The particle or droplet size distribution in the spray discharged from metered-dose inhalers, and the particle size distribution in the cloud discharged from dry powder inhalers, are important characteristics used in judging inhaler performance. While particle size measurement by microscopy can be used to evaluate the number of large particles, agglomerates, and foreign particulates in the emissions of metered-dose inhalers (e.g., *Epinephrine Bitartrate Inhalation Aerosol*), whenever possible this test should be replaced with a method to determine the aerodynamic size distribution of the drug aerosol leaving the inhaler. The aerodynamic size distribution defines the manner in which an aerosol deposits during inhalation. When there is a log-normal distribution, the aerodynamic size distribution may be characterized by the mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD). The aerodynamic size distribution of the drug leaving metered-dose and dry powder inhalers is determined using *Apparatus 1, 2, 3, 4, 5,* or *6* as specified in this chapter. A fine particle dose or fine particle fraction can also be determined as that portion of the inhaler output having an aerodynamic diameter less than the size defined in the individual monograph. This may be expected to correlate with the drug dose or that fraction of the drug dose that penetrates the lung during inhalation. Individual monographs may also define the emitted fractions of the delivered dose in more than one aerodynamic size range.

AERODYNAMIC SIZE DISTRIBUTION

Cascade impaction devices classify aerosol particles and droplets on the basis of those particles' aerodynamic diameters. The principle of their operation, whereby they separate aerosol particles and droplets from a moving airstream on the basis of particle or droplet inertia, is shown in *Figure 3.*

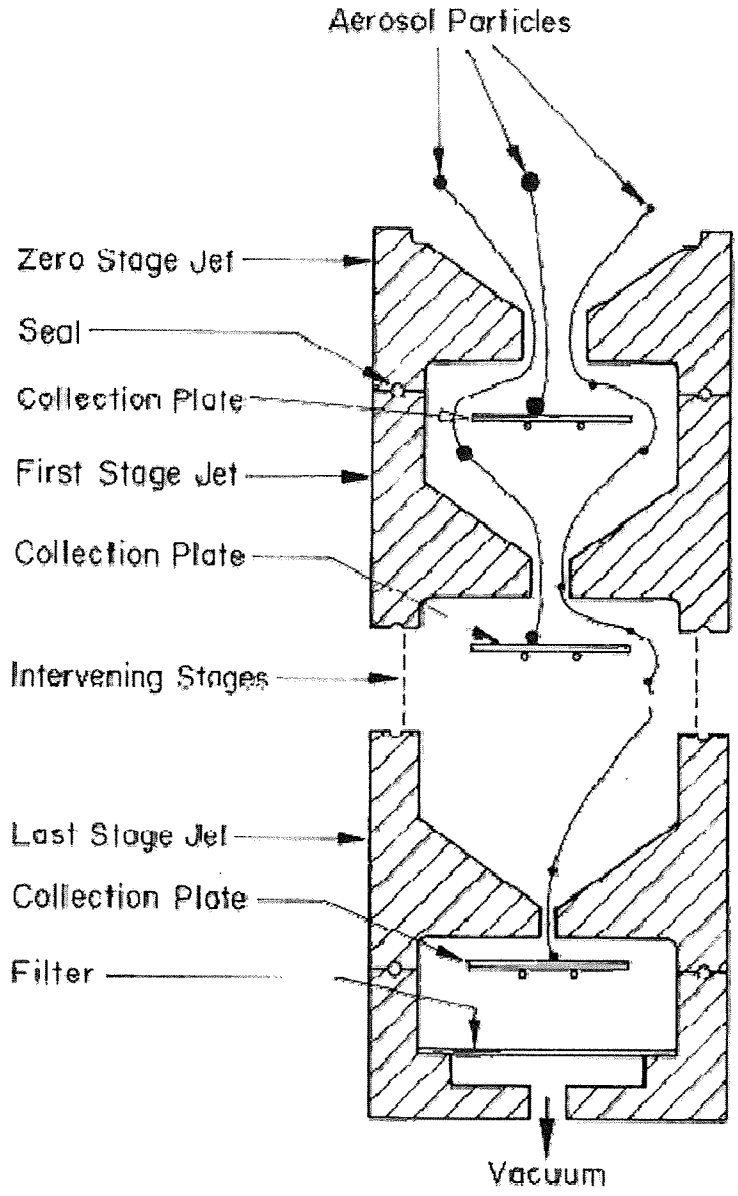

Fig. 3. Schematic representation of the principle of operation of cascade impactors. (A single jet per impactor stage is shown. Impactors with multiple jets in each stage function in the same manner.)

Because the dimensions of the induction port used to connect inhalers to the cascade impactors and impingers (shown in *Apparatus 1, 2, 3, 4, 5,* and *6*) also define the mass of drug that enters the aerodynamic sizing device, these are carefully defined and, where possible, are held constant between each apparatus (see *Figures 4, 6, 7, 8,* and *9*).

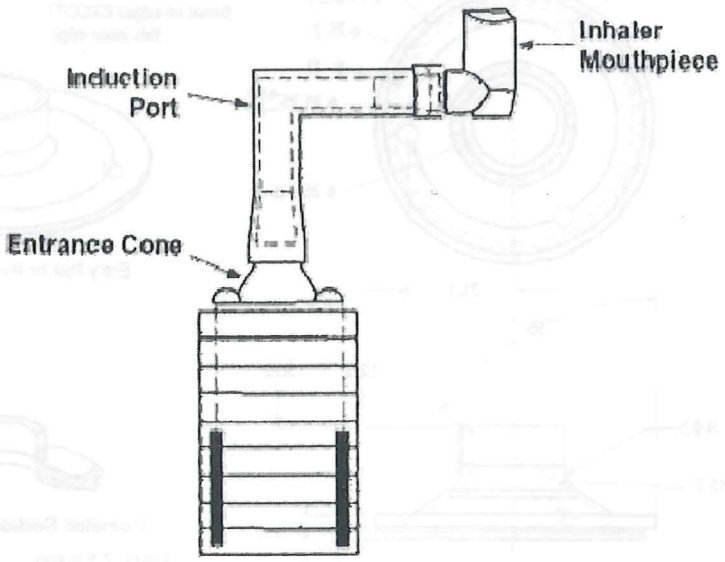

Fig. 4. Apparatus 1: Assembly of induction port and entrance cone mounted on cascade impactor.

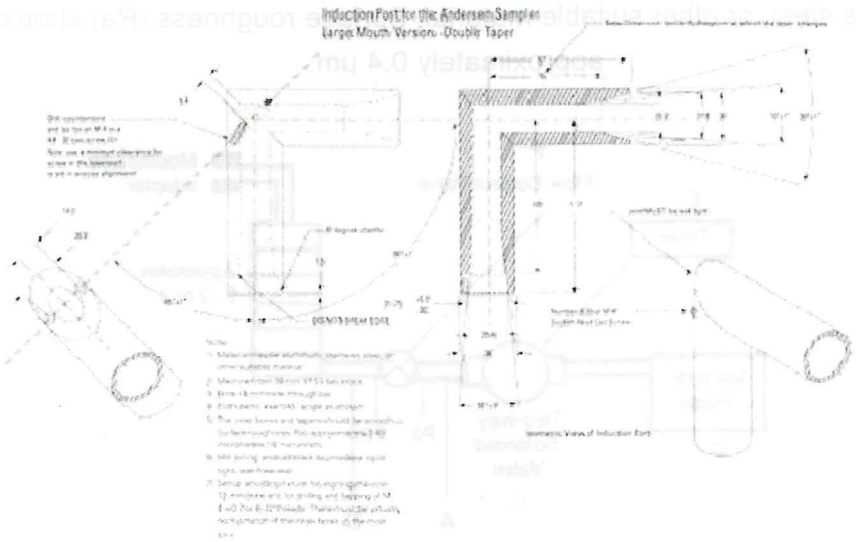

Fig. 4a. Apparatus 1: Expanded view of induction port for use with metered-dose and dry powder inhalers.

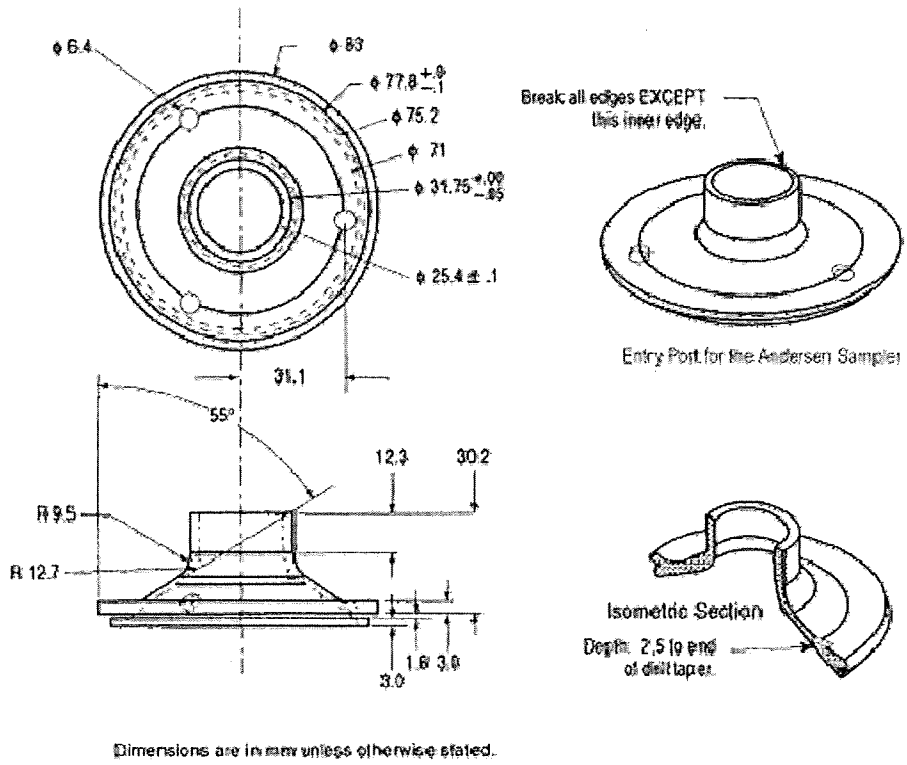

Fig. 4b. Apparatus 1: Expanded view of the entrance cone for mounting induction port on the Andersen cascade impactor without preseparator. Material may be aluminum, stainless steel, or other suitable material. Surface roughness (Ra) should be approximately 0.4 µm.

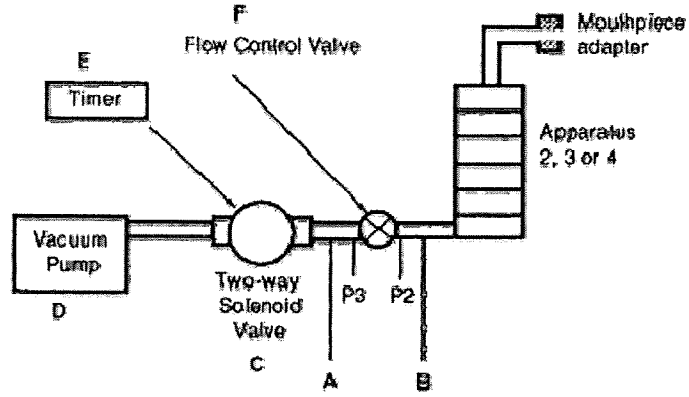

Fig. 5. Apparatus 2, 3, 4, or 5: General control equipment. (See *Table 3* for component specifications.)

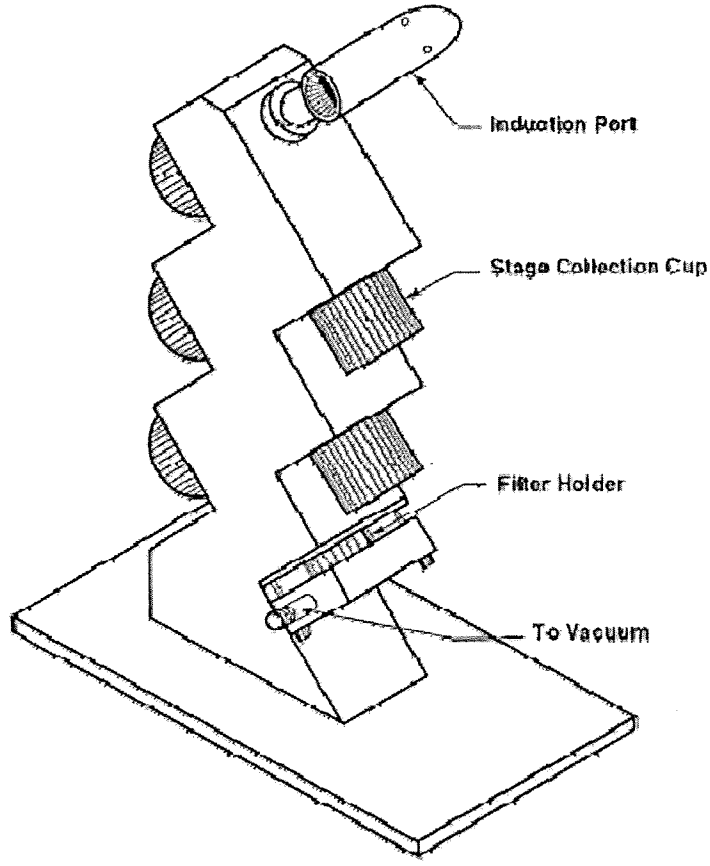

Fig. 6. Apparatus 2: Assembly of induction port, stage collector, and filter holder. (Marple-Miller impactor, Model 160 with USP induction port.)

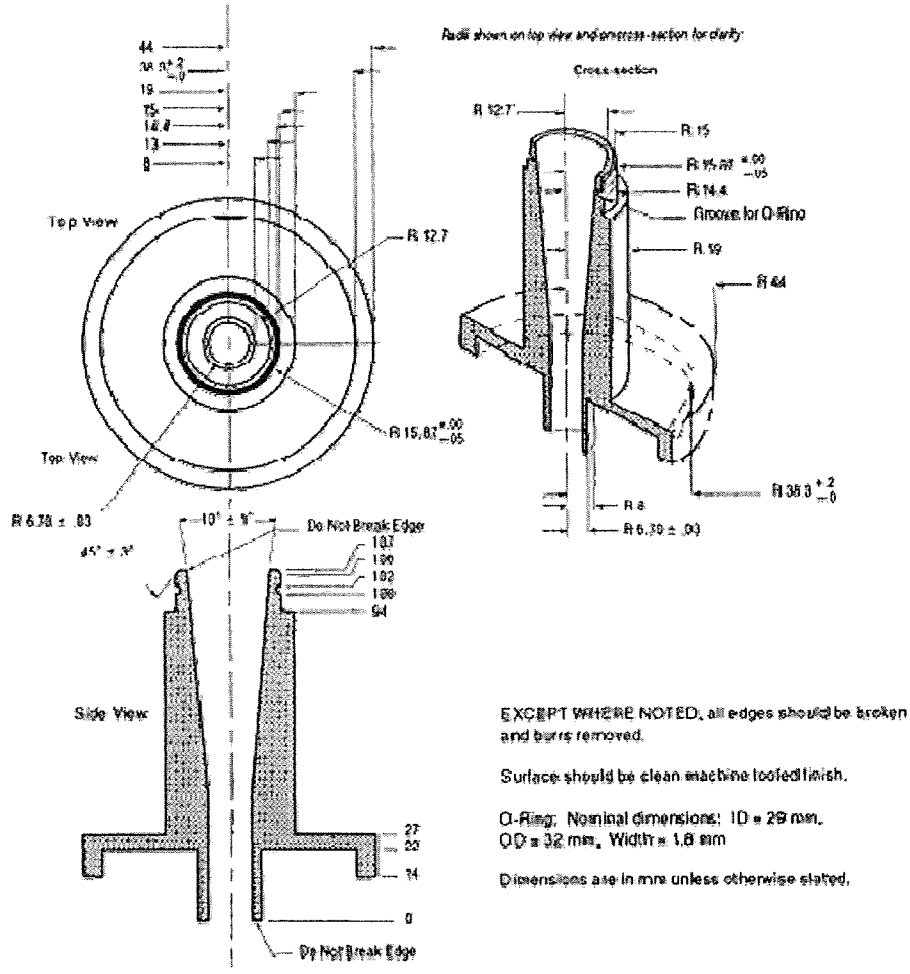

Fig. 7. Apparatus 3: Expanded views of top for the Andersen preseparator adapted to the USP induction port. Material may be aluminum, stainless steel, or other suitable material; interior bore should be polished to surface roughness (Ra) approximately 0.4 µm.

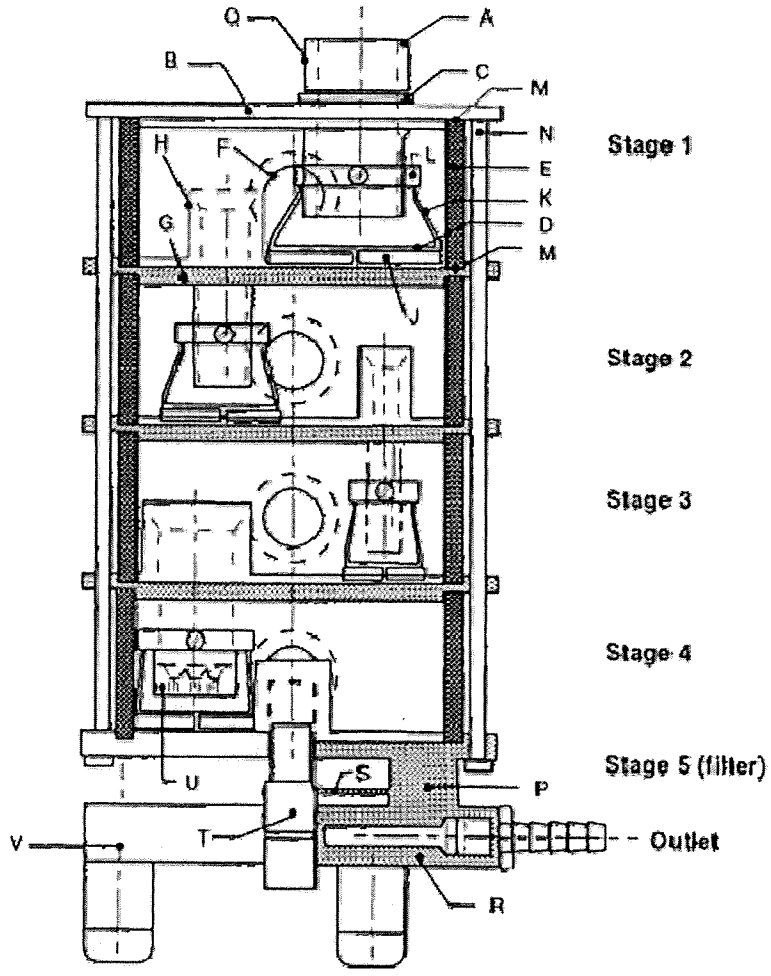

Fig. 8. Apparatus 4: Schematic of multistage liquid impinger. (See *Table 4* for component specifications.)

Because the size distributions produced by different impactors are often a function of impactor design and the airflow rate through them, there is a need to standardize the instruments that are used to test inhalers (i.e., *Apparatus 1* or *6* for metered-dose inhalers) or to provide guidelines on system suitability where different apparatuses may be used (i.e., *Apparatus 2, 3, 4,* or *5* for dry powder inhalers).

Because of the varied nature of the formulations and devices being tested, the cascade impaction system and technique selected for testing an inhaler should fulfill a number of criteria.

Stage Mensuration— Manufacturers of cascade impaction devices provide a definitive calibration for the separation characteristics of each impaction stage in terms of the relationship between the stage collection efficiency and the aerodynamic diameter of particles and droplets passing through it as an aerosol . Calibration is a property of the jet dimensions, the spatial arrangement of the jet and its collection surface, and the airflow rate passing through it. Because jets can corrode and wear over time, the critical

dimensions of each stage, which define that impaction stage's calibration, must be measured on a regular basis. This process, known as stage mensuration, replaces the need for repetitive calibration (using standard aerosols) and ensures that only devices that conform to specifications are used for testing inhaler output. The process involves the measurement and adjustment of the critical dimensions of the instrument.

Interstage Drug Loss (wall losses)— Where method variations are possible and there is no apparatus specified in the monograph, the selected technique should ensure that not more than 5% of the inhaler's total delivered drug mass (into the impactor) is subject to loss between the impaction device's sample collection surfaces. In the event that interstage drug losses are known to be greater than 5%, either the procedure should be performed in such a way that wall losses are included along with the associated collection plate, or an alternative apparatus should be used. As an example, the following procedures described for *Apparatus 1* and *3* have been written to include wall losses along with the associated collection plate. Provided, however, that such losses are known to be less than or equal to 5% of the total delivered drug mass into the impactor and that there are no instructions to the contrary in an individual monograph, the technique may be simplified by only assaying drug on the collection plates.

Re-Entrainment— Where method variations are possible, the selected technique should seek to minimize particle re-entrainment (from an upper to a lower impaction stage) on stages that contribute to size fractions defined in the individual monograph, especially where this may affect the amounts of drug collected. Minimizing the number of sampled doses, the use of coated particle collection surfaces, and proving that multiple-dose techniques produce statistically similar results to those from smaller numbers of doses, are all methods that can be used for this purpose. In the event that re-entrainment cannot be avoided, the number of doses collected, the time interval between doses, and the total duration of airflow through the cascade impaction device should be standardized. Under these circumstances, the presentation of impaction data should not presume the validity of the impactor's calibration (i.e., aerodynamic diameter ranges should not be assigned to drug masses collected on specific stages).

By using appropriate assay methods and a suitable mensurated impaction device, aerodynamic particle size distributions can be determined for drugs leaving the mouthpieces of metered-dose or dry powder inhalers. If temperature or humidity limits for use of the inhaler are stated on the label, it may be necessary to control the temperature and humidity of the air surrounding and passing through the device to conform to those limits. Ambient conditions are presumed, unless otherwise specified in individual monographs.

Mass Balance— In addition to the size distribution, good analytical practice dictates that a mass-balance be performed in order to confirm that the amount of the drug discharged

from the inhaler, which is captured and measured in the induction port-cascade impactor apparatus, is within an acceptable range around the expected value. The total mass of drug collected in all of the components (material balance) divided by the total number of minimum recommended doses discharged is not less than 75% and not more than 125% of the average minimum recommended dose determined during testing for *Delivered-Dose Uniformity*. This is not a test of the inhaler but serves to ensure that the test results are valid.

Use one of the multistage impaction devices shown below, or an equivalent, to determine aerodynamic particle size distributions of drugs leaving the mouthpieces of metered-dose or dry powder inhalers. *Apparatus 1* and *6* [*Figures 4* and *9* (without preseparator), respectively] are intended for use with metered-dose inhalers at a single airflow rate. *Apparatus 2, 3, 4,* and *5* (*Figures 6, 7, 8,* and *9,* respectively) are intended for use with dry powder inhalers at the appropriate airflow rate, Q_{out}, determined earlier, provided that the value of Q_{out} falls in the range 30–100 L per minute.

NOTE— If Q_{out} is greater than 100 L per minute, testing should be performed with Q_{out} set at 100 L per minute; if Q_{out} is less than 30 L per minute, testing is performed with Q_{out} at 30 L per minute.

Apparatus 1 for Metered-Dose Inhalers— Use this apparatus, or an equivalent, at a flow rate of 28.3 L per minute (±5%), as specified by the manufacturer of the cascade impactor.

Design— The design and assembly of this apparatus and the induction port to connect the device to an inhaler are shown in *Figures 4, 4a,* and *4b* [1].

Critical engineering dimensions applied by manufacturers to the stages of *Apparatus 1* are provided in *Table 2*. During use, some occlusion and blockage of jet nozzles may occur and therefore, "in use" mensuration tolerances need to be justified.

Table 2. Critical Dimensions for the Jet Nozzles of *Apparatus 1*

Stage #	Number of Jets	Nozzle Diameter (mm)
0	96	2.55 ± 0.025
1	96	1.89 ± 0.025
2	400	0.914 ± 0.0127
3	400	0.711 ± 0.0127
4	400	0.533 ± 0.0127
5	400	0.343 ± 0.0127
6	400	0.254 ± 0.0127
7	201	0.254 ± 0.0127

Procedure— Set up the multistage cascade impactor as described in the manufacturer's

literature with an after filter below the final stage to capture any fine particles that otherwise would escape from the device. To ensure efficient particle capture, coat the particle collection surface of each stage with glycerol, silicone oil, or other suitable liquid typically deposited from a volatile solvent, unless it has been demonstrated to be unnecessary. Attach the induction port and mouthpiece adapter to produce an airtight seal between the inhaler mouthpiece and the induction port as shown in *Figure 4.* Use a mouthpiece adapter that ensures that the tip of the inhaler mouthpiece is flush with the open end of the induction port. Ensure that the various stages of the cascade impactor are connected with airtight seals to prevent leaks. Turn on the vacuum pump to draw air through the cascade impactor, and calibrate the airflow through the system with an appropriate flowmeter attached to the open end of the induction port. Adjust the flow-control valve on the vacuum pump to achieve steady flow through the system at the required rate, and ensure that the airflow through the system is within ±5% of the flow rate specified by the manufacturer. Unless otherwise prescribed in the patient instructions, shake the inhaler for 5 seconds and discharge one delivery to waste. With the vacuum pump running, insert the mouthpiece into the mouthpiece adapter and immediately fire the minimum recommended dose into the cascade impactor. Keep the valve depressed for a duration sufficient to ensure that the dose has been completely discharged. If additional sprays are required for the sample, wait for 5 seconds before removing the inhaler from the mouthpiece adapter, shake the inhaler, reinsert it into the mouthpiece adapter, and immediately fire the next minimum recommended dose. Repeat until the required number of doses have been discharged. The number of minimum recommended doses discharged must be sufficient to ensure an accurate and precise determination of *Aerodynamic Size Distribution.* [NOTE— The number of minimum recommended doses is typically not greater than 10.] After the last dose has been discharged, remove the inhaler from the mouthpiece adapter. Rinse the mouthpiece adapter and induction port with a suitable solvent, and dilute quantitatively to an appropriate volume. Disassemble the cascade impactor, place each stage and its associated collection plate or filter in a separate container, and rinse the drug from each of them. [NOTE— If it has been determined that wall losses in the impactor are less than or equal to 5%, then the collection plates only may be used.]

Dilute each quantitatively to an appropriate volume. Using the method of analysis specified in the individual monograph, determine the mass of drug collected in each of the components. To analyze the data, proceed as directed under *Data Analysis.*

Apparatus 2 for Dry Powder Inhalers—

Design— The design and assembly of *Apparatus 2,* and the induction port to connect the device to an inhaler, are shown in *Figure 6.* [2] [NOTE— The induction port is shown in detail in *Figure 4a.*] The impactor has five impaction stages and an after filter. At a volumetric airflow rate of 60 L per minute (the nominal flow rate, Q_n), the cutoff aerodynamic

diameters $D_{50,Qn}$ of Stages 1 to 5 are 10, 5, 2.5, 1.25, and 0.625 µm, respectively. The after filter effectively retains aerosolized drug in the particle size range up to 0.625 µm. Set up the multistage cascade impactor with the control system as specified in *Figure 5.* To ensure efficient particle capture, coat the particle collection surface of each stage with glycerol, silicone oil, or other suitable liquid typically deposited from a volatile solvent, unless it has been demonstrated to be unnecessary. Assemble the impactor as described in the manufacturer's literature with an after filter below the final stage to capture any fine particles that otherwise would escape from the device. Attach the induction port and mouthpiece adapter to produce an airtight seal between the inhaler mouthpiece and the induction port. Use a mouthpiece adapter that ensures that the tip of the inhaler mouthpiece is flush with the open end of the induction port. Ensure that the various stages of the cascade impactor are connected with airtight seals to prevent leaks.

Turn on the vacuum pump, open the solenoid valve, and calibrate the airflow through the system as follows. Connect a flowmeter to the induction port. Use a flowmeter calibrated for the volumetric flow leaving the meter to directly determine Q_{out}, or, if such a meter is unobtainable, calculate the volumetric flow leaving the meter (Q_{out}) using the ideal gas law. For example, for a meter calibrated for the entering volumetric flow (Q_{in}), use the formula:

$$Q_{out} = Q_{in} P_0 / (P_0 - \Delta P)$$

where P_0 is the atmospheric pressure and ΔP is the pressure drop over the meter. Adjust the flow-control valve to achieve a steady flow through the system at the required rate, Q_{out}, so that Q_{out} is within ±5% of the value determined during testing for *Delivered-Dose Uniformity.* Ensure that critical flow occurs in the flow-control valve, at the airflow rate to be used during testing, by using the following procedure. With the inhaler in place, and the intended flow running, measure the absolute pressure on both sides of the flow-control valve (P2 and P3 in *Figure 5*). A ratio of P3/P2 ≤ 0.5 indicates critical flow. Switch to a more powerful pump, and remeasure the test flow rate if P3/P2 > 0.5. Adjust the timer controlling the operation of the two-way solenoid valve so that it opens this valve for a duration of *T* seconds as determined during testing for *Delivered-Dose Uniformity.* Prime or load the dry powder inhaler with powder for inhalation according to the labeled instructions. With the vacuum pump running and the two-way solenoid valve closed, insert the inhaler mouthpiece, held horizontally, into the induction port mouthpiece adapter. Discharge the powder into the apparatus by opening the two-way solenoid valve for a duration of *T* seconds. After the two-way solenoid valve has closed, remove the inhaler from the mouthpiece adapter. If additional doses are required for the sample, reload the inhaler according to the labeled instructions, reinsert the mouthpiece into the mouthpiece adapter, and repeat the operation until the required number of doses have been discharged. After discharge of the last dose, switch off the vacuum pump.

Rinse the mouthpiece adapter and induction port with a suitable solvent, and quantitatively dilute to an appropriate volume. Disassemble the cascade impactor, and place the after filter in a separate container. Rinse the drug from each of the stages and the filter, and quantitatively dilute each to an appropriate volume. Using the method of analysis specified in the individual monograph, determine the mass of drug collected in each of the components. Determine the cutoff diameters of each of the individual stages of the impactor, at the value of $Q = Q_{out}$ employed in the test by the formula:

$$D_{50,Q} = D_{50,Qn}(Q_n / Q)^{1/2}, \quad \text{(Eq. 1)}$$

where $D_{50,Q}$ is the cutoff diameter at the flow rate, Q, employed in the test, and the subscript, n, refers to the nominal values determined when Q_n equals 60 L per minute. Thus, when Q equals 40 L per minute, the cutoff diameter of Stage 2 is given by the formula:

$$D_{50,40LPM} = 5\ \mu m \times [60/40]^{1/2} = 6.1\ \mu m.$$

General Procedure— Perform the test using *Apparatus 2* at the airflow rate, Q_{out} determined earlier, during testing for *Delivered-Dose Uniformity,* provided Q_{out} is less than or equal to 100 L per minute. [NOTE— If Q_{out} is greater than 100 L per minute, use an airflow rate of 100 L per minute.] Connect the apparatus to a flow control system that is based upon critical (sonic) flow as specified in *Figure 5* (see also *Table 3*).

Table 3. Component Specifications for *Figure 5*

Code	Item	Description	Dimensions
A	Connector	(e.g., short metal coupling with low diameter branch to P3)	≥ 8-mm ID
B	Vacuum tubing	(e.g., silicon tubing with an outside diameter of 14 mm and an internal diameter of 8 mm)	A length of suitable tubing ≥8 mm ID with an internal volume of 25 ± 5 mL.
C	Two-way solenoid valve[a]	See *Fig. 5*	2-way, 2-port solenoid valve having an ID ≥8 mm and an opening response time of ≤100 milliseconds.
D	Vacuum pump[b]	See *Fig. 5*	Pump must be capable of drawing the required flow rate through the assembled apparatus with the dry powder inhaler in the mouthpiece adapter. Connect the pump to

			the solenoid valve using short and wide (≥ 10-mm ID) vacuum tubing and connectors to minimize pump capacity requirements.
E	Timer[c]	See *Fig. 5*	The timer switches current directly to the solenoid valve for the required duration.
P2, P3	Pressure measurements		Determine under steady-state flow conditions with an absolute pressure transducer.
F	Flow control valve[d]	See *Fig. 5*	Adjustable regulating valve with maximum $C_V \geq 1$.

[a] An example being ASCO product number 8030G13 (Automatic Switch Company, 60 Hanover Road, Florham Park, NJ 07932) or equivalent. See also Footnote *h* in *Table 1*.

[b] Gast product type 1023, 1423, or 2565 (Gast Manufacturing Inc., PO Box 97, Benton Harbor, MI 49022) or equivalent.

[c] An example being Eaton Product number 45610-400 (Eaton Corporation, Automotive Products Division, 901 South 12th Street, Watertown, WI 53094) or equivalent.

[d] Parker Hannifin type 8FV12LNSS, or equivalent (Parker Hannifin plc, Riverside Road, Barnstable, Devon EX31 1NP, UK). See also Footnote *h* in *Table 1*.

Table 4. Component Units of Multistage Liquid Impinger (see *Figure 8*)

Code[1]	Item	Description	Dimensions[2]
A,H	Jet tube	Metal tube screwed onto partition wall sealed	see *Figure 8a*

		by gasket (C), polished inner surface	
B,G	Partition wall	Circular metal plate, diameter	120
		Thickness	see *Figure 8a*
C	Gasket	e.g., PTFE	to fit jet tube
D	Impaction plate	Porosity O sintered-glass disk,	
		Diameter	see *Figure 8a*
E	Glass cylinder	Plane polished cut glass tube	
		Height, including gaskets	46
		Outer diameter	100
		Wall thickness	3.5
		Sampling port (F) diameter	18
		Stopper in sampling port	ISO 24/25
J	Metal frame	L-profiled circular frame with slit	
		Inner diameter	to fit impaction plate
		Height	4
		Thickness of horizontal section	0.5
		Thickness of vertical section	2
K	Wire	Steel wire interconnecting metal frame and sleeve (two for each frame)	
		Diameter	1
L	Sleeve	Metal sleeve secured on jet tube by screw	
		Inner diameter	to fit jet tube
		Height	6
		Thickness	5
M	Gasket	e.g., silicone	to fit glass cylinder
N	Bolt	Metal bolt with nut (six pairs), length	205
		Diameter	4
P	O-ring	Rubber O-ring, diameter × thickness	66.34 × 2.62
Q	O-ring	Rubber O-ring, diameter × thickness	29.1 × 1.6
R	Filter holder	Metal housing with stand and outlet	see *Figure 8b*
S	Filter support	Perforated sheet metal, diameter	65
		Hole diameter	3
		Distance between holes (center-points)	4
T	Snap-locks		
U	Multi-jet tube	Jet tube (H) ending in multijet arrangement	see inserts *Figure 8a*
V	Outlet	Outlet and nozzle for connection to vacuum	Internal diameter ≥ 10

			(Figure 8b)

[1] See Fig. 8.

[2] Measurements in mm unless otherwise stated.

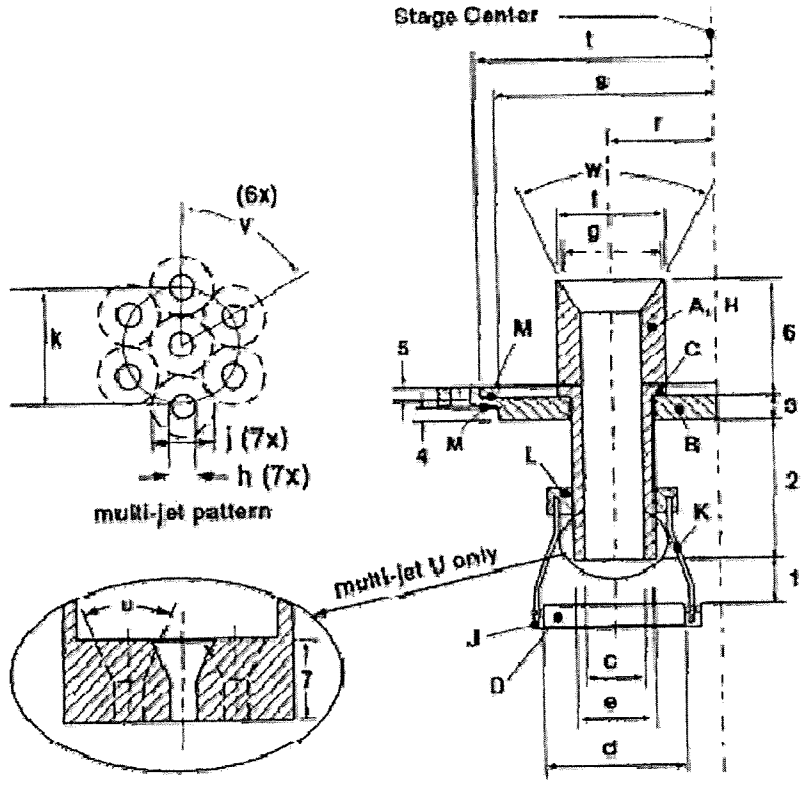

Fig. 8a. Apparatus 4: Details of jet tube and impaction plate. Inserts show end of multi-jet tube U leading to Stage 4. (See Table 5 for dimension specifications.)

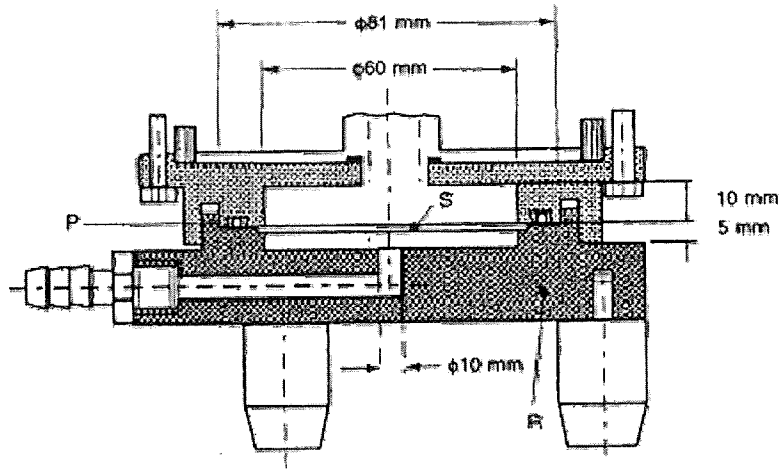

Fig. 8b. Apparatus 4: Expanded view of Stage 5. (See *Table 4* for component specifications.)

Table 5. Apparatus 4: Dimensions[1] of Jet Tube with Impaction Plate (see *Fig. 8a*).

Type	Code[2]	Stage 1	Stage 2	Stage 3	Stage 4	Filter (Stage 5)
Distance	1	9.5 (−.0, +.5)	5.5 (−.0, +.5)	4.0 (−.0, +.5)	6.0 (−.0, +.5)	n.a.
Distance	2	26	31	33	30.5	0
Distance	3	8	5	5	5	5
Distance	4	3	3	3	3	n.a.
Distance	5	0	3	3	3	3
Distance	6[3]	20	25	25	25	25
Distance	7	n.a.	n.a.	n.a.	8.5	n.a.
Diameter	c	25	14	8.0(±0.1)	21	14
Diameter	d	50	30	20	30	n.a.
Diameter	e	27.9	16.5	10.5	23.9	n.a.
Diameter	f	31.75 (−.05, +.00)	22	14	31	22
Diameter	g	25.4	21	13	30	21
Diameter	h	n.a.	n.a.	n.a.	2.70 (±.05)	n.a.
Diameter	j	n.a.	n.a.	n.a.	6.3	n.a.
Diameter	k	n.a.	n.a.	n.a.	12.6	n.a.
Radius[4]	r	16	22	27	28.5	0
Radius[4]	s	46	46	46	46	n.a.
Radius[4]	t	n.a.	50	50	50	50
Angle	w					

		10°	53°	53°	53°	53°
Angle	u	n.a.	n.a.	n.a.	45°	n.a.
Angle	v	n.a.	n.a.	n.a.	60°	n.a.

[1] Measurements in mm with tolerances according to ISO 2768-m, unless otherwise stated.

[2] See *Fig. 8a.*

[3] Including gasket.

[4] Relative centerline of stage compartment.

n.a.: not applicable.

Under steady flow conditions, at the appropriate volumetric airflow rate through the entire apparatus, ensure that critical (sonic) flow occurs in the flow control valve by determining the individual values for absolute pressure, P2 and P3, so that their ratio P3/P2 is less than or equal to 0.5. Coat the particle collection surface of each of the stages of the cascade impactor to ensure that particles that have impacted on a given stage are not re-entrained in the flowing airstream, unless this has been shown to be unnecessary. Analyze the data as directed under *Data Analysis.*

Apparatus 3 for Dry Powder Inhalers—

Design— Apparatus 3 is identical to *Apparatus 1 (Figure 4),* except that the manufacturer's preseparator is added atop Stage 0 to collect large masses of noninhalable powder prior to their entry into the impactor, and the outlet nipple, used to connect to vacuum tubing B *(Figure 5),* is replaced with one having an internal diameter ≥ 8 mm. To connect the preseparator of the impactor to the induction port *(Figure 4a),* a specially designed top for the preseparator must be used. This is shown in *Figure 7.* [3] The impactor, therefore, has eight stages, a preseparator (to collect large particulates), and an after filter. At a volumetric airflow rate of 28.3 L per minute (the nominal flow rate, Q_n), the cutoff aerodynamic diameters $D_{50,Qn}$ of Stages 0 to 7 are 9.0, 5.8, 4.7, 3.3, 2.1, 1.1, 0.7, and 0.4 µm, respectively. The after filter effectively retains aerosolized drug in the particle size range up to 0.4 µm. Connect the cascade impactor into the control system specified in *Figure 5.* Omit Stage 6 and Stage 7 from the impactor if the test flow rate, Q_{out}, used during testing for *Delivered-Dose Uniformity* was greater than or equal to 60 L per minute. To ensure efficient particle capture, coat the particle collection surface of each stage with glycerol, silicone oil, or other suitable liquid typically deposited from a volatile solvent, unless it has been demonstrated to be unnecessary. Assemble the impactor as described in the manufacturer's literature with an after filter below the final stage to capture any fine particles that otherwise would escape from the device. Place an appropriate volume (up to 10 mL) of an appropriate solvent into the preseparator, or coat

the particle collection surfaces of the preseparator to prevent re-entrainment of impacted particles. [*Caution— Some solvents form flammable vapor-air mixtures that may be ignited during passage through a vacuum pump. Take appropriate precautions (alternative solvents, use of vapor traps, minimal pump operating times, etc.) to ensure operator safety during testing.*] Attach a molded mouthpiece adapter to the end of the induction port to produce an airtight seal between the inhaler mouthpiece and the induction port. Use a mouthpiece adapter that ensures that the tip of the inhaler mouthpiece is flush with the open end of the induction port. Ensure that the various stages of the cascade impactor are connected with airtight seals to prevent leaks.

Turn on the vacuum pump, open the two-way solenoid valve, and calibrate the airflow through the system as follows. Prime or load the dry powder inhaler with powder for inhalation according to the labeled instructions. With the vacuum pump running and the two-way solenoid valve closed, insert the inhaler mouthpiece, held horizontally, into the induction port mouthpiece adapter. Once the inhaler is positioned, discharge the powder into the apparatus by activating the timer and opening the two-way solenoid valve for the required duration, $T \pm 5\%$, as determined during testing for *Delivered-Dose Uniformity.* After the two-way solenoid valve has closed, remove the inhaler from the mouthpiece adapter. If additional doses are required for the sample, reload the inhaler according to the labeled instructions, reinsert the mouthpiece into the mouthpiece adapter, and repeat the operation until the required number of doses have been discharged. After discharge of the last dose, remove the inhaler from the mouthpiece adapter, and switch off the vacuum pump.

Carefully disassemble the apparatus. Using a suitable solvent, rinse the drug from the mouthpiece adapter, induction port, and preseparator, and quantitatively dilute to an appropriate volume. Rinse the drug from each stage, and the impaction plate immediately below, into appropriately sized flasks. Quantitatively dilute each flask to an appropriate volume. Using the method of analysis specified in the individual monograph, determine the mass of drug collected in each of the samples. The aerodynamic cutoff diameters of the individual stages of this device, in the airflow range between 30 and 100 L per minute, are currently not well established. Do not use the formula in Equation 1 to calculate cutoff diameters.

Procedure— Proceed as directed in the *General Procedure* under *Apparatus 2*, except to use *Apparatus 3.*

Apparatus 4 for Dry Powder Inhalers—

NOTE— *Apparatus 4,* the multistage liquid impinger, has a small number of stages and is used extensively outside the USA. It is provided here for the benefit of users in countries other than the USA.

Design— The design and assembly of *Apparatus 4* are shown in *Figs. 8*, *8a,* and *8b.*[4] The

induction port, used to connect the device to an inhaler, is shown in *Fig. 4a*. The device is a multi-stage liquid impinger consisting of impaction Stages 1, 2, 3, and 4 and an integral after filter (Stage 5). The collection stages of the liquid impinger (see *Fig. 8* and *Table 4*) are kept moist, unlike those of traditional impactors, such as *Apparatus 1, 2, 3, 5,* and *6;* wetting may produce an effect similar to coating the stages of *Apparatus 2, 3, 5,* and *6* at certain flow rates, although this should be confirmed by demonstrating control over re-entrainment as described earlier. An impaction stage comprises an upper horizontal metal partition wall (B) through which a metal inlet jet tube (A) with its impaction plate (D) is protruding; a glass cylinder (E) with sampling port (F), forming the vertical wall of the stage; and a lower horizontal metal partition wall (G) through which a jet tube (H) connects to the lower stage. The tube into Stage 4 (U) ends in a multi-jet arrangement. The impaction plate (D) is secured in a metal frame (J), which is fastened by two wires (K) to a sleeve (L) secured on the jet tube (C). For more detail of the jet tube and impaction plate, see *Fig. 8a*. The horizontal plane of the collection plate is perpendicular to the axis of the jet tube and centrally aligned. The upper surface of the impaction plate is slightly raised above the edge of the metal frame. A recess around the perimeter of the horizontal partition wall guides the position of the glass cylinder. The glass cylinders are sealed against the horizontal partition walls with gaskets (M) and clamped together by six bolts (N). The sampling ports are sealed by stoppers. The bottom side of the lower partition wall of Stage 4 has a concentric protrusion fitted with a rubber O-ring (P) that seals against the edge of a filter placed in the filter holder. The filter holder (R) is a basin with a concentric recess in which a perforated filter support (S) is flush-fitted. The filter holder is designed for 76-mm diameter filters. The whole impaction stage assembly is clamped onto the filter holder by two snap locks (T). The impinger is equipped with an induction port (*Fig. 4a*) that fits onto the Stage 1 inlet jet tube. A rubber O-ring on the jet tube provides an airtight connection to the induction port. An elastomeric mouthpiece adapter to fit the inhaler being tested provides an airtight seal between the inhaler and the induction port.

At a volumetric airflow rate of 60 L per minute (the nominal flow rate, Q_n), the cutoff aerodynamic diameters $D_{50,Qn}$ of Stages 1 to 4 are 13.0, 6.8, 3.1, and 1.7 µm, respectively. The after filter effectively retains aerosolized drug in the particle size range up to 1.7 µm. Ensure that *Apparatus 4* is clean and free of drug solution from any previous tests. Place a 76-mm diameter filter in the filter stage, and assemble the apparatus. Use a low pressure filter capable of quantitatively collecting the passing drug aerosol , which also allows a quantitative recovery of the collected drug. Set up *Apparatus 4* using the control system as specified in *Figure 5.* Attach the induction port *(Figure 4a)* and mouthpiece adapter to produce an airtight seal between the inhaler mouthpiece and the induction port. Use a mouthpiece adapter that ensures that the tip of the inhaler mouthpiece is flush with the open end of the induction port. Ensure that the various stages of the apparatus are connected with airtight seals to prevent leaks. Turn on the vacuum

pump, open the two-way solenoid valve, and calibrate the airflow through the system as follows. Connect a flowmeter, calibrated for the volumetric flow rate leaving the meter, to the induction port. Adjust the flow-control valve to achieve a steady flow through the system at the required rate, Q_{out}, so that Q_{out} is within ±5% of the value determined during testing for *Delivered-Dose Uniformity.* Ensure that critical flow occurs in the flow-control valve, at the value of Q_{out} to be used during testing, using the following procedure. With the inhaler in place, and the intended flow running, measure the absolute pressure on both sides of the flow-control valve (P2 and P3 in *Figure 5*). A ratio of P3/P2 ≤ 0.5 indicates critical flow. Switch to a more powerful pump, and remeasure the test flow rate if P3/P2 > 0.5. Adjust the timer controlling the operation of the two-way solenoid valve so that it opens that valve for the same duration, *T*, as used during testing for *Delivered-Dose Uniformity.* Dispense 20 mL of a solvent, capable of dissolving the drug, into each of the four upper stages of *Apparatus 4*, and replace the stoppers. [*Caution— Some solvents form flammable vapor-air mixtures that may be ignited during passage through a vacuum pump. Take appropriate precautions (alternative solvents, use of vapor traps, minimal pump operating times, etc.) to ensure operator safety during testing.*] Tilt the apparatus to wet the stoppers, thereby neutralizing their electrostatic charge. Adjust the timer controlling the operation of the two-way solenoid valve so that it opens the valve for the same duration, *T,* as used during testing for *Delivered-Dose Uniformity.* Prime or load the dry powder inhaler with powder for inhalation according to the labeled instructions. With the vacuum pump running and the two-way solenoid valve closed, insert the inhaler mouthpiece, held horizontally, into the induction port mouthpiece adapter. Discharge the powder into the apparatus by activating the timer and opening the two-way solenoid valve for the required duration, *T* ± 5%. After the two-way solenoid valve has closed, remove the inhaler from the mouthpiece adapter. If additional doses are required for the sample, reload the inhaler according to the labeled instructions, reinsert the mouthpiece into the mouthpiece adapter, and repeat the operation until the required number of doses have been discharged. After discharge of the last dose, switch off the vacuum pump.

Dismantle the filter stage of *Apparatus 4.* Carefully remove the filter, and extract the drug with solvent. Rinse the mouthpiece adapter and induction port with a suitable solvent, and quantitatively dilute to an appropriate volume. Rinse the inside of the inlet jet tube to Stage 1 *(Figure 8)*, allowing the solvent to flow into the stage. Rinse the drug from the inner walls and the collection plate of each of the four upper stages of the apparatus, into the solution in the respective stage, by tilting and rotating the apparatus, while ensuring that no liquid transfer occurs between the stages. Using the method of analysis specified in the individual monograph, determine the mass of drug collected in each of the six volumes of solvent. Ensure that the method corrects for possible evaporation of the solvent during the test. This may involve the use of an internal standard (of known original concentration in the solvent and assayed at the same time as the drug) or the quantitative