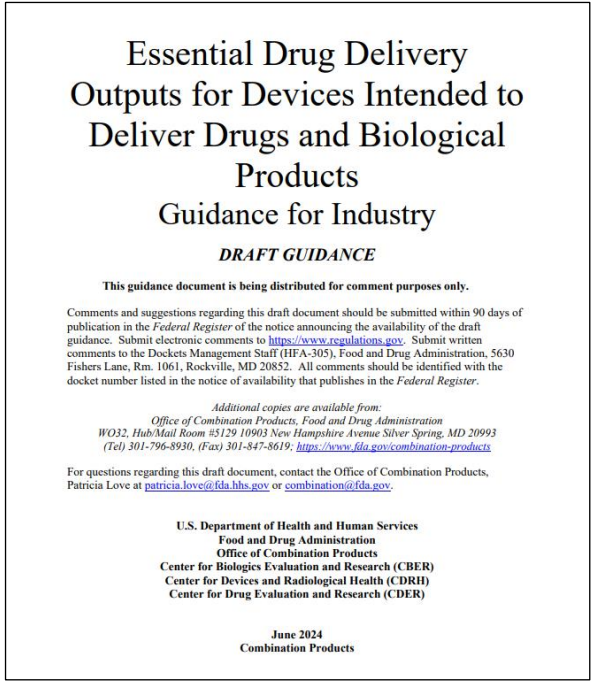
Design Transfer – Regulatory Inputs

New FDA guidance emphasises the need for manufacturers to understand, verify and control specific aspects of device performance (EDDOs).

Still in draft form and industry has submitted comments. There are sections relating to design verification, including pre-conditioning, and manufacturing control strategies.

This follows on from European MDR (with focus on device constituent part) and FDA guidance for emergency use drug delivery systems (also still in draft).



Essential Drug Delivery Outputs for Devices Intended to Deliver Drugs and Biological Products

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

Additional copies are available from:
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(Tel) 301-796-8930, (Fax) 301-847-8619; https://www.fda.gov/combination-products

For questions regarding this draft document, contact the Office of Combination Products, Patricia Love at patricia.love@fda.hhs.gov or combination@fda.gov.

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Center for Devices and Radiological Health (CDRH)
Center for Drug Evaluation and Research (CDER)

June 2024
Combination Products

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Design Transfer – *EDDOs for PFS & Autoinjectors

(*Note: based on current FDA draft document)

Device Platform	Delivery of intended dose	Delivery to target site	Product preparation	Initiation of dose delivery	Dose delivery	Dose delivery completion
Pre-filled syringe	Deliverable volume	Needle length	• Cap removal force (incl. RNS) • Withdrawal force	Break loose force	Glide force	• Glide force • Needle safety activation force
Auto-injector	Dose accuracy	Extended needle length	• Cap removal force • Activation force • Feedback of successful drug preparation	Activation force (shield) Activation force (button)	N/A	• Injection time • Feedback (audible/visual/ tactile)

Some EDDOs for an autoinjector are partly dependent on the PFS, and interactions with it. Non-EDDOs are likely to be as well, such as needle-shield deployment or primary pack integrity. Hence the need to characterise and understand each specific combination.

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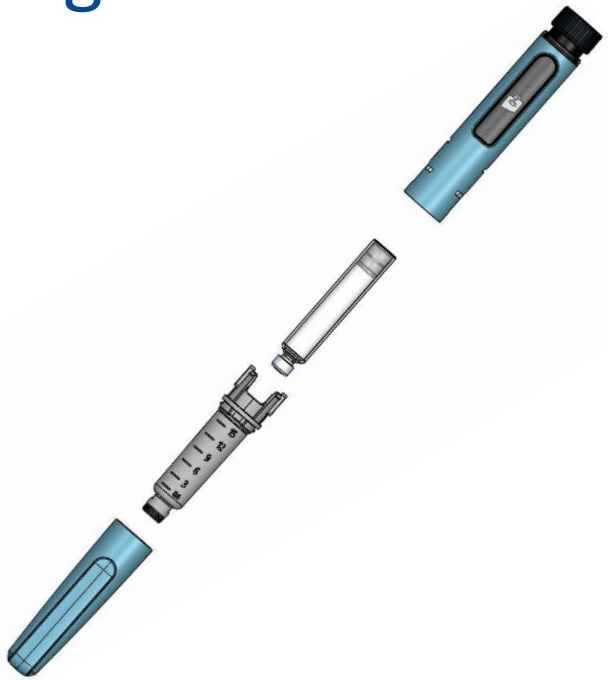
Design Transfer – Control Strategies

Establishing the appropriate control strategies is a critical part of Design Transfer, including:

- Process control and critical dimensions for components and sub-assemblies, and how and when to control them
- Setting acceptance criteria for these and other critical to quality attributes, including use of mean and standard deviation control limits
- Finding the right balance between sampling-based inspection and test versus 100% inline checks
- Use of Statistical Process Control and process capability versus AQLs and Pass/Fail acceptance criteria
- Capturing justification for these decisions e.g. risk-based, dependent on the required reliability levels



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Production trouble-shooting

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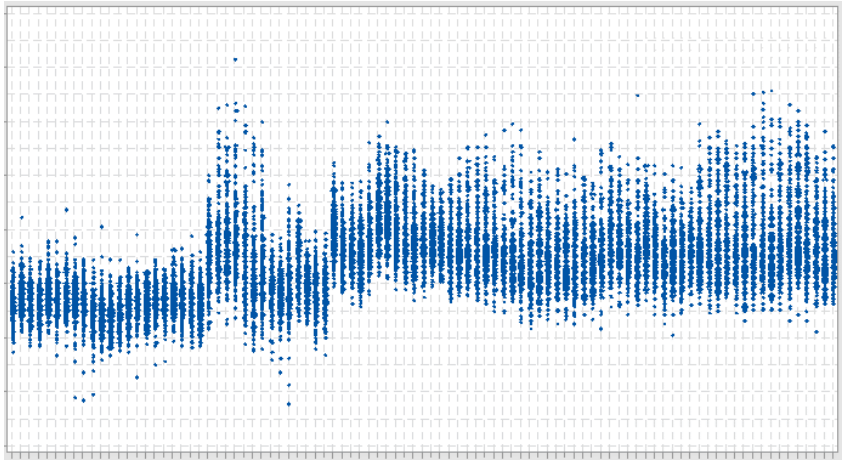
Case study – trouble-shooting AI activation force

- Commercial production of an autoinjector was disrupted when activation force shifted, resulting in some batches falling outside of upper specification limit
- A detailed review was carried out of all production process steps
- Assessment was guided by understanding which components and features most strongly influenced activation force
- This allowed rapid identification of several contributory root causes e.g. dimensional variability resulting from tool wear, introduction of new tooling
- Corrective actions were implemented, and process capability was restored



Activation force batch release test results by lot over time

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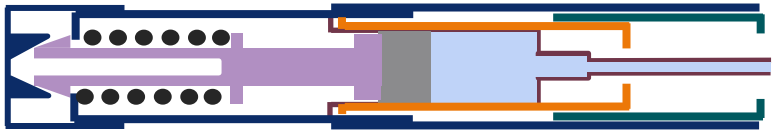
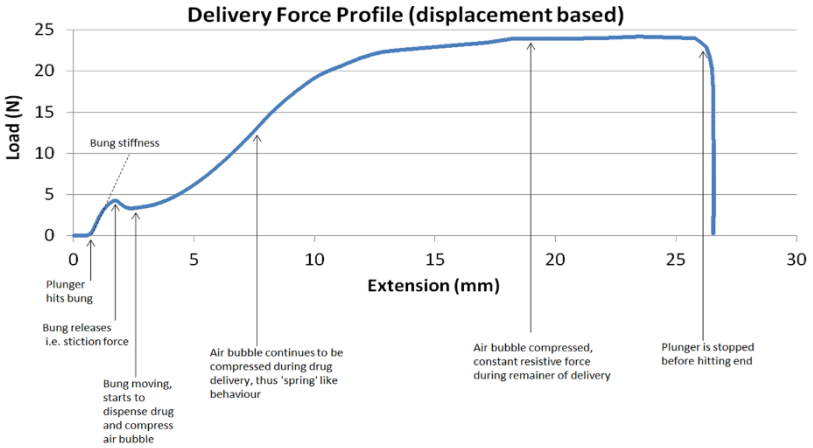
Case study – trouble-shooting AI wet injection

- A client was having issues with wet injection from an autoinjector
- A time-stepping math model of full autoinjector function allowed assessment of the delivery sequence through time
- Combining this with physical testing and high-speed video demonstrated that primary pack interaction with autoinjector needle safety features was not as expected
- Combined with inertial effects this resulted in premature stopper movement
- Minor design modifications were specified and implemented to resolve the issue





Summary

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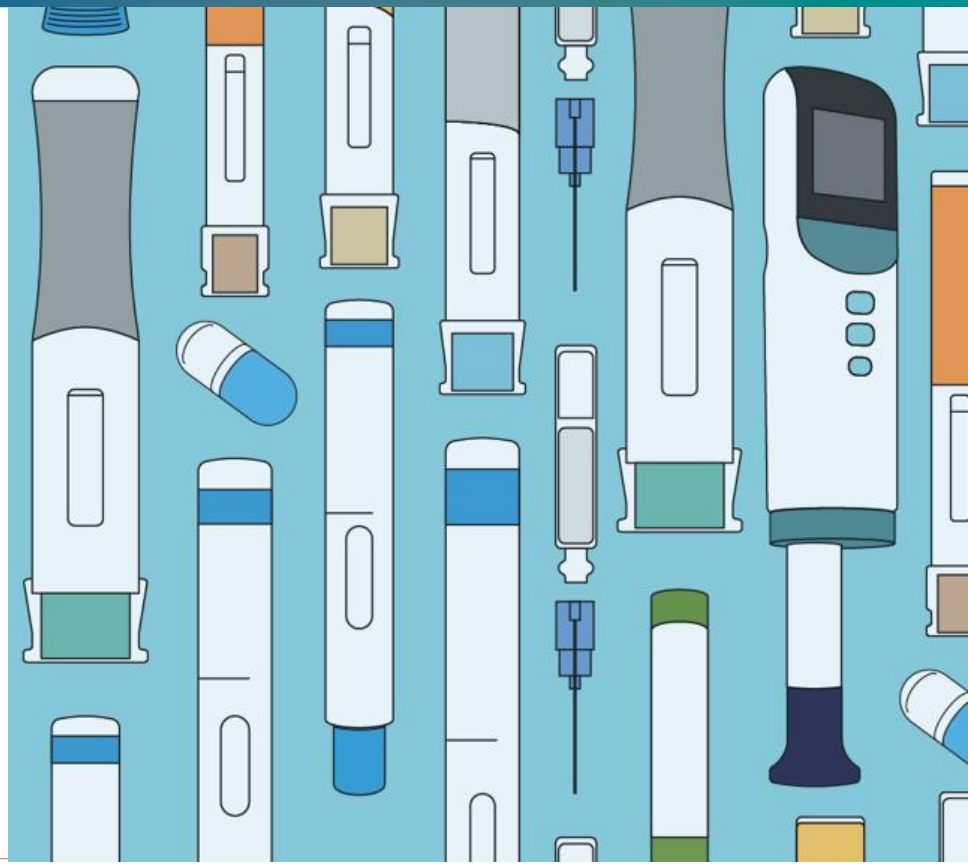
Summary

Key stages of the development process need to be carried out rigorously even when no original ‘design’ work is involved.

Ensuring a good understanding of system performance and sensitivities, alongside robust industrialisation processes, can strongly support design verification, design transfer and production trouble-shooting.

Regulatory inputs in US and Europe, including new standards and guidance, continue to increase the emphasis on the device component.



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Thank You!

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