Notes

we put patients first

Nemera

Vassel Graphique - Bron

www.nemera.net
information@nemera.net

Nemera - 20, Avenue de la Gare - 38290 LA VERPILLIERE - FRANCE
Tel: +33 (0)4 74 94 06 54 - Fax: +33 (0)4 74 94 90 60

Nemera

Integrated method for **Determination of Force profile and Stroke to fire** on pMDIs

Authors: Myriam Giraud, Olivier Joly, Pierre Pintus.
Design Engineers, Nemera, La Verpillière, France

1 | INTRODUCTION

Dose counters, which are increasingly common on pMDIs (Pressurized Metered Dose Inhalers), impose specific requirements on the valve as they rely on displacement or force to indirectly count remaining doses.
Indirect counters typically **fail in one of two modes:**

- **Undercounting** through fire-not-count events
- **Overcounting** through count-not-fire events

Undercounting is considered the **more serious failure** mode since it misleads a patient to believe a dose is present when it may not be. So strong design requires the dose counter to decrement the count before the valve releases the dose.

To avoid undercounting events on pMDIs using **displacement driven counters:**

- The valve stem displacement (or stroke) needed to decrement the dose counter mechanism has to be well defined
- The valve stroke to fire (STF) must be accordingly set and verified by the valve manufacturer

Our definition of the STF: the STF corresponds to the stroke (displacement) of the valve stem at the point when the fluid path between the dosing chamber (commonly known as the metering chamber) and the stem exhaustion channel opens, such that the pressurized formulation starts to be discharged from the valve as a spray.

To accurately determine the STF of a valve (and its associated variability) is challenging because it can depend on different factors linked with:

- **The valve** / component materials and their dimensions, tolerances, lubrication, crimp settings and variability
- **The formulation** / API and adjuvants
- **The patient** / actuation speed and acceleration

And to our knowledge, there is no "off the shelf" method available from lab equipment suppliers to measure the STF of a valve even we believe some company-specific methods exist.

2 | OBJECTIVE

As the force profile (FP) of the pMDIs valves is evaluated and monitored to understand mechanical behaviors, such as friction or blockage points all along the valve stem stroke, **the purpose was to develop a method which objectively determined the STF** and which can be **coupled to the existing FP evaluation.**

The principle of this **new integrated method that combines STF testing with the analysis of FP** is described hereafter. In addition to that, **its robustness and its reliability** are questioned through a preliminary evaluation.

All data presented were generated on pMDIs using prototyped valves derived from the Nemera's Inhalia® valve platform and filled with a proprietary salbutamol / HFA134a formulation designed to deliver 100µg/dose.

3 | METHOD

The STF detection system (Figure 1) developed is based on the **energy released during discharge of the spray** from the valve stem.

The spray acts on one end of a lever which forms **a flat impaction surface**. The other end of the lever is an opaque plastic flag with a small hole in its center.

In the absence of a spray, the lever is balanced such that a light beam is able to pass through the hole and fall on a detector.

When the inhaler is actuated and the STF is reached, the discharged spray impacts on one end of the lever causing the flag on the other end to occlude the light beam.

This results in a binary signal.

- **Condition 1** = at rest, light passes through the hole
- **Condition 0** = at STF position, light does not pass through the hole

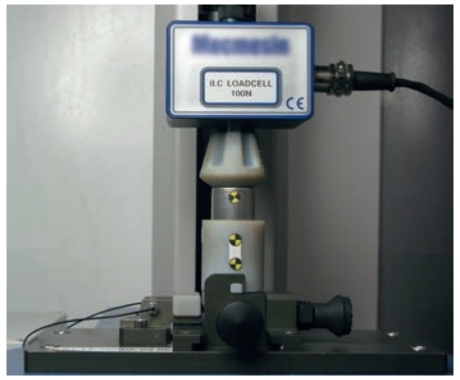

Figure 2. Customized tension and compression machine used to actuate the valve.

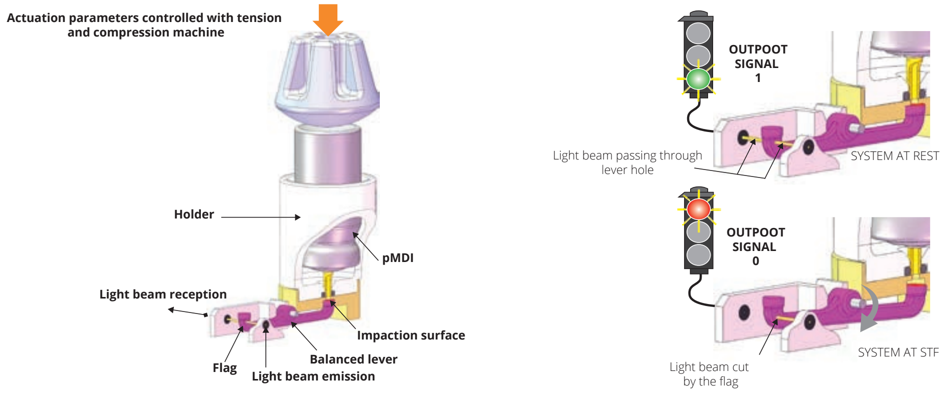

Figure 1. Stroke-to-fire detection fixture

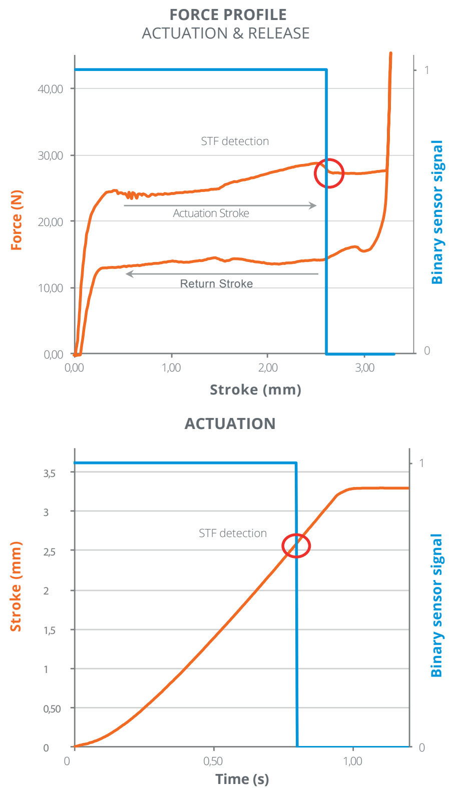

Figure 3. FP and raw STF are simultaneously determined using the Nemera method. (Top) Force and optical signal vs. stroke (Bottom) Stroke and optical signal vs. time during valve actuation

The detection system sensitivity is maximized using:

- A light weight lever, well balanced
- A low friction pivot
- A sensitive optical detector
- An accurate alignment of the hole into the flag and the light beam at lever rest position

This detection system is time-indexed to a customized tension and compression machine that is currently used to control the actuation parameters while measuring the FP of the pMDI valve (Figure 2). So FP and STF can be recorded simultaneously.

Thanks to this method, a STF value called the **raw STF** is **determined when the optical signal changes from Condition 1 to Condition 0.**

Figure 3 is an example of the data generated using this integrated system.

The raw STF is measured at approximately 2.6mm, which corresponds to the associated force of 27.9N.

However, **due to the detection system design itself, a difference between the raw STF and the actual STF was expected.** The initially released, and therefore visible spray, could carry insufficient energy to initially displace the lever.

A lag time for the lever to move far enough to occlude the light beam and a sensor response time were also anticipated.

Since **lowering the risk of a "fire not count" event is a key development goal for pMDIs** containing a displacement driven dose counter, it is **important to know the actual STF of a valve.**

That's why we attempted to correlate the raw STF determined by the method described above, with the actual STF observable using high speed photography as the discharge of spray can obviously be photographically detected.

4 | RESULTS

To obtain the raw to actual STF correlation, a high speed camera (HSC) was used to record several valve actuation test sequences into our dedicated fixture at 500 frames per second:

- Firstly, **with the detection lever in place** (Figure 4) allowing us to determine simultaneously the raw STF given by the system.
- Subsequently, **without the lever** to visualize the spray directly as it emerged from the exit of the valve stem.

This approach provides the most accurate and shortest estimate of STF that can be considered as the actual STF.

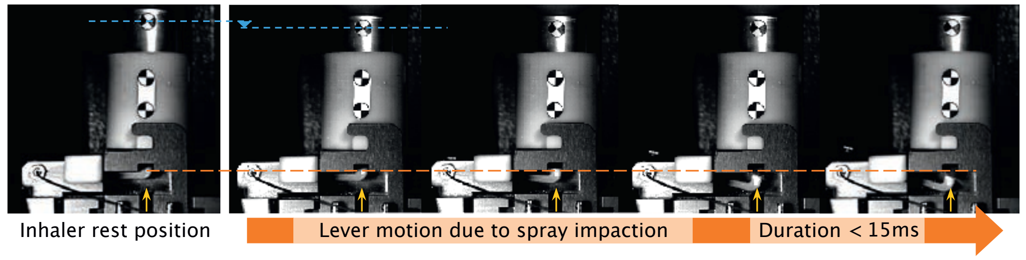

Figure 4. High speed camera images showing lever motion initiated by the valve discharge.

Using careful camera alignment and precision optical measurements, the outputs of the analysis are:

- The determination of the actuation speed profile in terms of valve stroke vs. time (for all sequences)
- The link between the start of the motion of the lever and the valve stroke (for the sequences recorded with the lever)
- The link between the start of the spray as the valve opens with the valve stroke (sequences recorded without the lever)

In addition to that, the comparisons of the sequences recorded with or without lever for a given sample allow to understand the lever movement relative to spray discharge.

The difference between the actual STF calculated from the initial high speed camera detected spray discharge to the raw STF is shown in Figure 5.

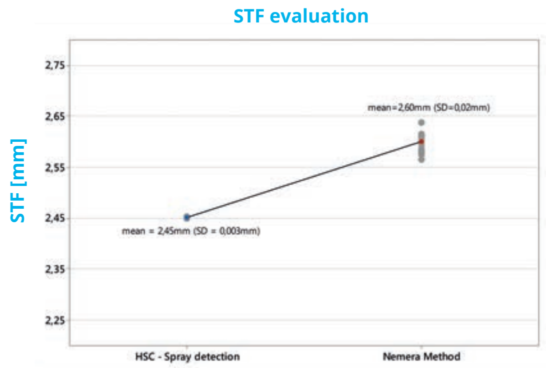

Figure 5.STF determination using high speed camera spray detection (5 determinations) and the Nemera mechanical lever method (20 determinations) at the same valve actuation speed of 250mm/min

As expected, the high speed camera-based method resulted in significantly lower STF values compared to the mechanical Nemera method (Mann-Whitney Test). The difference between the means is 0.15mm (SD = 0,02mm).

Based on high speed camera image analysis, with and without the lever in the fixture, the difference in STF between the two methods was equally attributed:

- To the time required to release sufficient spray energy to initiate the lever rotation
- To the time needed for the lever to rotate enough to change the optical sensor response (which includes the optical sensor response time)

CONCLUSION

Developing pMDIs using displacement driven counters requires the evaluation of the actual STF of the valve .

As the use of a high speed camera to determine the actual STF is technically demanding and time consuming, our approach to obtain data more efficiently is to measure a raw STF value during FP determination. Then subtract the measurable, constant difference between the STF derived from the Nemera and high speed camera methods, to calculate the actual STF. The constant to allow this calculation is derived from the correlation shown previously.

This poster reports only a limited set of parameters so other actuation speeds, metering valve volumes, material combinations, and formulations need to be studied to confirm and improve the method's reliability. The aim will be to fully understand how the raw STF values (nominal and variability) generated by the mechanical lever detection method correlate with the actual STF and to refine the constant that has to be used to calculate the actual STF.

The method described in this poster represents a useful and simple tool, now in use at Nemera's ICD (Innovation Center Devices) for design verifications on the Inhalia® metering valve platform and to support development of pMDIs with dose counters likely to be safe for patients and compliant with the current regulatory requirements [1].

Reference: [1] FDA Guidance (2003): Guidance for Industry. Integration of dose-counting mechanisms into MDI drug products