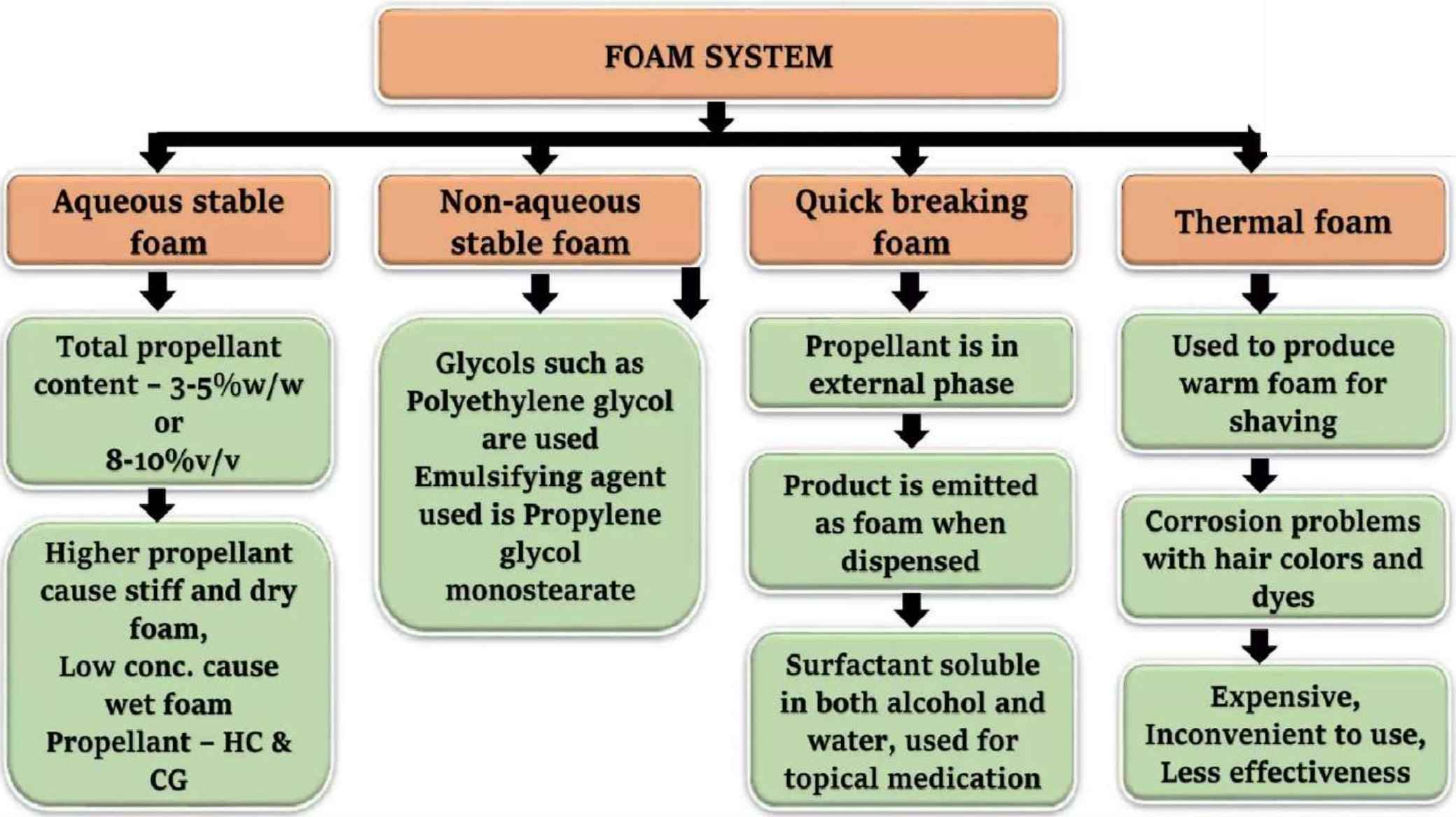
Suspension system

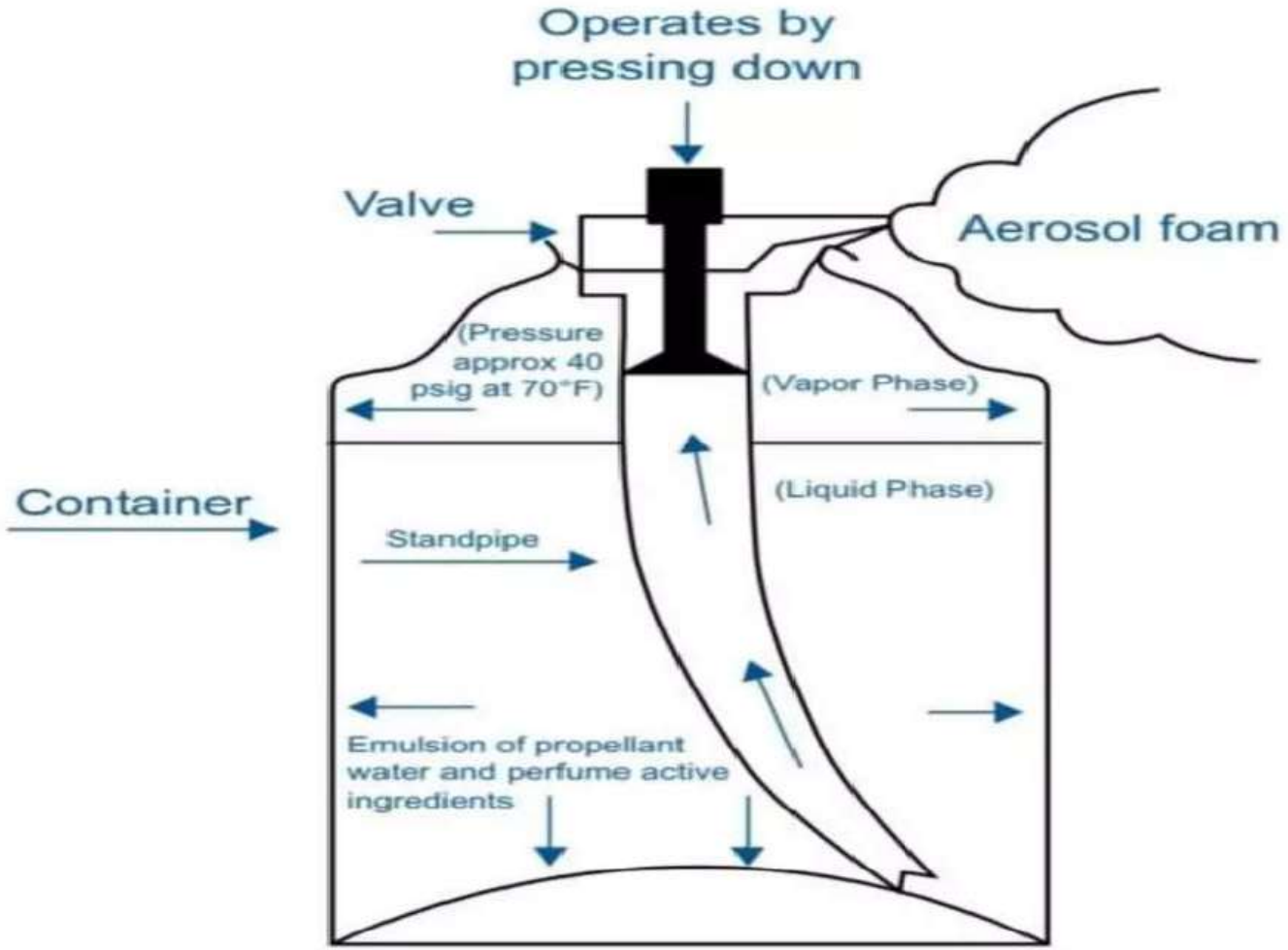
- It involves dispersion of active ingredient in the propellant or mixture of propellants.
- To decrease the rate of settling of dispersed particles, surfactants or suspending agents can be added.
- Primarily used for inhalation aerosols.
- Example:

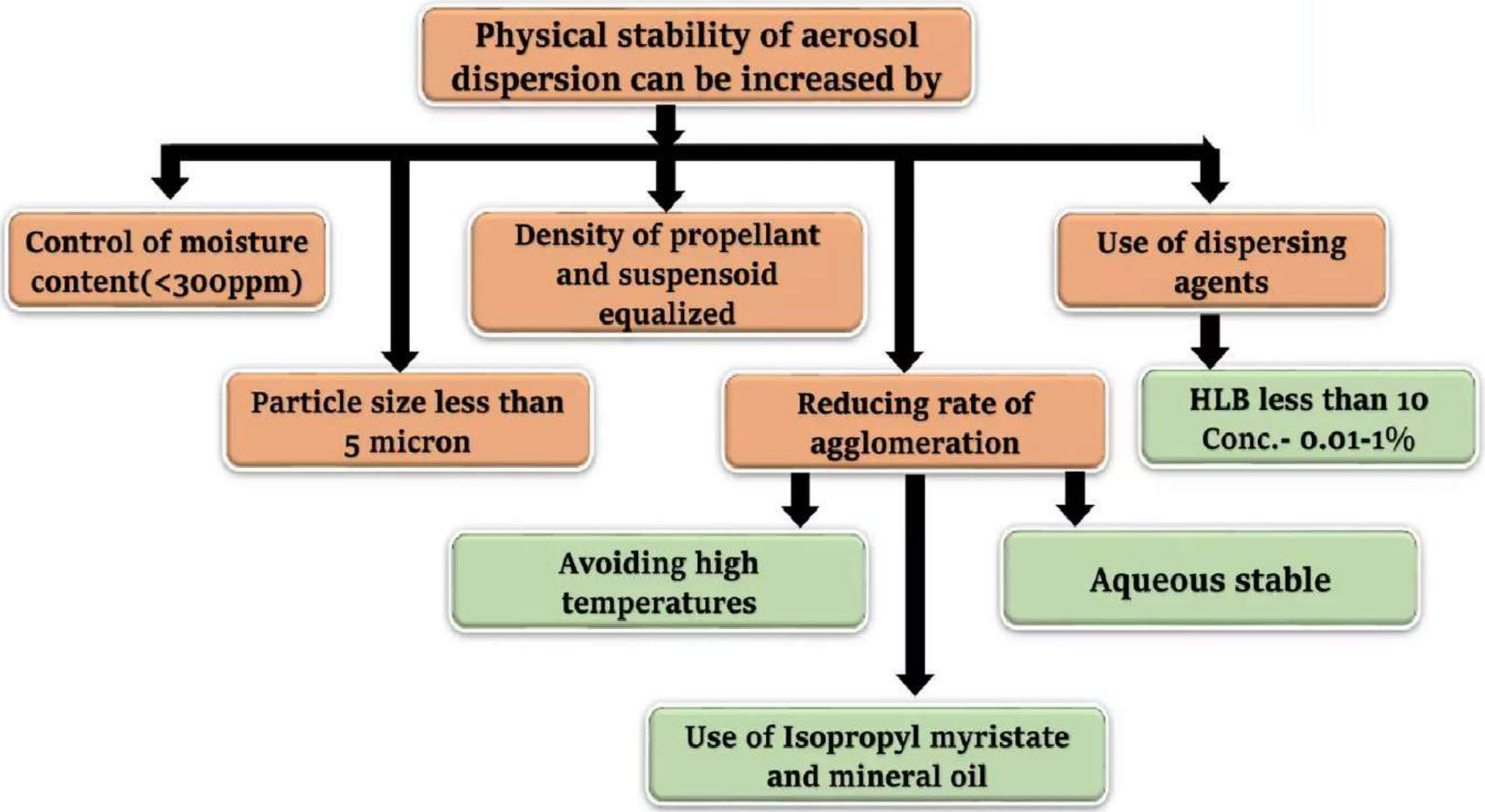
Formulation	Weight%
Epinephrine bitartrate(1-5 Microns)	0.50
Sorbitan trioleate	0.50
Propellant -114 + Propellant -12	99

- Epinephrine bitartrate has minimum solubility in propellant system but soluble in fluids in the lungs.

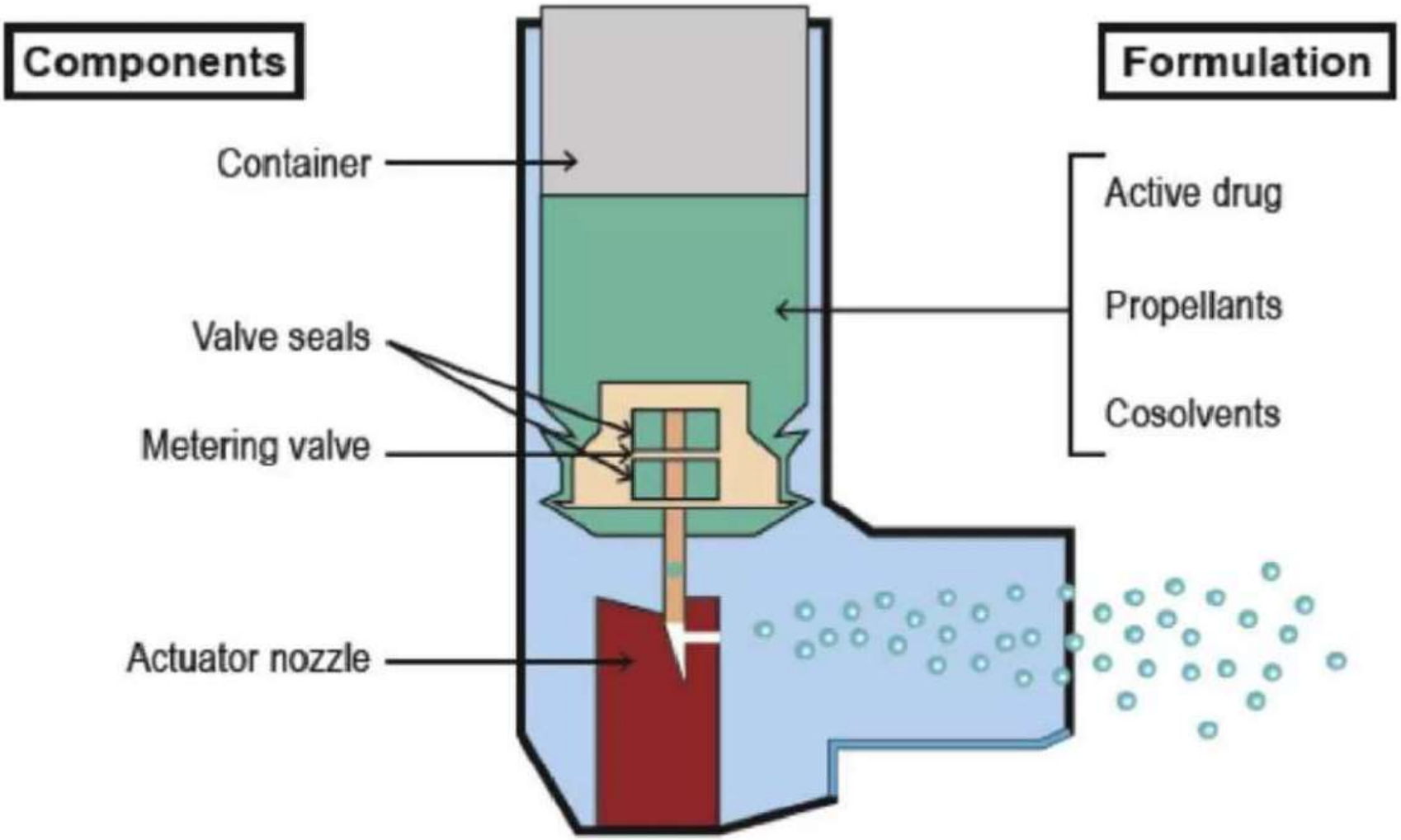

FOAM SYSTEM
Aqueous stable foam
Total propellant content – 3-5%w/w or 8-10%v/v
Higher propellant cause stiff and dry foam, Low conc. cause wet foam Propellant – HC & CG
Non-aqueous stable foam
Glycols such as Polyethylene glycol are used Emulsifying agent used is Propylene glycol monostearate
Quick breaking foam
Propellant is in external phase
Product is emitted as foam when dispensed
Surfactant soluble in both alcohol and water, used for topical medication
Thermal foam
Used to produce warm foam for shaving
Corrosion problems with hair colors and dyes
Expensive, Inconvenient to use, Less effectiveness

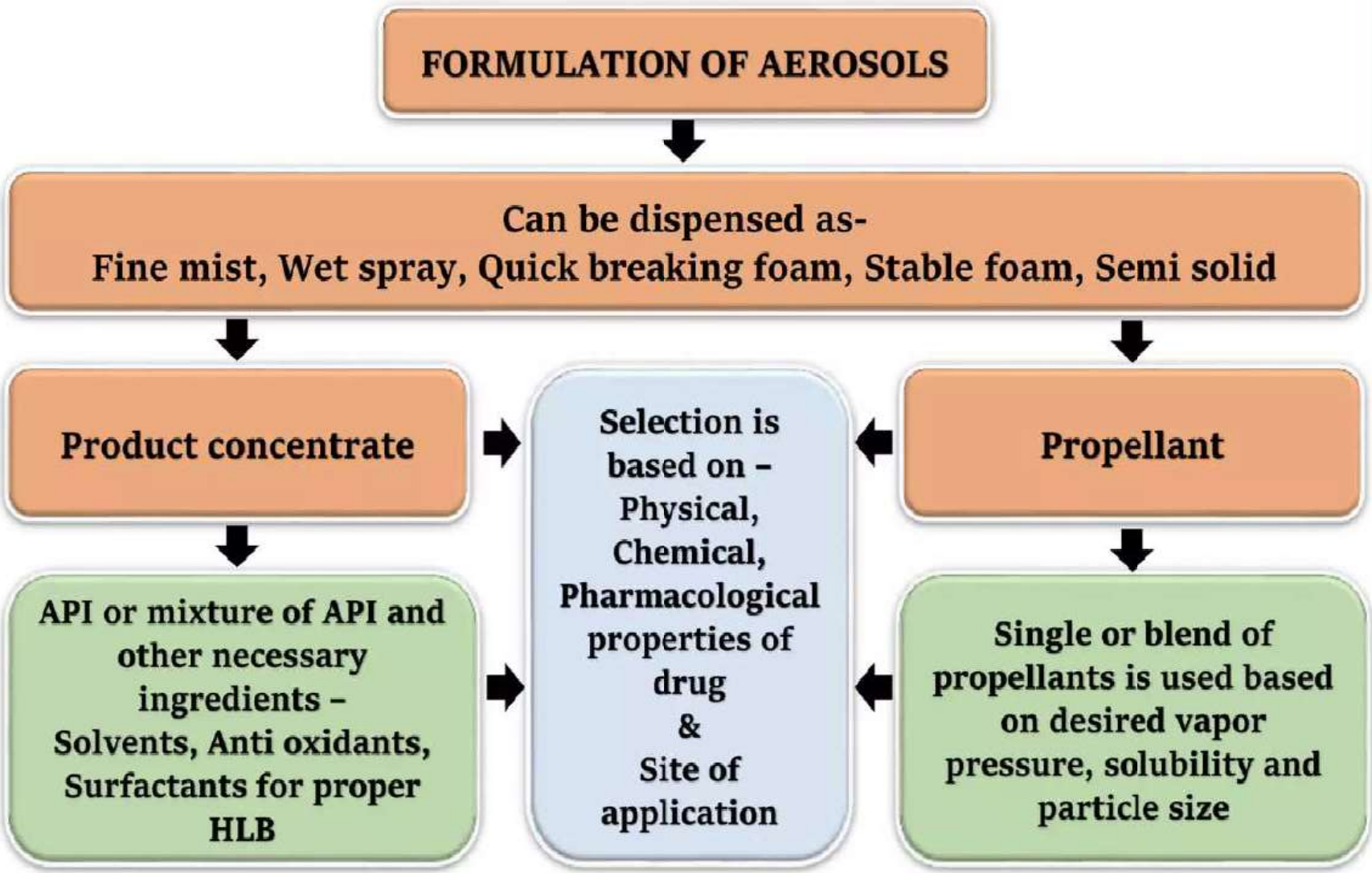
FOAM SYSTEM

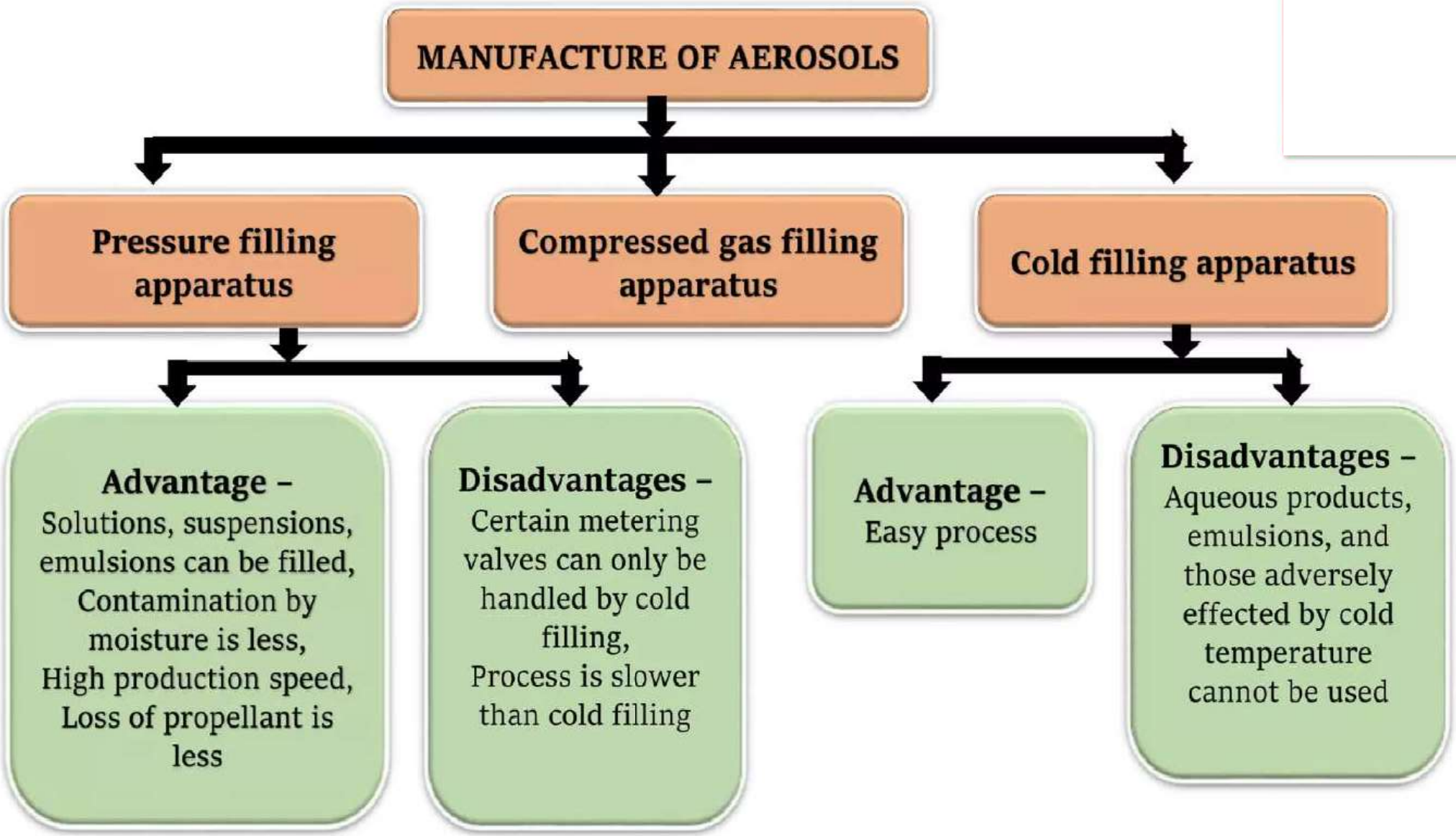

Operates by pressing down
Valve
Aerosol foam
(Pressure approx 40 psig at 70°F)
(Vapor Phase)
(Liquid Phase)
Container
Standpipe
Emulsion of propellant water and perfume active ingredients

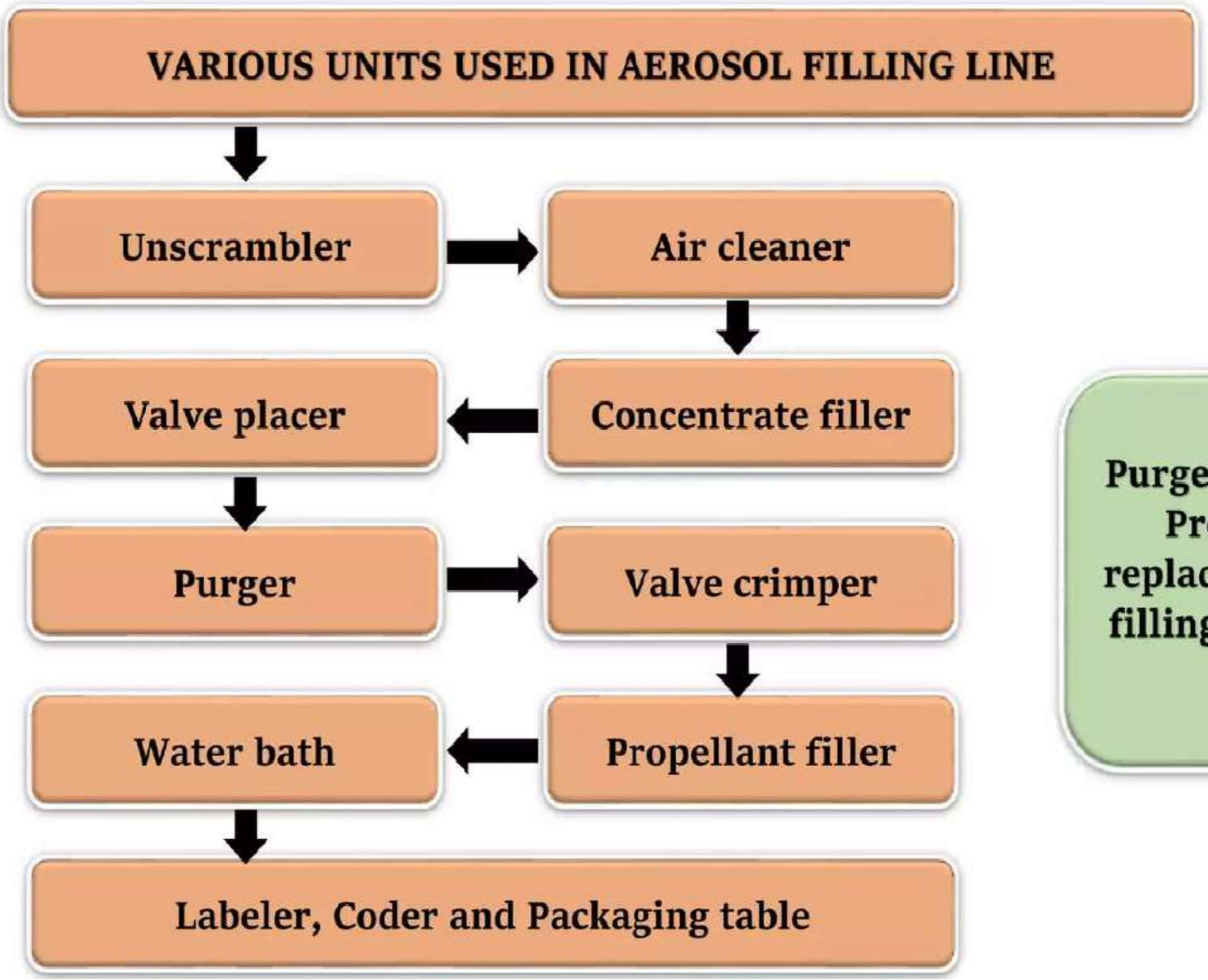

Physical stability of aerosol dispersion can be increased by
Control of moisture content(<300ppm)
Density of propellant and suspensoid equalized
Use of dispersing agents
Particle size less than 5 micron
Reducing rate of agglomeration
HLB less than 10 Conc.- 0.01-1%
Avoiding high temperatures
Aqueous stable
Use of Isopropyl myristate and mineral oil


Formulation
&
Manufacture
(AEROSOLS)


Components
Formulation
Container
Valve seals
Metering valve
Actuator nozzle
Active drug
Propellants
Cosolvents


FORMULATION OF AEROSOLS
Can be dispensed as-
Fine mist, Wet spray, Quick breaking foam, Stable foam, Semi solid
Product concentrate
Propellant
Selection is based on – Physical, Chemical, Pharmacological properties of drug & Site of application
API or mixture of API and other necessary ingredients – Solvents, Anti oxidants, Surfactants for proper HLB
Single or blend of propellants is used based on desired vapor pressure, solubility and particle size


MANUFACTURE OF AEROSOLS
Pressure filling apparatus
Compressed gas filling apparatus
Cold filling apparatus
Advantage – Solutions, suspensions, emulsions can be filled, Contamination by moisture is less, High production speed, Loss of propellant is less
Disadvantages – Certain metering valves can only be handled by cold filling, Process is slower than cold filling
Advantage – Easy process
Disadvantages – Aqueous products, emulsions, and those adversely effected by cold temperature cannot be used



Purger, Vaccum crimper, Pressure filler are replaced with single unit filling by "under the cap method"

Pressure filling apparatus

- It consists of a pressure burette capable of metering small volumes of liquefied gas into the aerosol container under pressure
- Propellant is added through an inlet valve located at the bottom or top of the pressure burette
- The propellant is allowed to flow with its own vapor pressure in the container through aerosol valve the trapped air escapes out from the upper valve
- Propellant stops flowing when the pressure of burette and container becomes equal
- Excess of the propellant is replaced into the container by help of positive pressure exerted by nitrogen from another container
- This type of device cannot be used for filling inhalation aerosols which have metered valves.

Procedure

- This method involves filling of the concentrate into the container at the room temperature
- Then the valve is placed in the container and crimped
- Through the opening of the valve the propellant are added or it can be added "under the cap"
- Since the opening of the valve are smaller in size ranging from 0.018-0.030 inches, it limits the production and the process becomes slow
- But with the use of rotary filling machines and newer filling heads where the propellants are filled through valve stem, the production rate is increased
- The trapped air in the container and air present in head space is removed before filling the propellant to protect the products from getting adversely affected.

Cold filling apparatus

- It consist of an insulated box fitted with copper tubings and the tubings are coiled to increase the area exposed to cooling
- The insulated box should be filled with dry ice or acetone prior to use
- The apparatus can be operated with or without metered valves
- Hydrocarbon propellant cannot be filled into aerosol containers using this apparatus because large amount of propellant escapes out and vaporizes
- This may lead to formation of an explosive mixture
- Fluorocarbon vapors do not form any explosive or flammable mixture though their vapors are heavier than air.

Procedure

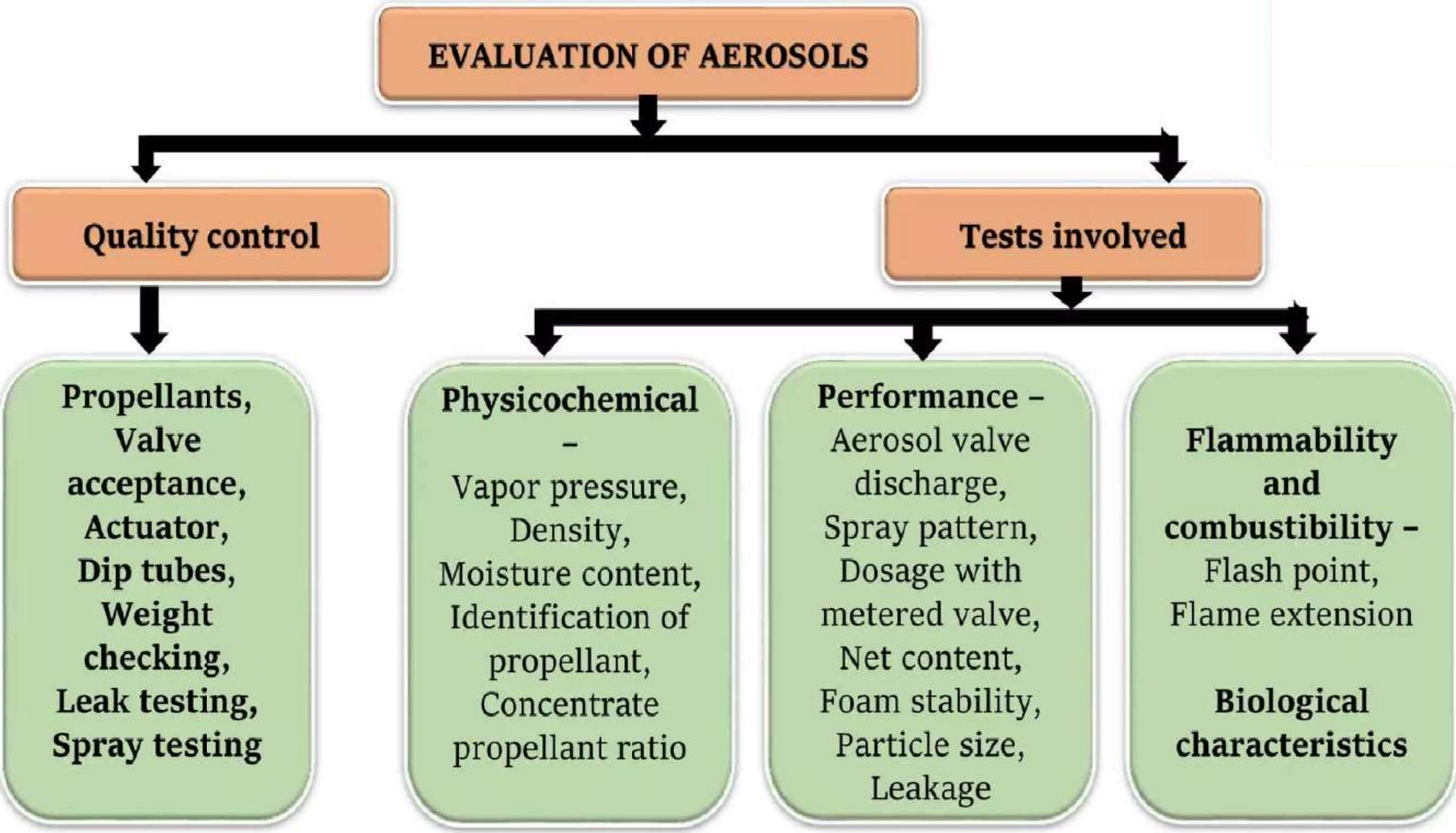
- Non aqueous products and products which can withstand low temperatures of - 40°F are used in this method
- The product concentrate is chilled to a temperature of - 40°F and filled into already chilled container
- Then the chilled propellant is added completely in 1 or 2 stages, depending on the amount
- Another method is to chill both the product concentrate and propellant in a separate pressure vessel to - 40 °F and then filling them into the container
- The valve is placed and crimped on to the container
- Then test for leakage and strength of container is carried out by passing container into a heated water bath, where the contents of the container are heated to 130°F. After this, the containers are air dried , capped and labeled.

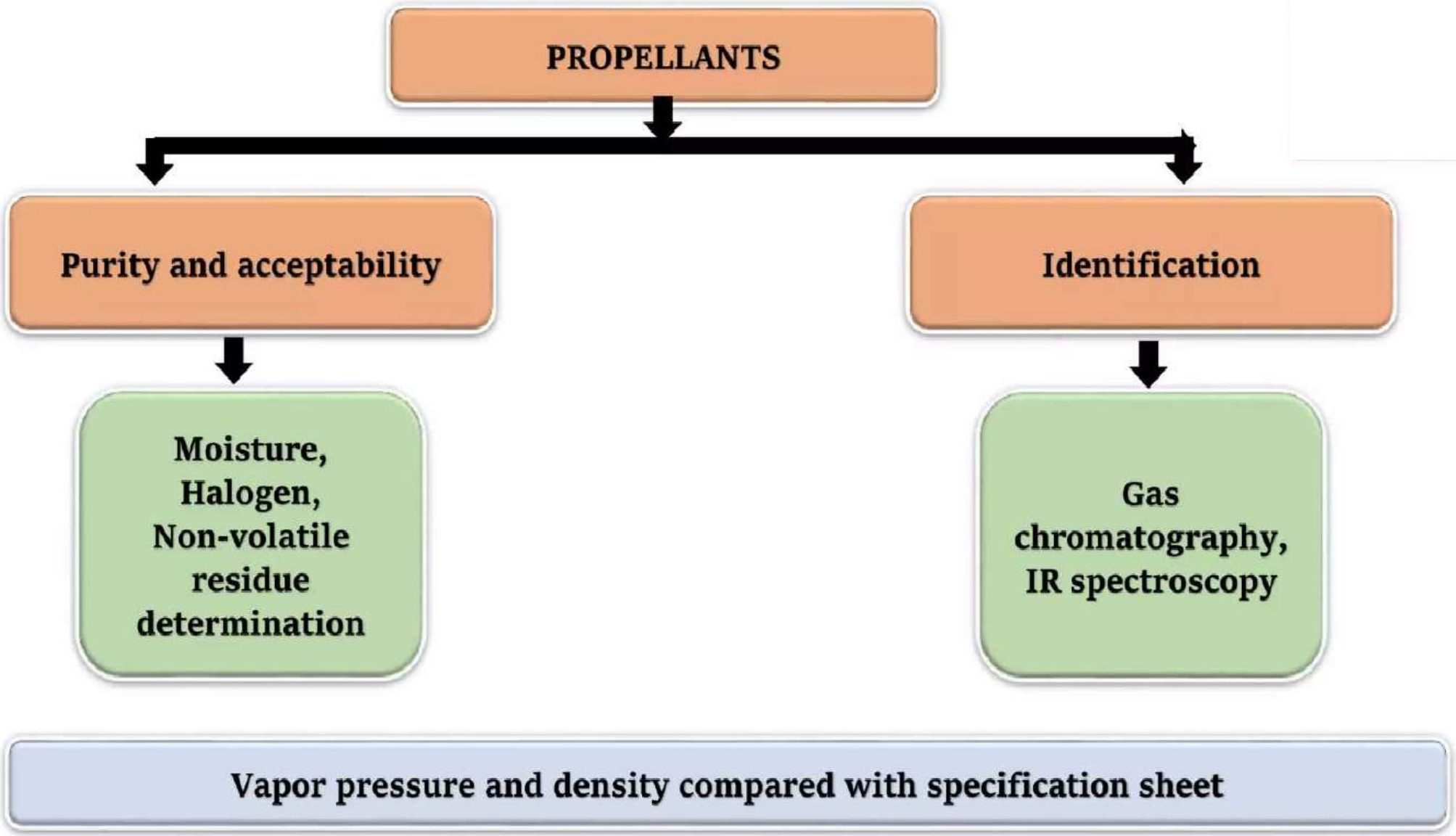
Compressed gas filling apparatus

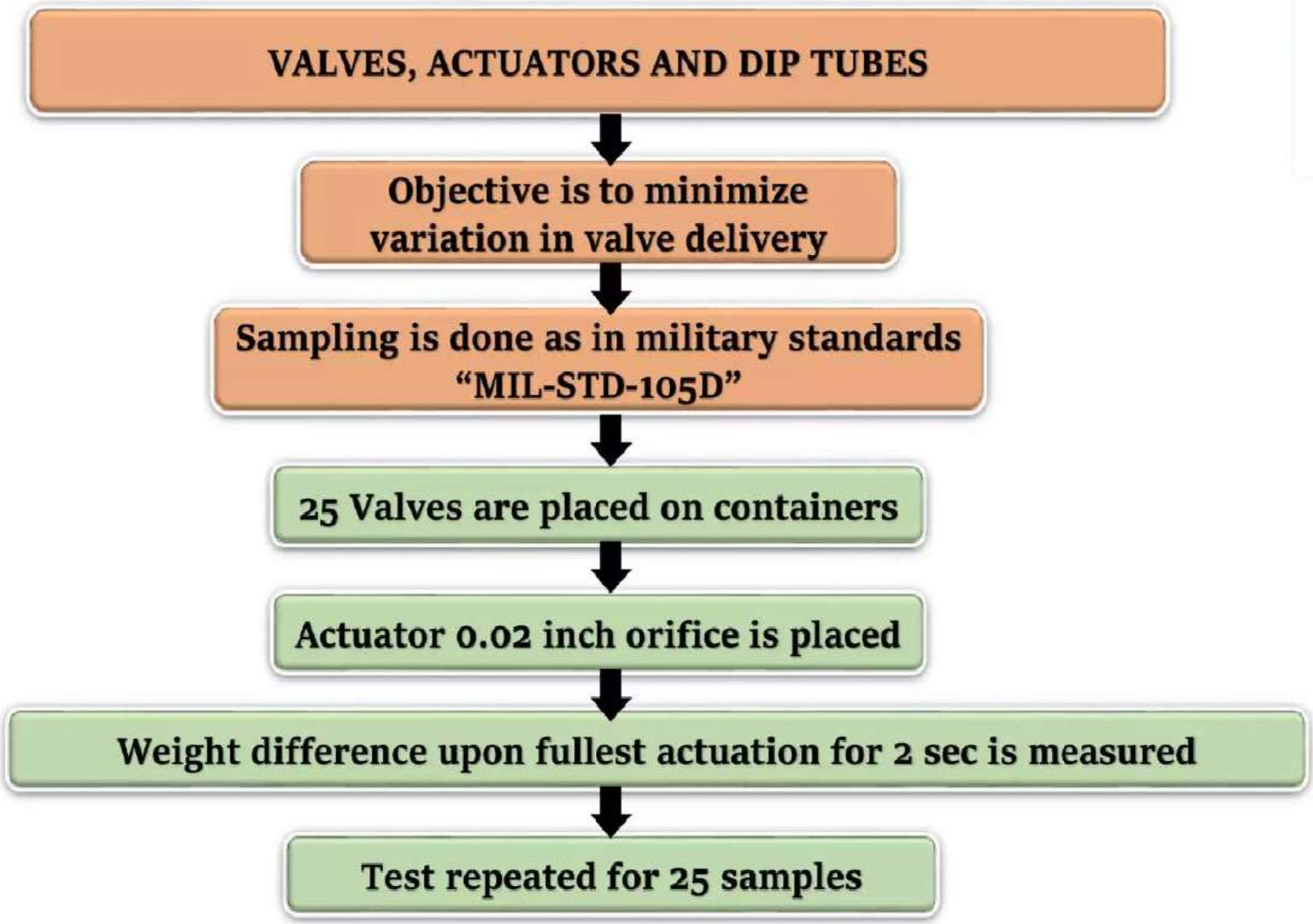
- Compressed gases have high pressure hence a pressure reducing valve is required.
- The apparatus consists of delivery gauge
- A flexible hose pipe which can withstand 150 pounds per square inch gauge pressure is attached to the delivery gauge along with the filling head
- A flow indicator is also present in specialized equipments.

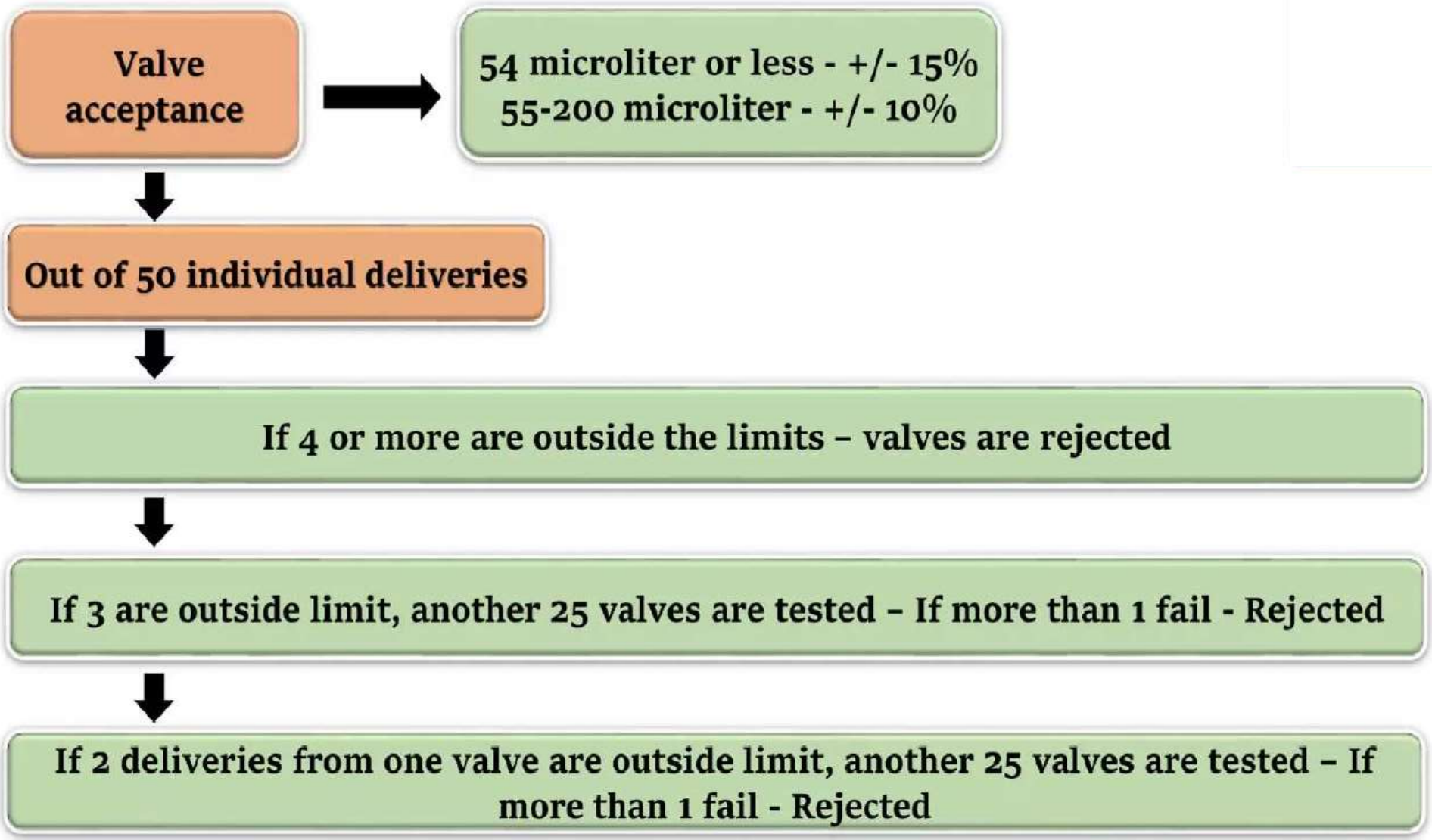
Procedure

- The product concentrate is filled into the container
- Valve is placed and crimped on the container
- With the help of vacuum pump the air is removed from the container
- Filling head is put in the opening of the valve and the valve is depressed and the gas is allowed to flow in to container
- The gas stops flowing if the delivery pressure and the pressure within the container become equal
- Carbon dioxide and nitrous oxide is used if more amount of gas is required
- High solubility of the gas in the product can be achieved by shaking the container manually or with the help of mechanical shakers.


EVALUATION OF AEROSOLS
Quality control
Tests involved
Propellants, Valve acceptance, Actuator, Dip tubes, Weight checking, Leak testing, Spray testing
Physicochemical – Vapor pressure, Density, Moisture content, Identification of propellant, Concentrate propellant ratio
Performance – Aerosol valve discharge, Spray pattern, Dosage with metered valve, Net content, Foam stability, Particle size, Leakage
Flammability and combustibility – Flash point, Flame extension
Biological characteristics


PROPELLANTS
Purity and acceptability
Identification
Moisture, Halogen, Non-volatile residue determination
Gas chromatography, IR spectroscopy
Vapor pressure and density compared with specification sheet


VALVES, ACTUATORS AND DIP TUBES
Objective is to minimize variation in valve delivery
Sampling is done as in military standards "MIL-STD-105D"
25 Valves are placed on containers
Actuator 0.02 inch orifice is placed
Weight difference upon fullest actuation for 2 sec is measured
Test repeated for 25 samples


Valve acceptance
54 microliter or less - +/- 15%
55-200 microliter - +/- 10%
Out of 50 individual deliveries
If 4 or more are outside the limits – valves are rejected
If 3 are outside limit, another 25 valves are tested – If more than 1 fail - Rejected
If 2 deliveries from one valve are outside limit, another 25 valves are tested – If more than 1 fail - Rejected

CONTAINERS

Containers are examined for defects in lining

Quality control aspects includes degree of conductivity of electric current as measure of exposed metals

Glass containers are examined for flaws

WEIGHT CHECKING

Done by periodic weighing of containers in two stages –
Before filling (tared weight)
After filling (increased weight is checked)

LEAK TESTING

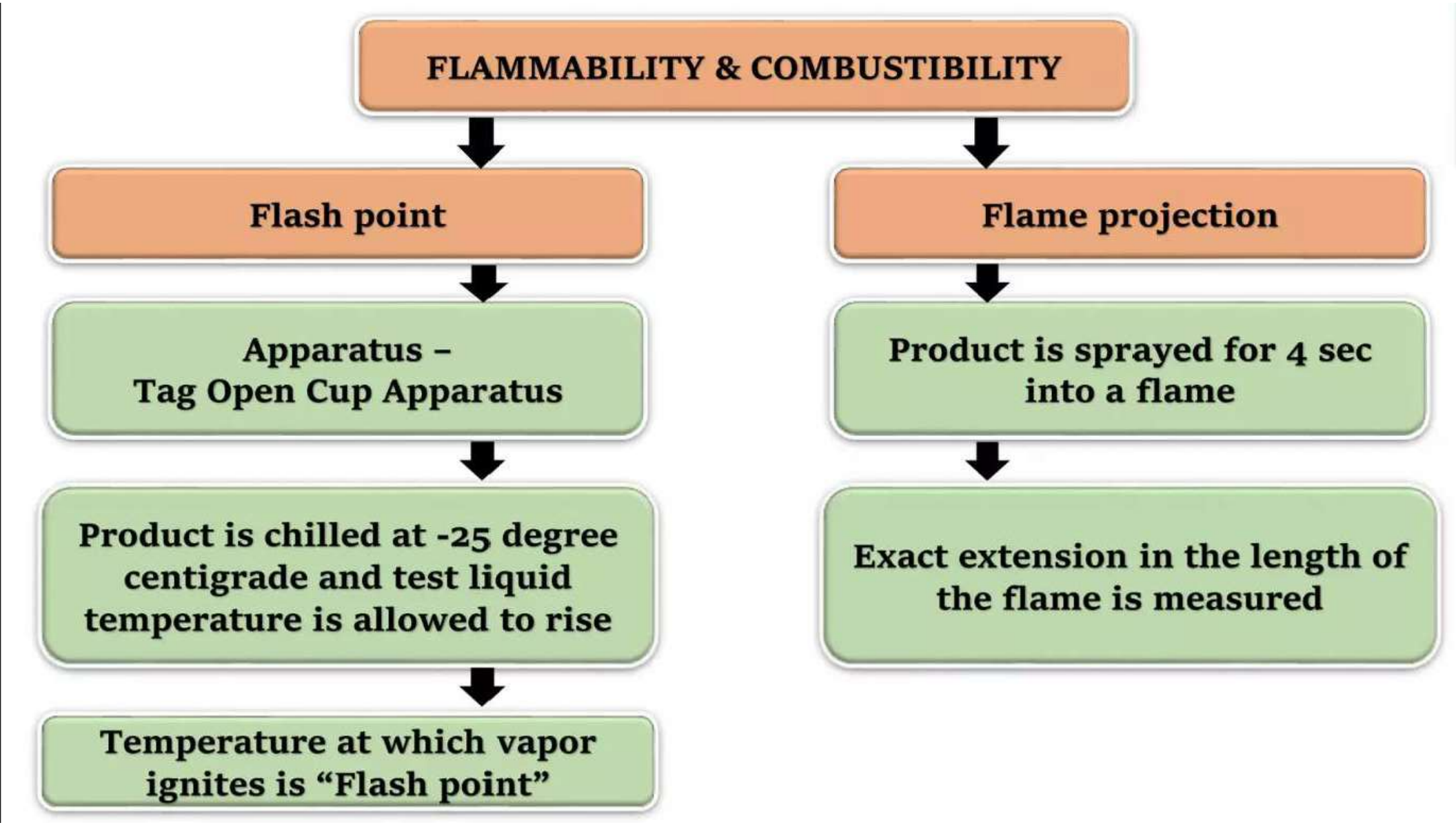
Checking crimping of valve and detect any defects (Crimp's dimension)

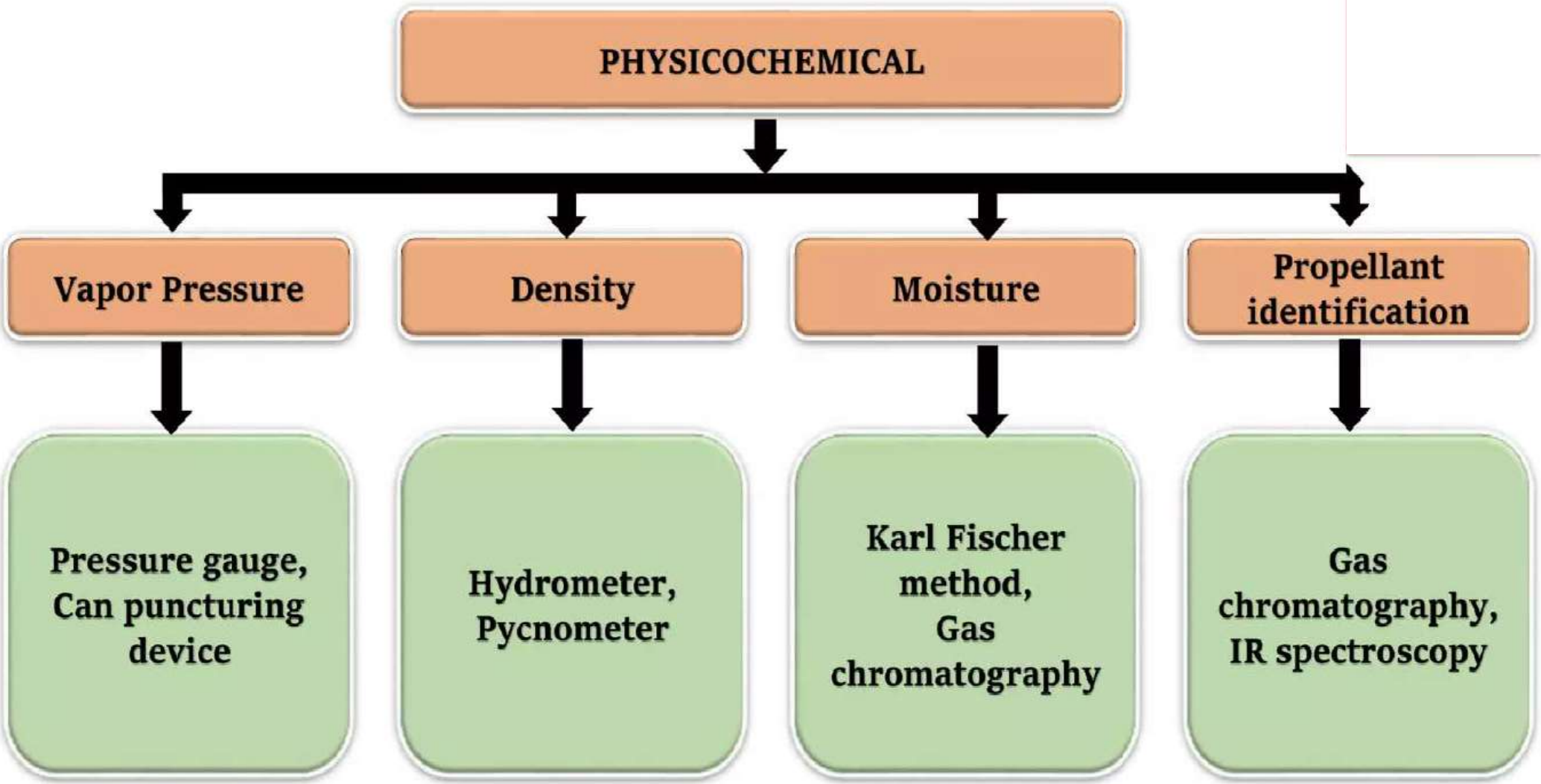
Final testing is done by passing filled containers through water bath

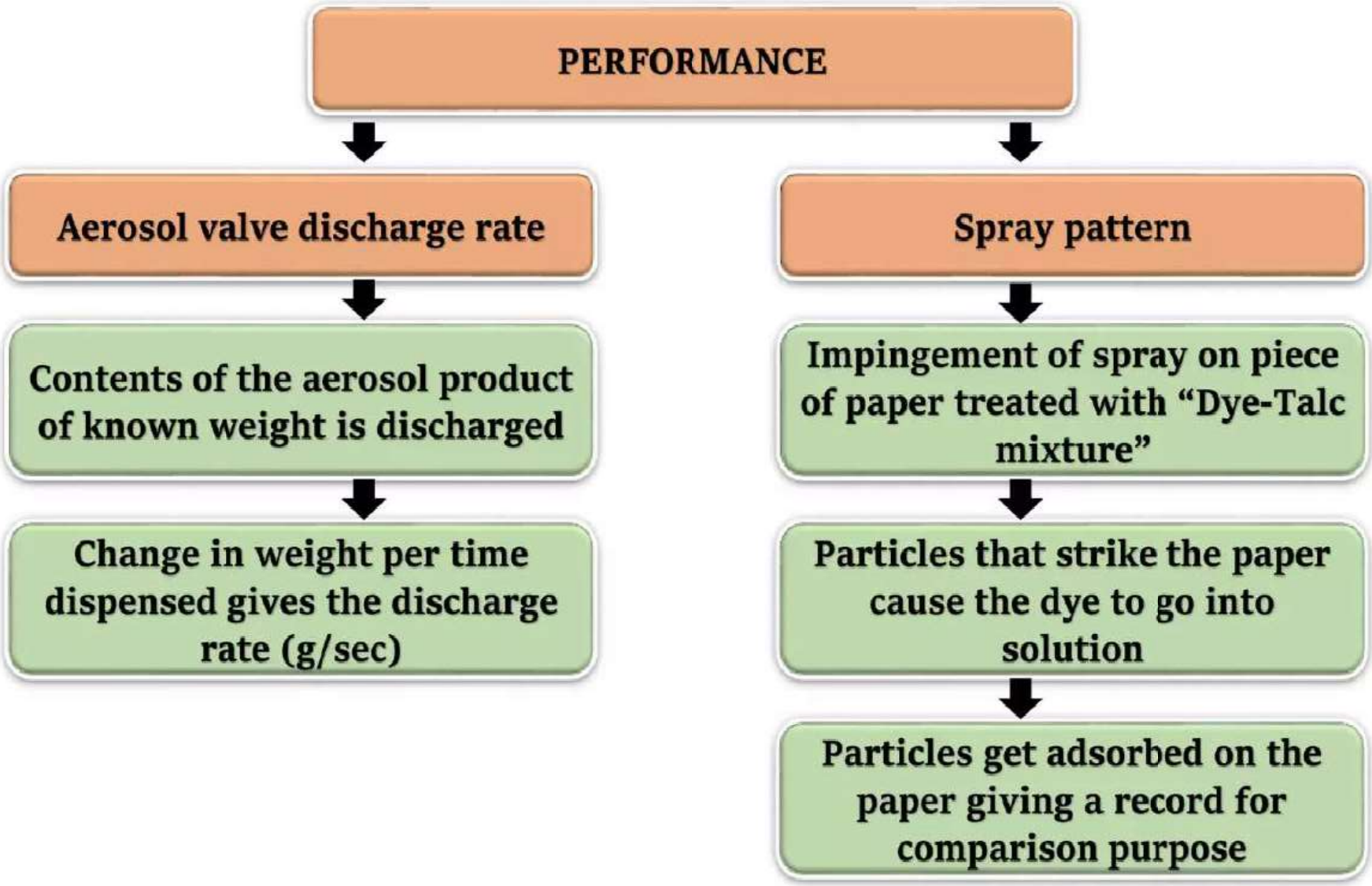
SPRAY TESTING

Most pharmaceutical aerosols are 100% spray tested

This checks for defects in valves and spray patterns


FLAMMABILITY & COMBUSTIBILITY
Flash point
Apparatus –
Tag Open Cup Apparatus
Product is chilled at -25 degree centigrade and test liquid temperature is allowed to rise
Temperature at which vapor ignites is “Flash point”
Flame projection
Product is sprayed for 4 sec into a flame
Exact extension in the length of the flame is measured


PHYSICOCHEMICAL
Vapor Pressure
Density
Moisture
Propellant identification
Pressure gauge, Can puncturing device
Hydrometer, Pycnometer
Karl Fischer method, Gas chromatography
Gas chromatography, IR spectroscopy


PERFORMANCE
Aerosol valve discharge rate
Contents of the aerosol product of known weight is discharged
Change in weight per time dispensed gives the discharge rate (g/sec)
Spray pattern
Impingement of spray on piece of paper treated with "Dye-Talc mixture"
Particles that strike the paper cause the dye to go into solution
Particles get adsorbed on the paper giving a record for comparison purpose

DOSAGE WITH METERED VALVES

↓

Reproducibility of dosage can be determined by -

↓

Assay techniques
Accurate weighing of filled container followed by dispensing of several dose and subsequent weighing

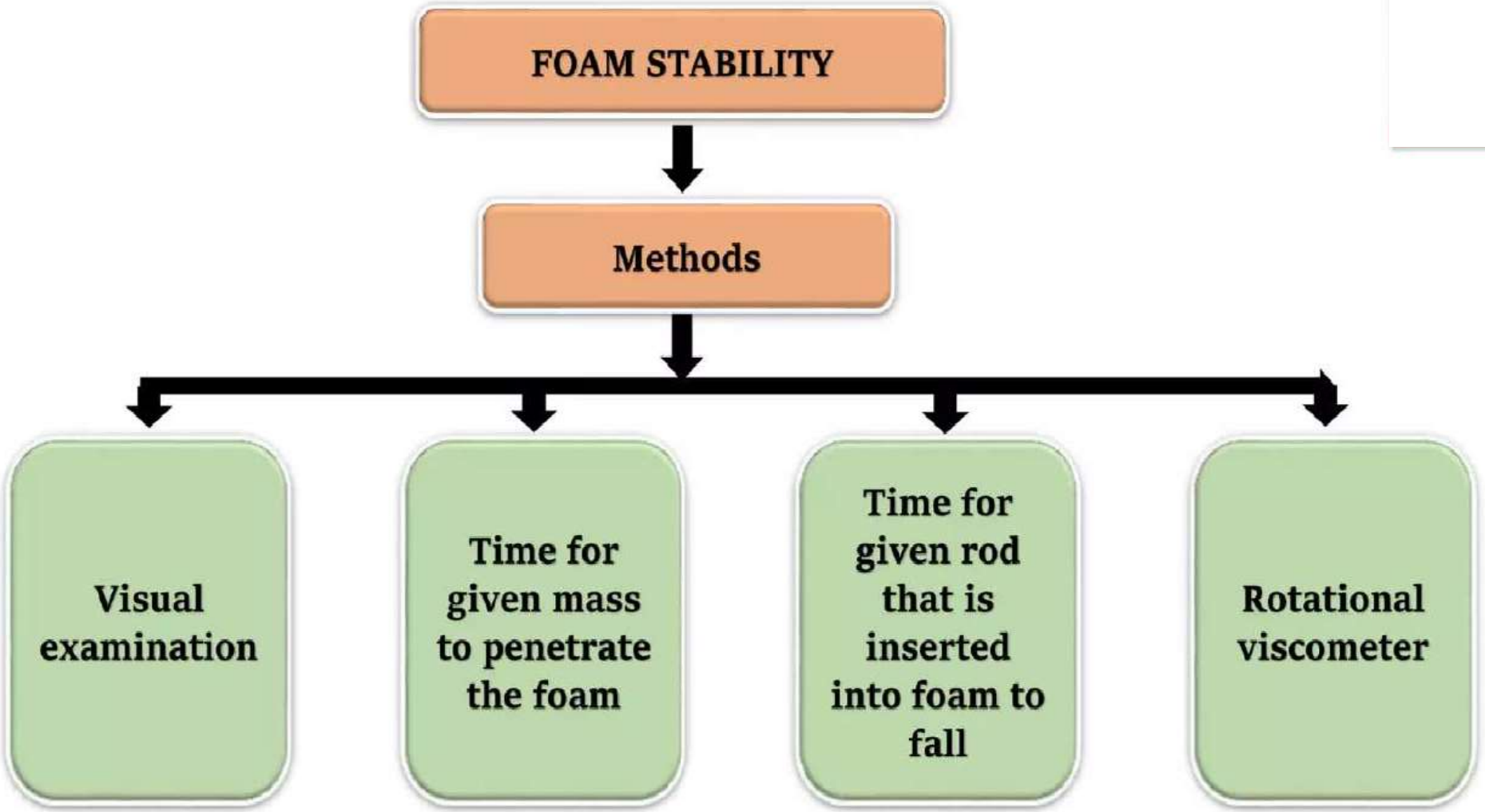
NET CONTENTS

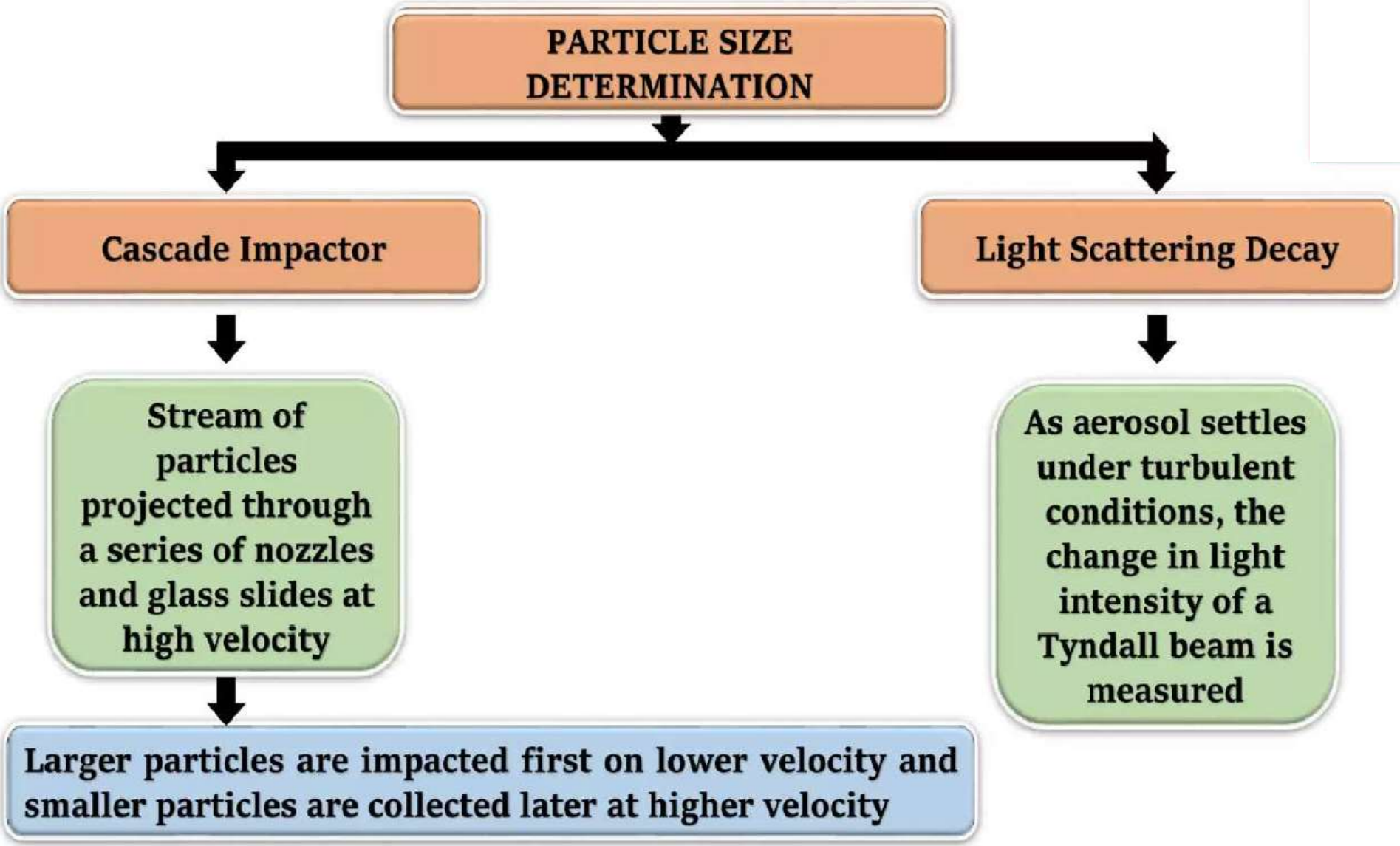
↓

Tared cans weighed and filled in lines and reweighed for difference

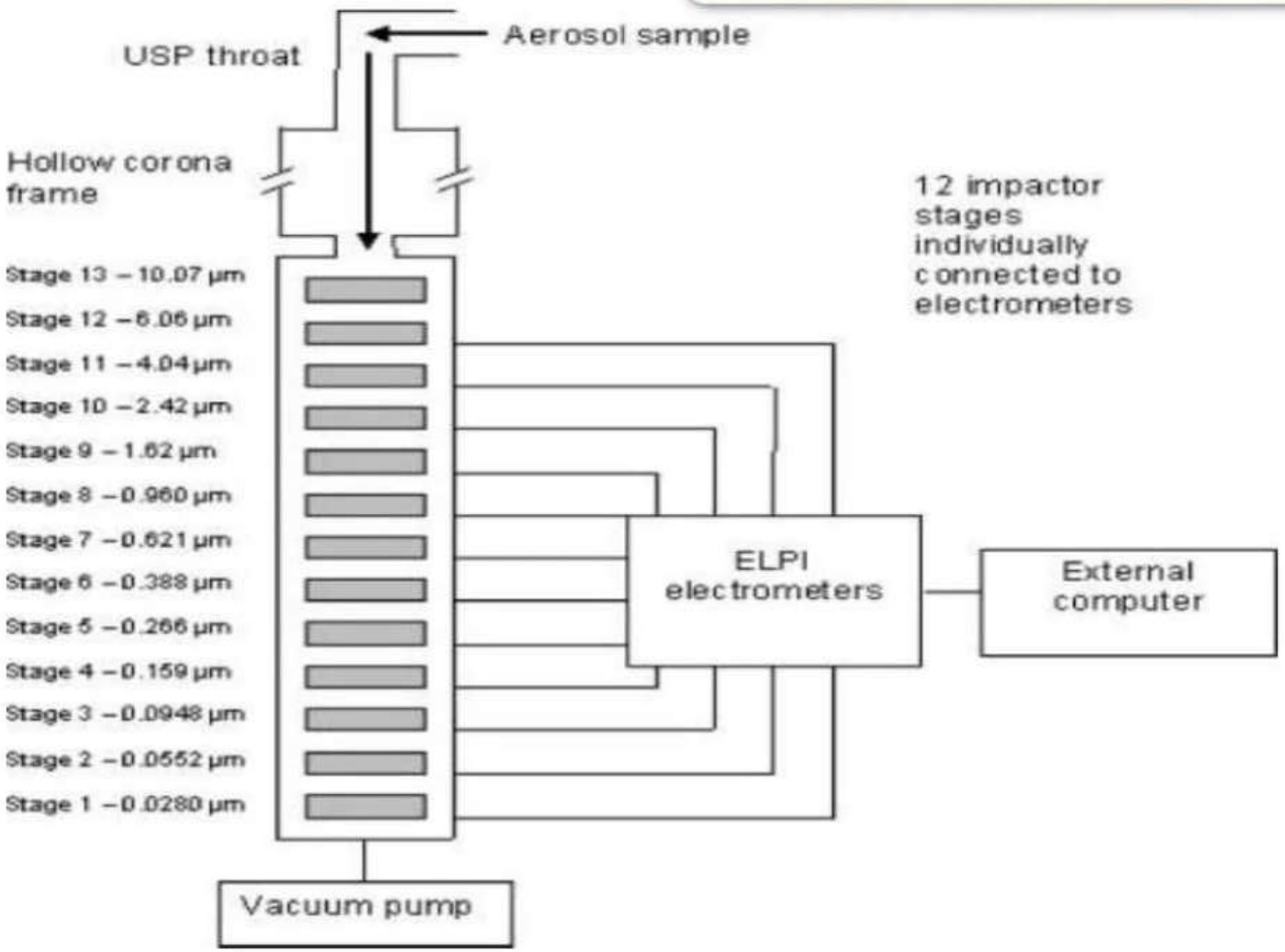
↓

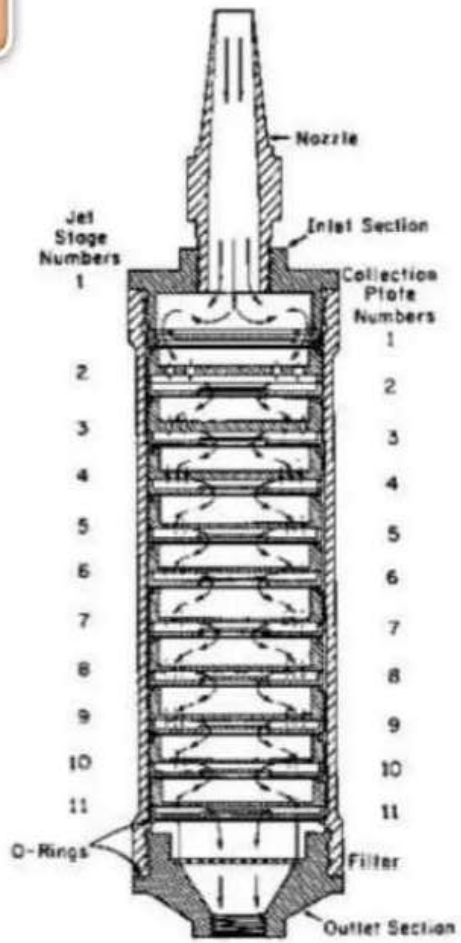
Destructive technique – weighing full container and then dispensing as much content as possible. Contents are weighed to get net content values


FOAM STABILITY
Methods
Visual examination
Time for given mass to penetrate the foam
Time for given rod that is inserted into foam to fall
Rotational viscometer

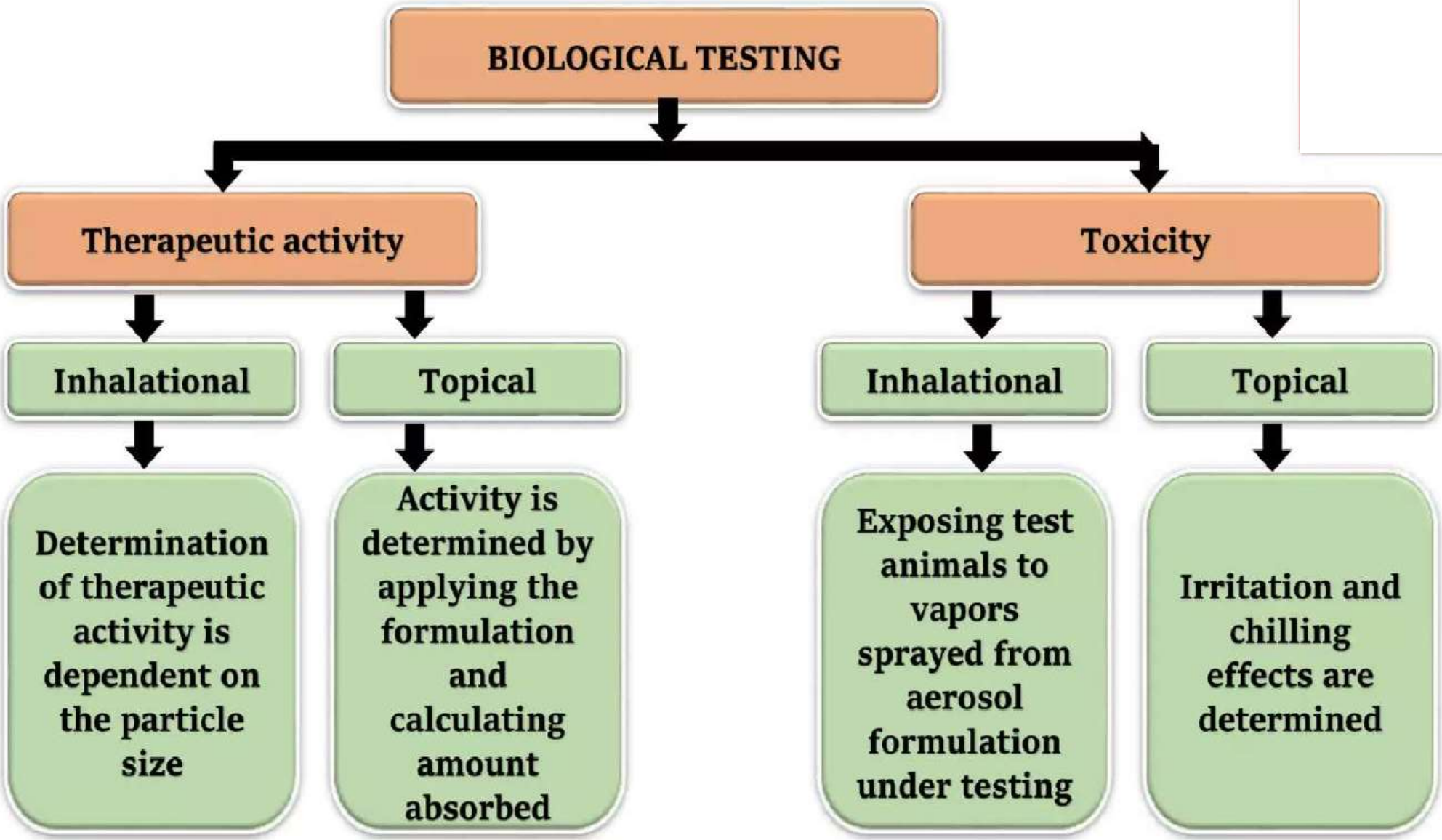

PARTICLE SIZE DETERMINATION
Cascade Impactor
Light Scattering Decay
Stream of particles projected through a series of nozzles and glass slides at high velocity
As aerosol settles under turbulent conditions, the change in light intensity of a Tyndall beam is measured
Larger particles are impacted first on lower velocity and smaller particles are collected later at higher velocity

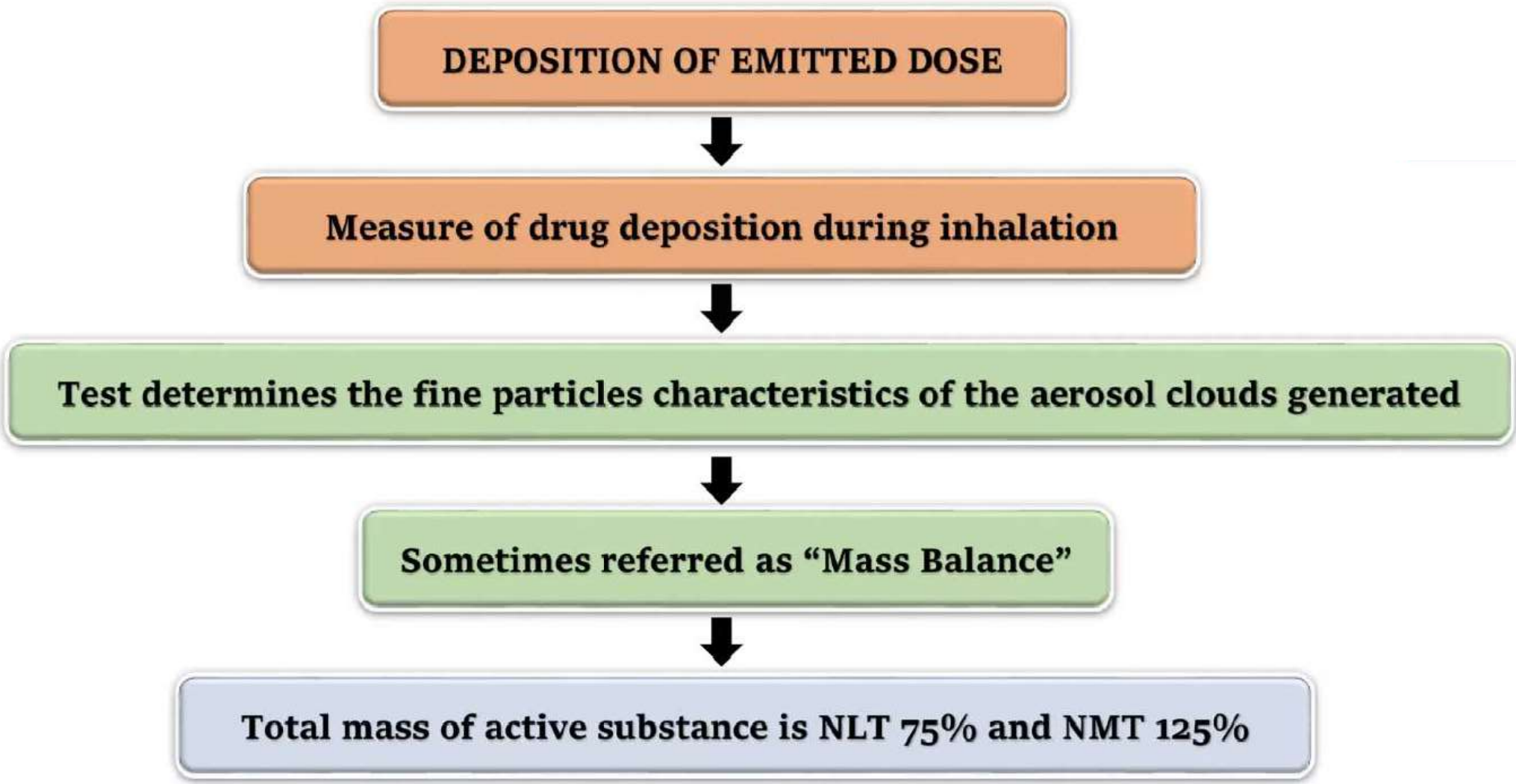
CASCADE IMPACTOR





DESCRIPTION	NUMBER	DIMENSION (microm.)
Stage 0 Nozzle diameter	96	2.55 +/- 0.025
Stage 1 Nozzle diameter	96	1.89 +/- 0.025
Stage 2 Nozzle diameter	400	0.914 +/- 0.0127
Stage 3 Nozzle diameter	400	0.711 +/- 0.0127
Stage 4 Nozzle diameter	400	0.533 +/- 0.0127
Stage 5 Nozzle diameter	400	0.343 +/- 0.0127
Stage 6 Nozzle diameter	400	0.254 +/- 0.0127
Stage 7 Nozzle diameter	201	0.254 +/- 0.0127


BIOLOGICAL TESTING
Therapeutic activity
Toxicity
Inhalational
Topical
Inhalational
Topical
Determination of therapeutic activity is dependent on the particle size
Activity is determined by applying the formulation and calculating amount absorbed
Exposing test animals to vapors sprayed from aerosol formulation under testing
Irritation and chilling effects are determined


DEPOSITION OF EMITTED DOSE
Measure of drug deposition during inhalation
Test determines the fine particles characteristics of the aerosol clouds generated
Sometimes referred as “Mass Balance”
Total mass of active substance is NLT 75% and NMT 125%