Strategies for successful design verification

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Introduction

Design Verification (DV) is an essential part of the design and development process for injectable drug delivery systems. A DV test program generates critical data to demonstrate that the injection device is safe, effective, and that the design outputs align with the design inputs.

Extensive experience in planning and executing DV test programs for various injection devices, including pre-filled syringes, autoinjectors, and other innovative systems, has led to valuable insights into the characteristics of a successful DV test program.

This poster provides guidance on de-risking DV test programs to ensure they are:

- Data-driven
- Time-efficient
- Cost-effective

Figure 1 highlights the key parameters to be considered to achieve this goal.

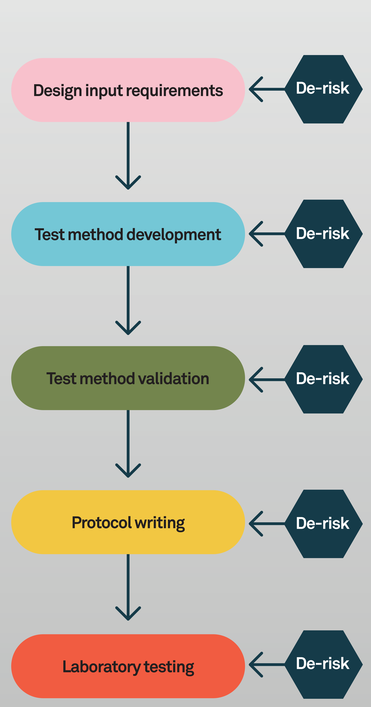

Figure 1
Key parameters for consideration

Design input requirements

Design Input Requirements capture the functional, performance, safety, and regulatory specifications of the injection device, ensuring they are clearly justified and aligned with user needs.

It is important to engage key stakeholders to critically challenge the requirement specifications, reducing subjectivity. Consider these aspects:

- Should the requirement be verified through association with another type of assessment e.g. tolerance analysis?
- Is the phrasing ambiguous, thereby making the requirement untestable?
- Can the values be justified?
- Is the quoted measurement precision necessary and achievable?
- Are the data types (continuous or attribute) and sampling requirements aligned with ISO standards?

Test method development

Effective test method development must consider the required measurement system capability, fixture design, and strategies to minimize inter- and intra-operator variability.

Measurement system capability

To ensure the measurement system is appropriately specified for the task, consider the following:

- Does it possess the required accuracy and precision?
- Is the overall resolution adequate?
- Has it been calibrated to a sufficient range, accommodating both expected values and potential outliers?
- Is the combined measurement uncertainty acceptable?

Fixtures

Well-designed fixtures reduce sources of variability while maximizing test throughput (Figure 2).
Key fixture design features to consider include:

1. Locating features that ensure precise fixture and sample alignment
2. Distinct open and close positions to facilitate sample loading and unloading
3. Pre-set clamping mechanisms to eliminate subjectivity and variation
4. Exclusive use of one size or type of fastenings to improve efficiency
5. Representative sample gripping mechanisms to ensure measurement is not unduly influenced
6. Ergonomic fit to improve operator efficiency and reduce errors caused by fatigue

Operators

To further reduce operator variability:

- Use consistent nomenclature for device components and features, along with clear and concise instructions with labelled diagrams
- Replace manual steps and data analysis with automation where possible

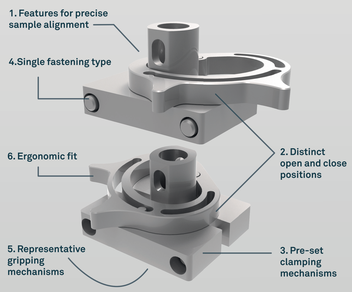

Figure 2
Key fixture design features

Test method validation

Test Method Validation (TMV), also known as measurement system analysis, is a pre-requisite for any DV test program. It provides evidence that the developed test method is fit for purpose and complies with regulatory requirements.

A key challenge in successfully performing TMV is ensuring that the measured variation is solely due to the measurement system, fixtures and operators, and has not been compounded by the inherent intra- and inter- variation of the sample set used. There are two basic types of tests, each with its own challenges:

Destructive tests

(e.g. safety guard override force) negate the ability to acquire repeat measurements from the same test sample. Consequently, repeat measurements typically come from different parts, necessitating that these parts be sufficiently similar to one another.

Non-destructive tests

(e.g. external diameter of a syringe barrel) allow repeat measurement from the same sample but present challenges in identifying or creating test samples from across the entire specification range.

In both types of tests, representative test samples may not be available or may be prohibitively expensive.

The use of surrogate devices as an alternative to injection device test samples offers a viable solution to these potential issues.

Surrogate devices

- Mimic the form and behavior of the test sample to allow seamless substitution
- Are resettable to allow for repeat measurements from the same part
- Can be created to represent different parts, capable of producing measurements across the desired specification range

Figure 3 contains a comparison of Gage R&R analysis using destructive test samples or surrogate devices.

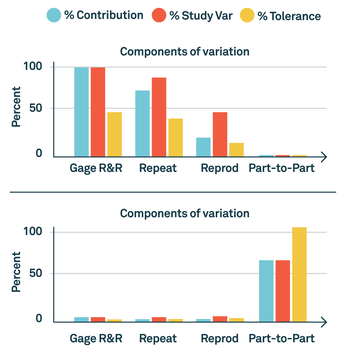

Figure 3
Gage R&R analysis-destructive (top) or surrogate (bottom)

Protocol writing

Mitigations

Reasonably foreseeable incidents should be addressed in the protocol. For example, specify actions for the following scenarios:

- If an operator drops a sample during testing, document whether further testing on this test sample is appropriate
- If an erroneous result is discovered, outline immediate actions, a defined timeline, responsible job roles, and reference any guidance or procedures for root cause investigations
- If continuous variable data does not pass a normality check, provide a process flow for potential solutions. (Figure 4)

Sample labelling & storage

- Maintain consistent and clear labelling nomenclature
- Consider mitigations to help operators easily identify samples required for specific tests or workflows
- Ensure test sample groups are stored together to minimize the risk of mix-ups

Workflows

Workflows are discrete sequences of testing within DV test programs. These can reduce bottlenecks in laboratory equipment, streamline timelines, and optimize resource utilization.

Additionally, if there is no impact from one test on the next in sequence, and the test sequence aligns with the user steps, multiple tests can be conducted in series on the same set of test samples, thereby reducing the overall number of test samples required.

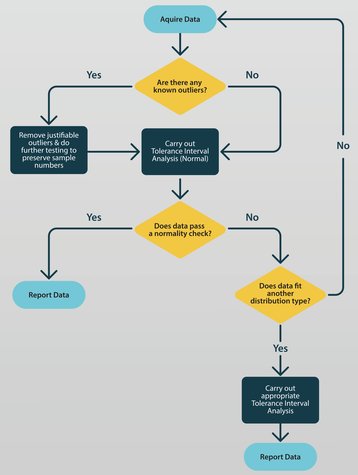

Figure 4
Example of a data analysis process flow

Laboratory testing

Maturity of device design

The design should be finalised, and samples should be commercially or clinically representative and sourced from multiple batches.

This approach minimizes the risk of manufacturing-related issues leading to failures and anomalies in the data, which must be rectified, explained, and justified. It also captures the types of in-specification variation expected across different batches.

System Suitability Tests (SSTs)

SSTs are conducted to demonstrate that the measurement system is accurate and fit for purpose at the time of use. They complement existing laboratory equipment calibrations and can be tailored to assess the instrument according to its specific intended use.

The frequency of SSTs is determined based on the impact of anomalous results (e.g. limited samples available for repeat testing) and the likelihood of drift or damage between calibrations.

A dry run

Commonly referred to as 'Pre-DVT', a dry run involves conducting an abridged version of the DV test program, typically using smaller sample sizes.

Completing Pre-DVT can:

- Provide an effective, informal indication of likely injection device performance
- Offer valuable insights into test and workflow inefficiencies
- Reduce the risk of test operator errors during the DV test program

Conclusion

Design Verification Testing (DVT) is an essential step in a device development program, but, without careful planning, it can easily become an arduous task.

In our experience, the key strategies for a successful DV test program are to:

- write unambiguous design input requirements
- create robust, validated test methods using surrogate devices where appropriate
- plan for success, whilst also mitigating for reasonably foreseeable errors