Understanding the setting of flow rate for testing dry powder inhalers (DPIs)

A fundamental look at everyday practices

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Introduction

When testing dry powder inhalers (DPIs) for the size of particles discharged during each dose, manufacturers largely choose a test protocol that is recognized by the regulatory community [1-4] and that walks a narrow pathway among device design, typical patient breathing characteristics and design principles of the cascade impactor that size-fractionates the discharged particles [5-12].

To simplify and standardize testing requirements, the United States Pharmacopeia (USP) [1] and related compendia [2, 3] require the flow rate to be established with the downstream-to-upstream pressure ratio across the flow control valve at a value of 0.5 or less. This condition is called "critical (sonic)" in the USP and simply "critical" in the European Pharmacopeia (Pharm. Eur.) [2] and the Japanese Pharmacopoeia [3]. The ratio of 0.5 is widely regarded as being derived from thermodynamic theory of the adiabatic expansion of air [13, 14]. According to this theory, at this pressure ratio condition, the mass flow rate remains fixed no matter how small the downstream pressure becomes, as long as the upstream conditions remain unchanged. This practice is widely adopted in the inhaler testing community and is regarded as a method of eliminating a certain degree of variability from test to test and of maintaining proper D_{50} values for each impactor stage, as easy to implement and as independent of the individual testing technician.

So far so good; but now let us take one step at a time, hypothetically, into the thoughts of a diligent tester of dry powder inhalers. This person might notice that, curiously, there appear to be no publicly available data that demonstrate or test this theory for control valves in routine inhaler testing practice. Nevertheless, the pharmacopeial compendia do speak to the nature of the flow control valve. According to the Japanese Pharmacopoeia and Pharm. Eur., the flow control valve must be one "with a maximum Cv ≥ 1." Again, curiously, this requirement comes with no definition of Cv. But Pharm. Eur. goes further and says, "with maximum Cv ≥ 1, (e.g., type 8FV12LNSS, Parker Hannifin plc., Barnstaple, EX31 1NP, UK), or equivalent." Until approximately calendar 2010, the USP mentioned this same Parker valve (type 8FV12LN) and included a footnote with the parameter Cv as follows: "with maximum $(Cv)^a \geq 1$" (the letter "a" here is the footnote indicator in the USP text). The current USP volume <601> retains this same footnote but no longer mentions the Parker 8FV12LN valve. These previous and current references in several pharmacopeial compendia largely explain why one often finds the Parker 8FV12LN valve in inhaler testing laboratories. But, even for the specific valve described in the pharmaceutical compendia, *there are no data in the literature* that show this valve reaches a fixed flow rate when the pressure ratio is 0.5 or less.

Surprising? Yes, especially for the informed test technician who is reading the pharmacopeial method and wants to apply it.

Now, digging one step further, our diligent technician reads that the footnote "a" in the USP defines the flow coefficient Cv as follows: "Flow coefficient, as defined by ISA S75.02 'Control valve capacity test procedures in Standards and Recommended Practices for Instrumentation and Control,' 10th ed., Vol. 2, Research Triangle Park, NC, Instrument Society of America, 1989." This method promises a defined test for quantifying Cv. Then one might ask, "Are there data in the open literature that show this Parker valve has a maximum flow coefficient larger than or equal to 1 as specified in the USP?"

A publication of such data would be very helpful, but there appears to be *no such document*. However,

Parker's online catalog has a good set of specifications for this class of valve (https://www.parker.com/content/dam/Parker-com/Literature/Instrumentation-Products-Division/Catalogs/IPD_Needle_Valves_Catalog_4110-NV.pdf). On page 6 of this online catalog, the reader can find that Cv is indeed larger than 1 (Figure 1, which is an excerpt of the table on page 6 of the Parker catalog). And in the footnote to this table, the reader can see that the test for Cv is in accordance with the same procedure as that called out in the USP, namely, ISA S75.02.

This footnote to the table in the Parker catalog is quite important, and for this reason, we reproduce it here (with parentheses around P_1-P_2 added for clarity): "Tested in accordance with ISA S75.02. Gas flow will be choked when $(P_1\text{-}P_2)/P_1 = X_T$."

Realizing that P_1 in the footnote under the table of the Parker catalog (Figure 1) is the upstream pressure and P_2 is the downstream pressure, we see that the Parker catalog is saying that "choked" flow occurs when the ratio of downstream pressure to upstream pressure equals $1\text{-}X_T$. According to the table in Figure 1, for valve 8FV12LN, choked flow occurs when X_T is 0.83; and that means choked flow occurs when $P_2/P_1 = 1\text{-}X_T = 0.17$. So what happened to the traditional, theoretical value of P_2/P_1 smaller than or equal to 0.5? Or do we need to ask if "choked" is the same as "critical" and "sonic?"

Frustrated User: Too much jargon; too many footnotes! Are there any data in the open literature on these matters of importance?

In this article, we assist our hypothetical, now frustrated, user by a) showing a method of testing inhaler flow control valves, b) showing test data for the Parker valve 8FV12LN, c) explaining the reasons for the confusing terminology (sonic, choked, critical) that typifies discussions of proper flow control and d) explaining why the valve test method in the pharmacopeia is irrelevant to inhaler testing. Overall, the article emphasizes the need for testing and understanding flow control valves that are in routine use for setting the flow rate for DPI testing.

Apparatus for testing valve performance

Figure 2 depicts a simple apparatus for testing a valve for the conditions under which the flow rate reaches a maximum value at fixed upstream conditions, a flow rate that does not increase regardless of how much one reduces the downstream pressure with a vacuum pump, no matter how powerful the vacuum pump. Operationally and for meeting regulatory purposes, this condition of "does not increase" is a sufficient and valuable definition of "choked." The equipment shown does not determine if the flow rate reaches the speed of sound at the control valve. And there is nothing about the flow that is measured to be "critical" in any sense of the word. (More content appears below on the words "critical" and "sonic.")

Figure 1

Specifications of a family of Parker Needle Valves, including 8FV12LN

Basic Part Number		End Connections		Stem	Flow Data			
		Inlet	Outlet		Orifice		Inline	
Inline	Angle	(Port 1)	(Port 2)	Type	Inch	mm	C_V	X_T*
8F-V12LR	8F-V12AR			Blunt			1.23	0.87
8F-V12LN	8F-V12AN	1/2" Female NPT		Needle	0.312	7.9	1.05	0.83
8F-V12LK	8F-V12AK			PCTFE			1.29	0.91
8W-V12LR	8W-V12AR			Blunt			1.23	0.87
8W-V12LN	8W-V12AN	1/2" Tube Socket Weld		Needle	0.312	7.9	1.05	0.83
8W-V12LK	8W-V12AK			PCTFE			1.29	0.91
10A-V12LR	10A-V12AR			Blunt			1.23	0.87
10A-V12LN	10A-V12AN	5/8" Compression A-LOK		Needle	0.312	7.9	1.05	0.83
10A-V12LK	10A-V12AK			PCTFE			1.29	0.91
10Z-V12LR	10Z-V12AR			Blunt			1.23	0.87
10Z-V12LN	10Z-V12AN	5/8" Compression CPI ™		Needle	0.312	7.9	1.05	0.83
10Z-V12LK	10Z-V12AK			PCTFE			1.29	0.91
12A-V12LR	12A-V12AR			Blunt			1.23	0.87
12A-V12LN	12A-V12AN	3/4" Compression A-LOK		Needle	0.312	7.9	1.05	0.83
12A-V12LK	12A-V12AK			PCTFE			1.29	0.91
12Z-V12LR	12Z-V12AR			Blunt			1.23	0.87
12Z-V12LN	12Z-V12AN	3/4" Compression CPI ™		Needle	0.312	7.9	1.05	0.83
12Z-V12LK	12Z-V12AK			PCTFE			1.29	0.91

* Tested in accordance with ISA S75.02. Gas flow will be choked when $P_1 - P_2 / P_1 = X_T$.
† For CPI™ and A-LOK®, dimensions are measured with nuts in the finger tight position.

Table 1 identifies each component of the apparatus in Figure 2. When testing a valve (item 6, Table 1), ambient air is drawn with a vacuum pump, first through an in-line HEPA filter and a flow meter and then into a straight pipe that allows for measurement of the stagnation temperature and the stagnation pressure *upstream* of the valve under test. *Downstream* of the valve under test, there is another section of straight pipe and a sampling port for the stagnation pressure. The air then passes through a second valve, but one with significantly larger flow capacity than the valve under test. This larger valve allows the operator to adjust the mass flow rate of air drawn through the system. Finally, the air leaves the apparatus by way of the vacuum pump and returns to the surroundings.

The pipe sections with the sampling ports for the stagnation temperature and pressures (items 3 and 7) are the same as those described in a previous study [15]. The overall lengths of the upstream and downstream sections are approximately nine inches and six inches, respectively (15 and 10 pipe diameters). The pipe inside-diameter is 0.62" (size 12AN). Each of the sampling ports is an annular sampling manifold (six taps, 60 degrees apart), known commonly as a piezometer ring, which ensures the P and T measurements are the stagnation values. The chosen downstream pressure transducer (item 8) measures the differential pressure relative to ambient pressure, and the ambient pressure is monitored before and after the test with the Mensor Model CPT6020 absolute

Figure 2

Laboratory equipment for testing flow control valves

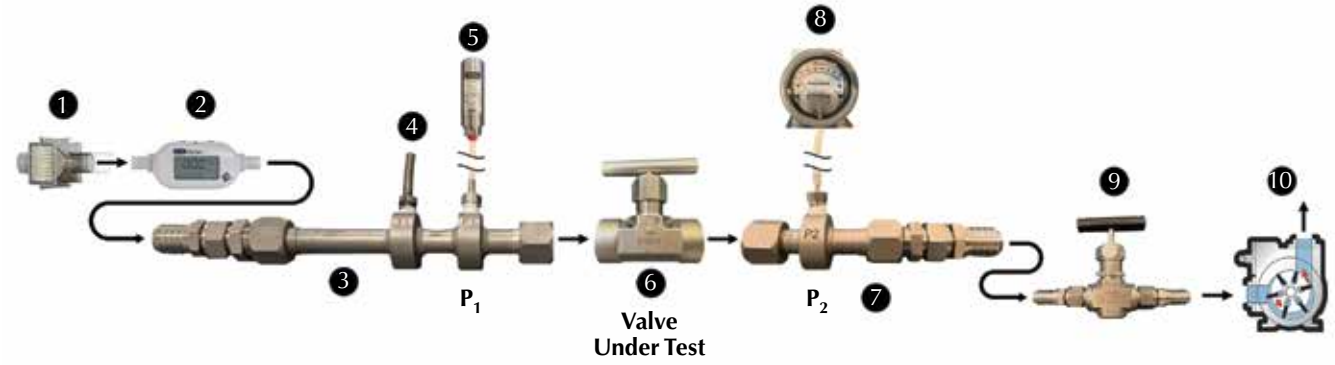


Table 1

Components of Valve Testing Apparatus

Item Number	Item Name	Manufacturer or Supplier
1	HEPA Filter	Model BB50T Breathing Circuit Filter, Global Life Sciences Solutions USA, LLC, Marlborough, MA, US
2	Mass Flow Meter	Model 4043, TSI Incorporated, Shoreview, MN, US
3	Upstream Sampling Fixture	Flow Systems Inc., Berthoud, CO, US
4	Stagnation Temperature Sensor	Model P3A-NPT4-125-PX-0.5-PFSB-72-STWL, Evolution Sensors and Controls, Mullica Hill, NJ, US
5	Upstream Stagnation Pressure Transducer (P_1)	Model CPT6020, Mensor LP, San Marcos, TX, US
6	Valve Under Test	Model 8FV12LN, Parker Hannifin Corporation, Jacksonville, AL, US
7	Downstream Sampling Fixture	Flow Systems Inc., Berthoud, CO, US
8	Downstream Stagnation Pressure Transducer (P_2)	Part Number 2000-75KPA-AHU2, Dwyer Instruments, LLC, Michigan City, IN, US
9	System Control Valve	Part Number 18RS8, Swagelok Company, Solon, OH, US
10	Vacuum Pump	Model VT 4.8, Becker Pump Corporation, Cuyahoga Falls, OH, US

pressure transducer (Mensor LP, San Marcos, Texas, US) (item 5). The downstream absolute pressure, P_2, is then calculated from the ambient pressure minus the differential pressure reading.

The test protocol calls for the valve under test to be open a fixed amount, the vacuum pump to be turned on, and the flow rate adjusted with the system control valve so the downstream pressure is only about 30% of the ambient pressure. Achieving these conditions requires some trial and error when testing a valve with unknown behavior. Once the desired range of operation is set, the valve under test must remain unchanged. Now, the first data point with the downstream pressure at about 30% of the upstream pressure is measured by recording the mass flow rate of air entering the system along with the pressure upstream and downstream of the valve under test. Next, the system control valve is closed slightly until the pressure downstream of the valve under test increases to 35% of the upstream pressure, then to 40%, and continues in increments of 5% until the downstream pressure is approximately 70% of the upstream pressure. At each value of the downstream pressure, the user records the mass flow rate of air entering the system and the pressure upstream and downstream of the valve under test. In this way, the pressure ratio across the valve under test increases from about 0.3 to about 0.7 and, importantly, thoroughly covers values in the range of the ratio 0.5, where theoretically the flow changes from choked to unchoked.

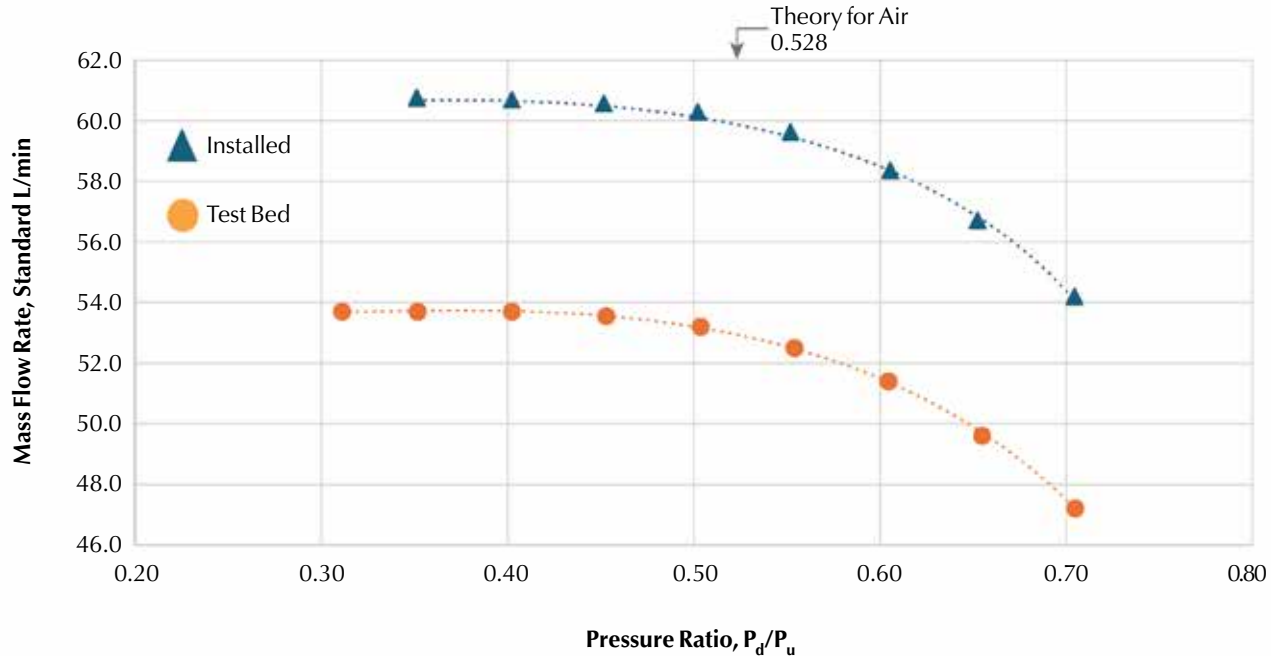
Figure 3 shows data with this apparatus when testing the Parker valve 8FV12LN. Here, the y-axis is the air mass flow rate in standard liters per minute (standard conditions T = 21.1 °C, P = 101.3 kPa). The mass flow rate through the Parker valve 8FV12LN is indeed choked when the ratio of the downstream pressure to the upstream pressure is smaller than approximately 0.5. A more complete academic analysis would quantify and display the slope of the curve of mass flow rate versus pressure ratio, but the "eyeball" reaction to the data in Figure 3 is sufficient for the current discussion.

There are two curves in Figure 3. The round data points show the results when the Parker valve is in the controlled test bed shown in Figure 2. The triangular data points show the results where the same model of Parker valve is the flow control valve installed in a commercially available flow control unit. The curves do not overlap in Figure 3 only because the valve under test was more open when tested in the commercial flow controller equipment than it was when tested alone in the designed test bed. The important matters are that there is a change in slope from approximately parabolic (to the right of 0.5) to flat (to the left of 0.5) and that this change takes place for both data sets at a pressure ratio of approximately 0.5. (The theory for air is noted at a pressure ratio of 0.528, as given by equation 7, below.)

The reason to show both curves here is not to call out a particular commercial product but only to highlight that the same method described for the test bed also serves to test commercial flow control equipment. The test of any similar valve in a designed test bed (Figure 2) and the test of that valve in its com-

Figure 3

Onset of choked flow for Parker Valve 8FV12LN installed in commercial equipment and in a stand-alone valve test bed



mercial equipment would ideally support the same conclusions regarding the onset of choked flow—but might not. In concept, one curve represents the character of the valve (round data points), and one curve represents the character of the equipment (triangular data points). Practicing inhaler testing personnel may be interested only in the performance of their test equipment or additionally in the performance of the stand-alone control valve. The ability to test commercial flow control equipment begs the question of specifications for suitability of the commercial equipment for its intended purpose. Currently, no such specifications exist.

As a final point, we reiterate that the test method completely ignores the term "sonic" and the term "critical." The method does not call for the measurement of the velocity at any point to see if it reaches sonic speed and there is nothing that is "critical" anywhere in the flow path.

Critical? sonic? choked?

Experimentally, the Parker valve 8FV12LN becomes choked at a ratio of P_d/P_u close to 0.5. So what are we to make of the Parker product literature that says that choked flow with this valve occurs when P_d/P_u is smaller than 0.17? This question must be addressed, but first it is essential to examine the underlying sources of the terms "critical," "sonic" and "choked," focusing the discussion on air flow under temperature and pressure conditions typical of inhaler testing.

The following discussion draws on thermodynamic principles articulated in what are now considered historical college-level textbooks [reference 16, section 8.5 and reference 17, chapter 4].

Of the terms "critical," "sonic" and "choked," "critical" is the most removed from the practical realities of inhaler testing. This term is taken from calculus and is a point where the derivative of a function is equal to zero [reference 18, page 187]. That point can be a local maximum or minimum value of the function or an inflection point. When we analyze the source of the word "sonic," below, we will explain exactly what function whose derivative gives rise to the term "critical." We are confident that the inhaler testing community is generally not aware of this calculus. Furthermore, this calculus result is not tested by setting P_d/P_u to have a value smaller than 0.5. Finally, the term "critical" does not describe the flow at all, and the inhaler testing community would lose no information (and even reduce some of the tension that inhaler testers and quality control personnel experience), if the term "critical" were dropped from the jargon of setting the flow rate in the testing of dry powder inhalers.

To understand the source of the word "sonic," it is important first to define the speed of sound. The speed of sound is the speed at which a compression wave will pass through a gaseous medium and has nothing to do with how fast the gas may or may not be flowing. (Think of thunder, which is a noise that travels at about 1,000 ft/sec, much faster than wind speed). In a gas, the speed of sound is often given the symbol "c" and is defined by how the gas pressure changes when the gas density changes (equation 1):

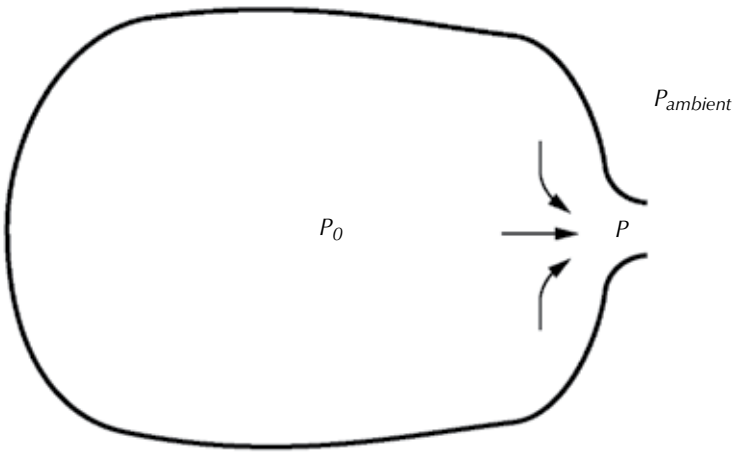
$$c = \sqrt{\left(\frac{\partial P}{\partial \rho}\right)_S} \tag{1}$$

Equation 1 indicates the speed of sound is the square root of the change in pressure (P) when the density (ρ) changes and in a process with no change in the entropy (S). For an ideal gas, the simple relationships in equation 2 can be derived from equation 1:

$$c = \sqrt{\gamma \frac{P}{\rho}} = \sqrt{\gamma \frac{RT}{MW}} \tag{2}$$

Figure 4

Air flow through a converging nozzle



Here, γ is the ratio of the heat capacity per unit mass at constant pressure divided by the heat capacity per unit mass at constant volume. In addition, R is the universal gas constant, MW is the molecular weight of the gas and T is the absolute gas temperature.

A definition of the speed of sound is an important first step. But to understand why the inhaler testing community speaks of "sonic" flow, it is important to consider some of the scientific fundamentals.

Consider the flow out of a nozzle, as depicted in Figure 4. Here the flow comes from a large, constant-pressure reservoir through a constricting passageway where the cross-sectional area of the passageway decreases constantly until the air exits through a small opening. This passageway is commonly called a "nozzle," and, because its cross-sectional area decreases constantly in the direction of flow, it is called a "converging" nozzle. Air will flow at sonic speed out of a converging nozzle under some circumstances. To understand the conditions thereof, one must apply three principles: 1) conservation of mass, 2) conservation of energy and 3) the ideal gas law.

Conservation of mass

Conservation of mass states simply that the mass rate of air flow is a constant at all locations in the air flow path (equation 3):

$$\dot{M}=\rho VA=constant \tag{3}$$

Equation 3 is valid for all points of the air flow in the nozzle, including those just before the nozzle discharges into the surroundings. For simplicity, we postulate that the reservoir is so large that the mass flow rate of air leaving the reservoir makes no difference to the conditions in the reservoir (P_0 is constant).

Conservation of energy

Conservation of energy requires consideration of heat entering or leaving the system through the walls of the vessel and of heat generated by fluid viscosity. Stagnant air is one of the best thermal insulators so heat gain or loss through the walls of a large vessel is typically considered negligible. Frictional heat derived from viscous forces can also be neglected as a first approximation. These approximations render the flow to be considered "adiabatic and reversible."

Ideal gas law

For an ideal gas flowing under adiabatic and reversible conditions, the mass flow rate at any point in the air flow path and the velocity of the air stream can be written in terms of the source conditions and the physical properties of air (γ and MW):

$$\dot{M}/_A=\rho V=\sqrt{\frac{2\gamma}{\gamma-1}P_0\,\rho_0\,(r^{2/\gamma}-r^{(\gamma+1)/\gamma})} \tag{4}$$

$$V=\sqrt{\frac{2\gamma}{\gamma-1}*\frac{RT_0}{MW}\left(1-r^{(\gamma-1)/\gamma}\right)} \tag{5}$$

In equations 4 and 5, the symbol "r" is the ratio of the pressure in the nozzle, P, to the source pressure, P_0 ($r = P/P_0$).

Equation 4 will lead to an understanding of "critical" and equation 5 will lead to an understanding of "sonic."

The quantity ρV in equation 4 is the mass flow rate divided by the cross-sectional area of the nozzle. This flow rate reaches a maximum value when the function of r inside the square root sign of equation 4 reaches its maximum value. To find the value of r at the maximum flow rate, we find the first derivative of this function of r and set it equal to zero (equation 6):

$$\frac{d}{dr}\left(r^{2/\gamma}-r^{(\gamma+1)/\gamma}\right)=\frac{2}{\gamma}r\left(\frac{2}{\gamma}-1\right)-\frac{\gamma+1}{\gamma}r^{1/\gamma}=0 \tag{6}$$

This equation can be solved for r (equation 7):

$$r^*=\left(\frac{2}{\gamma+1}\right)^{\frac{\gamma}{\gamma-1}} \tag{7}$$

Here, we have used the superscript (*) to denote the value of r that satisfies equation 6. Because r* is the pressure ratio where the derivative equals zero, this value of r is called "critical" in the common jargon of calculus [reference 18, page 187]. The second derivative at this value of r is negative, confirming that the mass flow rate is at a maximum at this pressure ratio, not a minimum nor an inflection point [reference 18, page 203].

Finally, because γ is equal to 1.4 for air, the value of r* is 0.528 for typical inhaler testing conditions. It is this figure that gives rise to the common advice that P_d/P_u should be less than 0.5 to achieve sonic conditions when testing a dry powder inhaler.

Now, returning to the word "sonic," we place equation 7 into equation 5, and find the velocity of the air flow when the mass flow rate of air is at its maximum value (equation 8):

$$V=\sqrt{\frac{2\gamma}{\gamma+1}*\frac{RT_0}{MW}}=\sqrt{\gamma\frac{RT}{MW}} \tag{8}$$

But *we recognize equation 8 as the speed of sound, noted in equation 2.* (The second step in equation 8 involves the adiabatic condition $P\rho^{-\gamma}$=constant, valid for an ideal gas). Equation 8 is the reason that the flow rate is called "sonic" when P_d/P_u is equal to r*. (For values of P_d/P_u smaller than r*, the velocity cannot increase further in a converging nozzle; see reference 16, section 8.5 and reference 17, chapter 4). The word "sonic" does characterize the flow in an ideal

situation, so the term itself does have a conceptual value in the inhaler testing community, even though no one actually measures this velocity at any point in any valve nor in any flow control equipment.

The bottom line is simply this—the assumptions of adiabatic, isentropic flow of an ideal gas allows the air flow velocity to reach the speed of sound in a converging nozzle when the pressure ratio r reaches a certain value (equation 7) that maximizes the mass flow rate of air. *It is from this approximate analysis that the word "sonic" emerges, and it is from the math of this analysis that the word "critical" emerges.*

"Ideal versus real" control valve shape

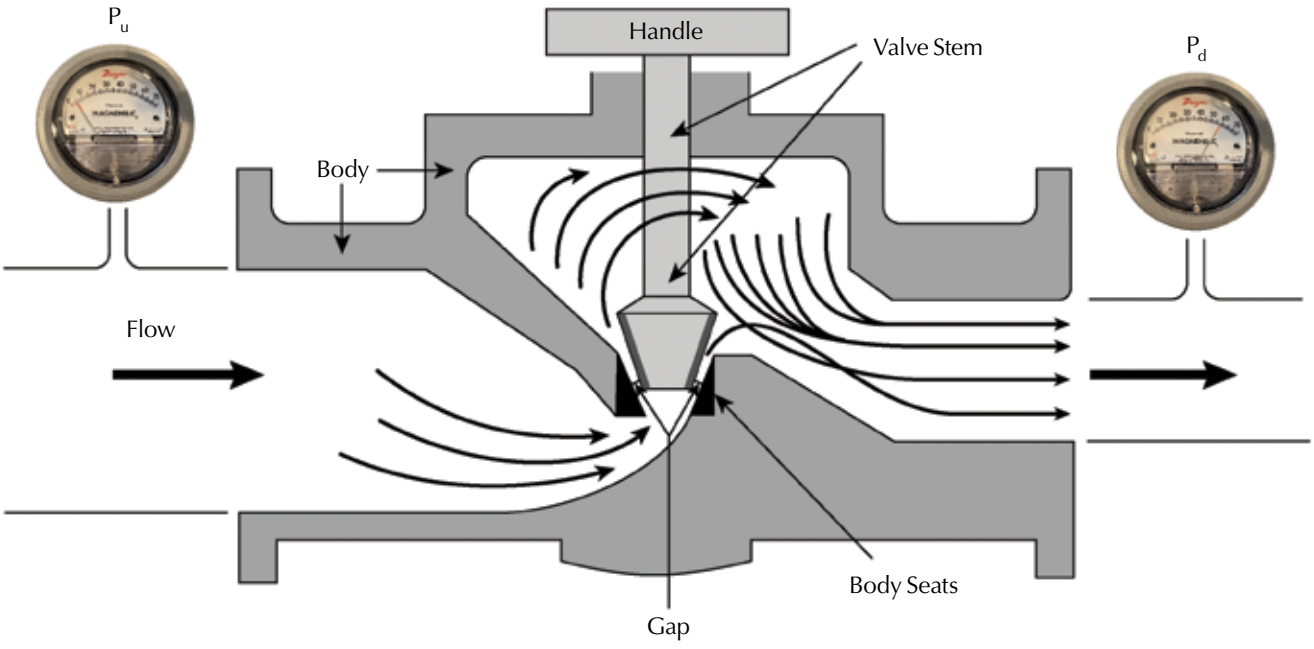
The thoughtful reader will anticipate that the approximations described in the analysis above, including the approximation of a converging nozzle shape, will not hold as well for real flow control valves as they do in the hypothetical converging nozzle in Figure 4. A real needle valve has a stem that retracts when the user rotates the handle in a counter-clockwise direction (Figure 5). A small adjustable gap forms between the stem and the wall of the valve body. With a pressure drop across the valve, air accelerates as it approaches this gap and can theoretically reach, in some circumstances, sonic velocity at the narrowest point of the gap. That is the idea of flow control via a needle valve.

The design of such a flow control valve requires thinking about how best to make the air flow path inside the valve approximate a converging nozzle that leads to a final gap; and for the inhaler testing application, the size of the gap needs to restrict the flow velocity, ideally to a fixed, possibly sonic, speed at a convenient mass flow rate. Also, ideally, the angle of the expansion after the constricting gap is not so abrupt that the gas density decreases enough to induce super-sonic flow velocities with their attendant energy losses. So the slope of the walls of the body and of the base of the valve stem significantly affect the ability to approximate "reversible and adiabatic" air flow through the gap. It is also unavoidable that the gap is annular, and that geometry creates an annular downstream air flow shape, rather than a circular jet depicted in Figure 4, as the air stream flows over the base of the valve stem and moves out of the valve. The air streamlines meet on the other side of the valve stem in a controlled but irregular manner, another one of many practical realities that work against the ideal situation envisioned in Figure 4 with its "adiabatic and reversible" conditions.

Even if the physical design issues could simulate the flow conditions of Figure 4, it is important to ask, "Is the flow sonic simply because P_d/P_u is smaller than 0.5?" One might have high confidence in the hypothetical example of Figure 4. But the pressure gauges in Figure 5 depict another issue one faces with real equipment, namely that the measurements of the upstream pressure and of the downstream pressure do not take place immediately before and after *the flow-restricting gap*. Real equipment requires these pressures to be measured at some convenient locations (shown in Figure 5 to the left and to the right of the flow control valve; each gauge here is reading a pressure relative to atmospheric). Even if test personnel *wanted* to measure the pressure just upstream and just downstream of the flow restricting gap, it would be very difficult to create small channels to access these

Figure 5

Flow path through a typical needle valve



points so as to attach pressure-measuring devices that can detect the pressure at these ideal locations.

So we again must ask the question, "Is it correct to use the term 'sonic' when describing the flow through a control valve simply because P_d/P_u is smaller than 0.5?" Likely not. Finally, industry participants do not measure the air velocity near the exit of the flow control gap and would find it rather expensive to measure, even if they wished to do so. In the end, the air flow could be close to sonic when testing dry powder inhalers with current methods; but since the air flow velocity is *not measured*, the testing does not depend on whether the flow velocity is actually sonic. These realities obviate the value of the term "sonic."

The difficulties with "critical" and "sonic" are a major part of the reason that the term "choked" is much more practical, conveying the sense of what is happening at the valve and why the flow is indeed controlled. The term "choked" has the advantage of being qualitative…it means "restricted" or "constrained" or "suppressed"…and all these terms convey what the user actually sees in the process of setting the flow rate for testing inhalers. It is also a term that can be measured and quantified with equipment like that in Figure 2. As described earlier, "choked" means that no matter how capable the system vacuum pump may be and how hard it may work, the mass flow rate of air will reach a maximum value and stay there, if the upstream conditions are constant. When a team of inhaler testing personnel knows it has set its equipment to reach the condition where the flow is "choked," those team members can be confident that the mass flow rate of air will be the same test after test and for each user. For many reasons then, "choked" is far preferred as the term that describes the setting of the flow rate for testing dry powder inhalers.

What about the specifications of valve 8FV12LN stated in its product literature?

We can now return to the question, "How can the Parker product literature for valve 8FV12LN say that 'choked flow' takes place when P_d/P_u is equal to 0.17 or less?" Our data (Figure 3) says that the flow becomes choked when P_d/P_u is very nearly the theoretical thermodynamic value of 0.528. Parker has an excellent technical reputation and very likely has *unpublished* data to back up the specifications in its product literature. So, where do we turn for an explanation?

We cannot be certain of the reasons for the Parker specification for choked flow. However, a plausible explanation lies in the test method that Parker has used (ISA S75.02; reference 19; see the footnote in Figure 1; and see section 8.2 of ISA S75.02 for the definition of "choked" flow). This protocol calls for the valve under test to be *fully open when tested* (or at least tested with enough data points where the valve is nearly fully open, allowing the user to extrapolate confidently to the condition of being fully open). The mass flow rate of air under these circumstances is rather large, 10x to 100x the mass flow rate that will pass through this valve under inhaler testing conditions. For this reason, additional and different equipment than that shown in Figure 2 would be needed to test the valve under the ISA S75.02 protocol and these test conditions would be unrelated to inhaler testing conditions.

If we think about what the valve is like when it is fully open (Figure 6), it is easy to imagine the air flow aggressively passing around the valve stem and, with some swirling motion, passing out through the body of the valve that surrounds the valve stem. It then turns and moves to the exit port. So the "fully open valve" required under ISA S75.02 has a flow path and resistance to flow that is significantly different than the path depicted in Figure 5 for a controlling needle valve, wherein the gap and the upstream and downstream shape of the flow are more carefully defined. In a fully open valve, rather than encountering a converging flow path leading to a specific point of constriction, the air flows through the body of the valve with the stem retracted into the chamber from which the flow exits. This flow path is ill-defined and can consist of preferred channels of flow with residence times much less than average (and some much larger). And downstream of the narrowest constriction, the flow could become supersonic, with significant energy loss in the attendant shock. In this environment, the approximations of adiabatic and isentropic flow very likely are irrelevant. Under the ISA S75.02 protocol then, there are several mechanisms by which energy is lost; and so it is not surprising that greater pumping power is needed (the smaller value of P_d/P_u) to obtain choked flow conditions.

Nevertheless, until the requisite testing equipment, protocol and data are explained in an open publication, the exact reasons for the Parker specifications *will remain unknown.* As a result, we question the wisdom of including the Parker choked flow specification and the ISA S75.02 protocol in the pharmacopeial compendia.

Discussion and conclusions

We have traced the meaning of several terms that describe the setting of the flow rate in the testing of dry powder inhalers, specifically "critical," "sonic" and "choked." Of these, the most practical and meaningful term is the word "choked," indicating an inability to increase the flow rate regardless of how strong the vacuum pump pulling the flow through the control valve. The phenomenon of "choked" allows personnel in a practicing inhaler testing laboratory to achieve the same flow rate from test to test and from technician to technician, exactly what a testing team wants for good quality data. It can be described

as a "sufficient" condition for achieving the desired flow control. At the same time, it is not a "necessary" condition since there are many ways to control flow besides those typical of inhaler testing [20, 21].

The terms "critical" and "sonic" arise in an approximate thermodynamic analysis that likely does not apply to real flow control valves. The term "sonic" is shown to be needless by 1) the approximate nature of this thermodynamic analysis and 2) the fact that the practicing inhaler community does nothing to measure this velocity. The term "critical," arising simply from the calculus of the derivation of sonic conditions in the approximate thermodynamic analysis, contributes only a hypothetical, mathematical remark about the nature of the flow. For these reasons, we recommend that the terms "sonic" and "critical" are best dropped from written and oral communications in the inhaler testing community, including the regulatory community.

Unfortunately, in the inhaler testing community, the term "critical" has taken on the meaning of "necessary to comply with standard testing protocols." That meaning has nothing to do with the science of the air flow and serves only to imply that the proper pressure ratio is necessary and sufficient for practical testing. Our assertion is that in the absence of data like those in Figure 3, relying on P_d/P_u alone carries risk when in-use commercial equipment has not been tested for choked flow behavior, especially since the performance of commercial equipment can change over time.

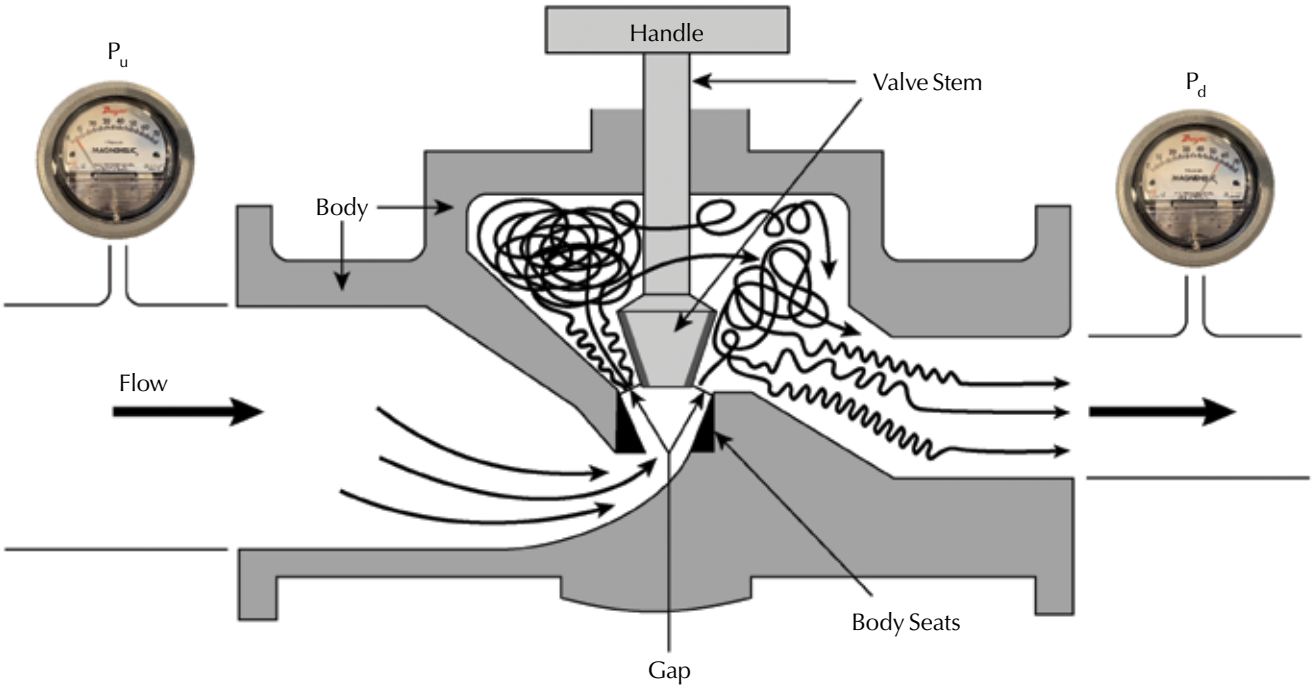
It would be a welcome simplification if the term "choked" would be used exclusively to specify the flow control for the testing of dry powder inhalers. This condition has the substantial advantage that it can be tested experimentally with equipment such as that in Figure 2.

The pharmacopeial compendia have unintentionally added to the lack of clarity in the terminology by highlighting a specific flow control valve whose manufacturer states will exhibit "choked" flow only when the pressure ratio across the valve (P_d/P_u) is smaller than or equal to 0.17. Our data with this Parker valve 8FV12LN (Figure 3) show clearly that the air flow is choked when P_d/P_u is smaller than or equal to approximately 0.5, rather close to the value of 0.528 expected from the approximate thermodynamic analysis. We attribute the seemingly anomalous pressure ratio value of 0.17 in the Parker product literature to the test protocol (ISA S75.02) that is stated in the Parker product literature. This test protocol requires a fully open flow control valve, quite different than the conditions of inhaler testing. We can hope for an explanatory publication of the data behind the manufacturer's product literature that would elucidate the reasons for the "choked" P_d/P_u value of 0.17. Absent these data, we recommend that references to the Parker choked flow condition and ISA S75.02 should be removed from the pharmacopeial compendia.

Future work in this arena should focus on practical methods to document the "in-use" performance of flow control equipment in the testing of dry powder inhalers, possibly including solenoid valves as well as

Figure 6

Flow path through a wide-open flow control valve



the flow control valves described herein. Also, changing the language of flow control to the practical word "choked," rather than the hypothetical words "sonic" or "critical," should be a priority for the industrial, academic and regulatory communities involved with inhaler testing. These changes would provide clarity for many in the community and enable quantitative testing to qualify flow control equipment, perhaps on an annual basis.

Nomenclature

A –cross-sectional area of converging nozzle (cm^2)

c –speed of sound (cm/s)

D_{50} –aerodynamic particle size captured with 50% efficiency on a given impactor stage (µm)

$\dot{M}$ –mass flow rate of air stream (g/sec)

MW –molecular weight of air (gm/mole)

P –absolute pressure of a flowing air stream (kPa)

P_0 –absolute pressure of the source of the air flow (kPa)

P_1, P_u –absolute pressure of the air flow stream upstream of the flow control valve (kPa)

P_2, P_d –absolute pressure of the air flow stream downstream of the flow control valve (kPa)

r –ratio of the pressure in an air flow stream divided by the pressure at the source of the air flow (P/P_0)

R –universal gas constant, 82.05 cm^3-atm/(Kelvin*mole)

S –entropy (joule/Kelvin)

T –absolute temperature (Kelvin)

V –velocity of air flow stream (cm/s)

X_T –ratio of the pressure drop across the flow control valve to the upstream pressure in Parker product literature

Greek symbols

γ –ratio of the heat capacity per unit mass at constant pressure divided by the heat capacity per unit mass at constant volume

ρ –gas density (g/cm^3)

ρ_0 –gas density at the source of the air flow (g/cm^3)

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