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Research Article

EVALUATION OF INHALATION DEVICES: A SYSTEMATIC REGULATORY REVIEW

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A B S T R A C T

Inhalation therapy is the best treatment method for treating respiratory disease mainly used for the treatment for lung disease such as asthma and chronic obstructive pulmonary disease (COPD).A vast number of inhalation devices are known to be used for the treatment dating back from 1,500 B.C.to present and today, each device has its specific features and mechanism of drug delivery with a purpose to deliver. Being responsible for the treatment of world respiratory burden of 500 million it needs to comply with regulatory requirement for the approval of their Quality, Safety and Efficacy of the drug product along with its delivery system as per the International standards. Even, with innovation and awareness in the use and variety of benefits in terms of its delivery medication directly to the effected site to the lungs have resulted in great acceptance and growth among the patients. Also, Proper device selection is crucial as per the severity of patients, clinical expectation and results of inhalation therapy. Several studies with higher citations along with demographical observation providing the estimates of their treatment prevalence are the main basis. Where no. of challenges industry is facing and the upcoming trends in the inhalation market is evaluated. Thus, the quality articles with the overview of the market trends are reviewed highlighting the major finding as result.

INTRODUCTION

Inhalation therapy hasa rich history of ingenuity and inventiveness that has accompanied its development throughout the ages. Our understanding of the engineering, pharmacological, and medical science involved has improved vastly. It has been use in wide variety have so many wide effect. Inhalation therapy ispracticed by various civilizations in Egypt, Greece, India, and People's Republic of China as evidenced with one of the most renowned use of henbane - Opium vapor and other herbs in combination for the treatment of respiratory disorders. Even artifacts are displayed in museums, assuring inhalation therapy as the first used for the breathing problem. At the same time we have now lifted our sights higher, aiming to use inhalation therapy to treat diseases that involve systems other than the lungs.[1]

Inhalation therapy is the best option for lung diseases like asthma, cystic fibrosis, and chronic obstructive pulmonary disease (COPD). These therapies make use of smaller doses and reducesystemic side effects. Pulmonary delivery, as a systemic route of administration offers fast absorption from alveoli and also avoids first pass effect. Inhaled drugs are mainly used in pulmonary diseases such as asthma and chronic obstructive pulmonary disease. [1–6]

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Asthma and COPD ranks as two most common chronic respiratory diseases affecting more than 300 million and 200 million people respectively worldwide. These pulmonary diseases are characterized by chronic inflammation and constriction of the airways. Symptoms include breathlessness, chronic cough, fatigue and wheezing. There is currently no cure for these diseases however; they may be controlled using inhaler medication.[7–15]

Pulmonary Drug Delivery System

Pulmonary drug delivery system has attracted tremendous interest in the past two decades. In order to get both local and systemic effects, lungs as the main part of the respiratory system offer an interesting route to non-invasive drug administration. Inhalation therapy has several advantages over other drug delivery routes; large surface area available in alveolar sacs and high vascularization make the lungs an appropriate site of drug absorption. [7–19]

Advantages of pulmonary drug delivery together with the outstanding attributes of nano scaled systems, such as:

1. Reduced size and increased surface to volume ratio,
2. High drug-loading efficiency, and
3. Efficient absorbance to the lung epithelium and avoidance of pulmonary clearance make inhaled nanoparticles an ideal drug delivery approach.

This provides a brief introduction to pulmonary drug delivery, inhalers, nanoparticles, and the advantages and fate of inhaled nanoparticles.

Advantages of pulmonary drug delivery system[20]

- ❖ It supply drug directly to the blood stream.
- ❖ It mainly provides a non-invasive method of drug delivery.
- ❖ It provide a very furnish action as I.V. route.
- ❖ Deposition of the drug is directly in the lungs so it minimizes the dose requirement and provides a good circulation.
- ❖ As the whole body is not exposed to drug that's why it has negligible side effect.
- ❖ When drug is given through pulmonary route it provides a quick onset of action.

According to WHO report asthma is

- ❖ According to WHO estimates, 235 million people suffer from asthma.
- ❖ Asthma is the most common chronic disease among children.

Types of Inhalation Device

- ❖ Pressurized Metered Dose Inhalers (pMDI)
- ❖ Nasal Sprays (aqueous, powder, and propellant driven)
- ❖ Dry Powder Inhalers (DPI)
- ❖ Nebulizer Solutions and Suspensions.

Pressurized Metered Dose Inhalers (pMDI)

Pressurized metered dose inhaler are the most common inhaler used to treat the respiratory diseases such as asthma, chronic obstructive pulmonary disease and it consist of canister, metering valve, actuator and a mouth piece .

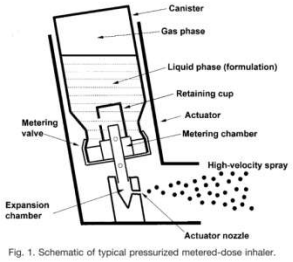


Fig. 1. Schematic of typical pressurized metered-dose inhaler.

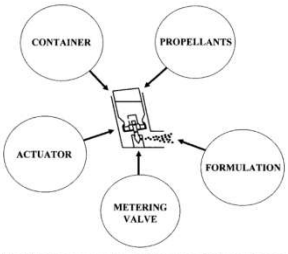
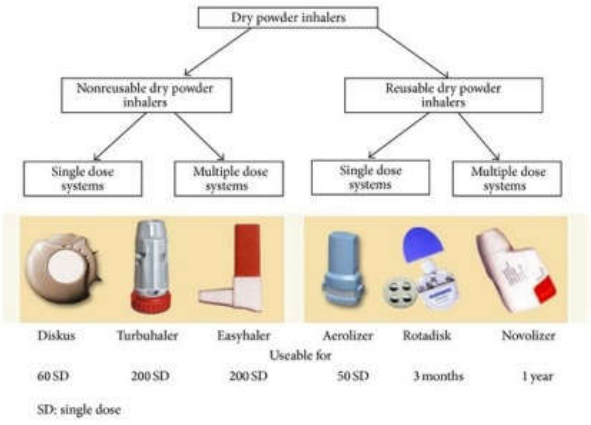


Fig. 2. The key component parts of the pressurized metered-dose inhaler.

Dry Powder Inhalers (DPI)

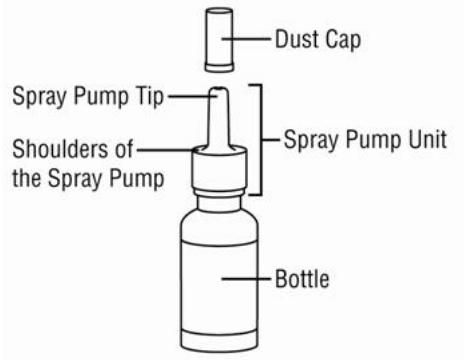
Dry powder inhalers are the portable devices which require minimum patient co-ordination between breathing and actuation of the devices to deliver the powder form medication .These drug formulation are chemically stable than liquid. Efficacy of DPI depends on the powder formulation and on the design of the inhaler devices.

DPI classification: It can be classified as single unit dose, multi-unit dose, multi dose reservoirs .In single dose DPIs, the dose is supplied in individual capsule. Multi- unit dose DPIs can hold multiple doses at the same time without having to be reloaded. Multi-dose reservoir DPIs stores the powder in bulk and they have mechanism to meter individual doses upon actuation. It can be classified as passively-or-actively-actuated devices.



Nasal spray (Soft mist Inhalers)

Nasal spray drug products contain therapeutically active ingredients (drug substances) dissolved or suspended in solutions or mixtures of excipients (e.g., preservatives, viscosity modifiers, emulsifiers, buffering agents) in non-pressurized dispensers that deliver a spray containing a metered dose of the active ingredient. The dose can be metered by the spray pump or could have been pre-metered during manufacture. A nasal spray unit can be designed for unit dosing or can discharge up to several hundred metered sprays of formulation containing the drug substance. Nasal sprays are applied to the nasal cavity for local and/or systemic effects.



Nebulizer

There are two type of neublizer, jet and ultasonicthat differ in forces used to generate aerosal from the liquid. It do not require patient cordination between inhalation and actuation nebulizers generate 1–5 μm droplets. They have the capacity of delivering large doses. Liquid formulation used in neublizer are cheaper and easy to develop compared to formulation in DPI ndpMDI. They are useful for elderly, non concious patient who are unable to use pMDI. Jet neubilizers are mainly based on venturi's principle which states that fluid pressure decreases as its passes through a narrow sectional area. ultrasonicneubilizer, sound waves are mainly created due to vibration of piezoelectric crystals at high frequency, creating crest that break the liquid into small droplets.

Categorization of Devices

Mechanism of Action	Products
Using Aerosols	manual-activated **MDI – Metered Dose Inhaler**, manual-activated MDI with spacer, breath-actuated MDI and soft mist inhaler (**pMDIs – Pressurized Metered Dose Inhaler**, CFC-free inhalers, breath-actuated inhalers, Clenilmodulite, pMDIs + pacer, autohaler, easibreathe, respimat) **Single-dose capsule DPI** (Breezhaler, aerolizer, handihaler)
Using DPI – Dry Powder Inhaler	**Multi-dose DPI with medium resistance:** (accuhaler [Diskus], novolizer, genuair, ellipta) **Multi-dose DPI with medium–high or high resistance** (Turbohaler, Clickhaler, Pulvinal, Twisthaler, easyhaler, Duoresp)

Products Which Are Available In The Market[21]

S.No	Drug Class	Drug/Device(Brand Name)	Dose Available
1.	**pMDIs+**		
	Anticholinergics	Ipratropium bromide (Atrovent) -	21 ug
	b2-adrenergic agonists	Formoterol (Atimos or Foradil1)	12 ug
		Salmeterol (Serevent)	25 ug
		Levalbuterol (r-salbutamol) (Xopenex)	45 ug
	Corticosteroids	Beclomethasone (QVAR)	50 and 100 ug
2.	**BA-pMDIs+**		
	B2- adrenergic agonists	Salbutamol	100ug
	Corticosteroids	Beclomethasone (QVAR)	50 and 100ug
		Formoterolfumarate inhalation solution (Perforomist)	20 mg/2 mL 0.083%
3.	**Nebulisers**	Salbutamol inhalation solution	
	B2- adrenergic agonists	Arformoterol tartrate (r-formoterol)	Vials with 1, 2 and 5
		Levalbuterol (r-salbutamol)	mg/mL-1 15 mg
	Nonsteroidal anti-inflammatories	Metaproterenol sulfate (Alupent)	0.31 mg/3 mL, 0.63 mg/3
		Cromolyn sodium	mL and 1.25 mg/3 mL 0.5,
		Tobramycin inhalation solution 300 mg/5 mL (TOBI)	0.6 and 5% 20 mg 300 mg/5 mL (TOBI)
		Colistin inhalation solution (Promixin)	75mg/2ml
	Corticosteroids		0.25, 0.5 and 1mg
		Aztreonam Inhalation solution(Cayston)	(Pulmicort Capsules)
		Budesonide inhalation suspension	
4.	**Soft mist inhalers**		
	Anticholinergics	Tiotropium bromide	2.5 ug
	Combination	Fenoterol/ipratropium bromide	50/20ug
5.	**DPIs**		
	Aerolizer	Budesonide	200ug
		Formoterol	12ug
	Diskhaler	Beclomethasone	100,200 and 400 ug

Products in Development 2019[22]

S.No.	Product Name	Sponsor	Indication	Development Status
1	APC-4000 (fluticasone dry powder	Adamis Pharmaceuticals San Diego, CA	asthma	Phase II www.adamispharmaceuticals.c
2	**Arcapta® Neohaler® Indacaterol** inhalation powder	Novartis Pharmaceuticals East Hanover, NJ	asthma (pediatric)	Phase II www.novartis.com
3	**Armon Air™ RespiClick®** fluticasone propionate inhalatio	Teva Pharmaceuticals North Wales, PA	asthma (4-11 years old)	Phase III www.tevapharm.com
4	**EmphyClear®** drug free COPD/asthma spray	EmphyCorp Danville, NJ	asthma	Phase II completed www.emphycorp.com
5	**EmphyClear® 70%** 70% lower steroid oral spray	EmphyCorp Danville, NJ	asthma	Phase III www.emphycorp.com
6	PT001 (**glycopyrrolate** inhaled)	AstraZeneca (Pearl Therapeutics) Wilmington, DE	asthma	Phase II/III www.astrazeneca.com
7	PT007 (**salmeterol** metered-dose inhalation)	AstraZeneca (Pearl Therapeutics) Wilmington, DE	asthma	Phase II completed www.astrazeneca.com
8	**Seebri® Neohaler®** glycopyrrolate inhalation	Novartis Pharmaceuticals East Hanover, NJ	asthma	Phase II completed www.novartis.com
9	ARD-3150 (**liposomal ciprofloxacin** inhalation)	Aradigm Hayward, CA	non-cystic fibrosis (CF) bronchiectasis (Fast Track)	application submitted www.aradigm.com
10	**tobramycin** dry-powder inhalation	Novartis Pharmaceuticals East Hanover, NJ	non-CF bronchiectasis	Phase II www.novartis.com
11	CHF 5259 (glycopyrrolate inhalation)	ChiesiFarmaceutici Parma, Italy	COPD	Phase II completed www.chiesi.com
12	PUR0200 (VR410) (tiotropium bromide inhalation)	Pulmatrix Lexington, MAVectura Wiltshire, United Kingdom	COPD	Phase II www.pulmatrix.com www.vectura.com
13	RVT-1601 (sodium cromolicate inhalant)	Respivant Sciences San Diego, CA	chronic cough associated with idiopathic pulmonary fibrosis	Phase II www.nerretherapeutics.com
14	epinephrine nasal spray	INSYS Therapeutics Chandler, AZ	anaphylaxis (Fast Track)	Phase II www.insysrx.com
15	inhaled AAT ORPHAN DRUG	Kamada Rehovot, Israel	alpha-1 antitrypsin lung disease	Phase II completed www.kamada.com
16	**molgramostim** inhalation (inhaled ranulocyte-macrophage colony-stimulating factor) ORPHAN DRUG	Savara Pharmaceuticals Austin, TX	pulmonary alveolar proteinosis	Phase III www.savarapharma.com

Limitation to Aerosol Therapy

Every Inhalation device is not appropriate for all the patients, There are differences in the way the devices perform and the need to master specific inhalation techniques, which require varying levels of cognitive ability depending on the device.[23]

Various Factors defining these are

Particle and patient-related factors that influence aerosol deposition - Aerodynamic diameter is generally thought to be the most important particle-related factor that affects aerosol deposition. Upon enter- ing the oral cavity, particles will deposit by impaction, sedimentation and Brownian motion depending on their size. Particles .5 mm are most likely to deposit by impaction in the oropharynx and be swallowed. Thus, becauseof the inertia associated with the particle's mass, which reduces its ability to follow the airstream when it changes direction toward the lower airways. It is important to minimize corticosteroid deposition in the oropharynx because it can give rise to local side-effects, such as hoarseness and oral candidiasis with ICS.

Lung Disease and Deposition - Degree of lung disease influences the central airway deposition is enhanced as mucus plugging, turbulent airflow and airway obstruction increase.

Drug Receptor - Receptors for inhaled bronchodilators are distributed through- out the lungs, but they have their greatest effect onreceptors in the smooth muscle located in the conducting airways. By targeting these receptors, bronchodilators open up (dilate) the larger airways

Nasal versus Oral Inhalation - Nose is a more effective filter than the mouth. Thus, inhalation through the mouth is the preferred route for aerosol delivery to the lungs.

Patient Behavior and Deposition

Choice of Delivery device

Pharmacokinetic Method

Pharmacokinetic methods are used mainly for estimating the total systemic delivery via the oral and inhaled routes and thus it will provide valuable data which predict extrapulmonary effects. Delivery can be calculated by comparing area under the curve data or urinary drug excretion for inhalation products.

***Gamma Scintigraphy*:** Following methods are used for evaluation[7,8,10,23–28]

a. Two- dimesional gamma scintigraphy
b. SPECT (single photon emission computed tomography)
c. PET (Positron emission tomography)

Regulatory Overview of Inhalation Products in Us And India

Right Regulatory Pathwayin United States

In 2002, FDA established the Office of Combination Products (OCP) to facilitate integration of combination products into the existing regulatory pathways for drugs, devices, and biologics. More specifically, the OCP helps classify combination products to the Center for Biologics Evaluation and Research (CBER), the Center for Drug Evaluation and Research (CDER), or the Center for Devices and Radiological Health

(CDRH) based on the product's **primary mode of action** (PMOA).

The PMOA is defined by the component of the combination product most responsible for treating the product's targeted condition. Sponsors can determine their product's PMOA, and thereby predict which center will have jurisdiction over the product, by characterizing the product's clearest indication and defining the product component primarily responsible for treating that indication. If the PMOA is unclear, a sponsor can petition the OCP to assign its product to a review center through a Request for Designation (RFD), also known as letter of request. In its RFD, a sponsor can suggest how a product should be categorized. The OCP decision is final, and the designated center will regulate all decision-making regarding the approval and risk classification of the product.

Quality Consideration

MDIs and DPIs are combination products (see 21 CFR 3.2(e)).3As drug-device combination products, they are subject to the current good manufacturing practice (CGMP) requirements for drugs and devices (see 21 CFR part 4).[29]
In particular, design controls (21 CFR 820.30) apply to any combination product that includes a device constituent part that is subject to them, including all MDIs and DPIs. Essentially, design control activities confirm that there are no negative interactions between constituent parts, an assure that their combined use results in a combination product that is safe and effective and performs as expected. [30]

Guidance for industry on pharmaceutical development addresses product design and development procedures, reflecting quality by design principles. While quality by design and design controls share similar characteristics and goals, the device Quality System regulation (21 CFR 820) includes specific requirements for design development that manufacturers must satisfy. It may be possible to leverage many aspects of pharmaceutical development as described in ICH 115 Q8 (R2) to achieve compliance with design controls.
For example,

The **Quality Target Product Profile** (QTPP) (see section III.A. below) is similar to "**design inputs**" (21 CFR 820.30(c)), which ensure that design requirements are appropriate to address the intended use of the product.

Studies conducted to verify that the **critical quality attributes** (CQAs) are met in the finished products may also address requirements for design "**verification**" and "**validation**" (21 120 CFR 820.30(f), (g)), which ensure that the product's "design outputs" (21 CFR 820.30(d)) result in a product that safely and effectively meets user needs and achieves its intended effects.

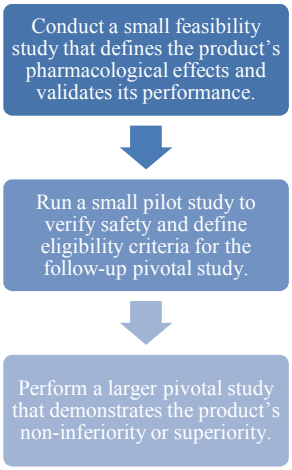
Considerations for Combination product trials

Once the OCP designates a combination product to a center, clinical trials can begin, but the challenges don't stop there.
By their nature, combination products are complex; it can be difficult to classify them and to define their risks. For example, if a drug has achieved past FDA approval, combining it with a medical device can reveal additional benefits and uncover previously unseen risks. An injection device, for instance, may help a patient deliver the correct dose of a drug, but if the device experiences a glitch, it may over- or under-deliver the drug, creating a hazard for the patient. Consequently, regardless of the regulatory status of the individual components, FDA treats combination products as entirely new. A sponsor, therefore, must start from scratch with safety and efficacy testing.

Sponsors of combination products may feel intimidated by the regulatory hurdles facing them, and no task may be more challenging than the process of collecting the right data to achieve regulatory clearance. A three-step approach for combination product clinical trials can help sponsors streamline the data collection process and move a product ahead to market.

This approach is optimized for products that combine a drug or biologic with a delivery device. It concentrates on collecting sound **bioavailability (BA) and bioequivalence (BE) data**: two metrics that will likely change when a drug or biologic is delivered via a new device.

The three-step approach to clinical trials for combination products is:[31]



Step one: Conduct a small feasibility study

If a drug or biologic is delivered via a new device, its BA (the proportion of the dose that reaches circulation) and BE (its pharmacokinetic similarity to other drugs), might change. These changes could affect the drug or biologic's safety and efficacy. Consequently, even if the drug or biologic itself has not changed, sponsors must demonstrate that the new delivery method has not altered these measures**.**

Step two: Run a small pilot study

After a sponsor demonstrates the BA and BE of its combination product, it needs to begin testing the product's safety and efficacy against a previously cleared product, or the current standard of care.

Role of Sponsor

A sponsor should run a prospective, two-arm, controlled study that is at least partially blinded. One cohort of patients should receive the drug or biologic on its own, and the other cohort should receive treatment with the combination product. This pilot study should use approximately 50 patients to verify the safety of the combination product and confirm the eligibility criteria for the study before the sponsor continues with the larger pivotal trial.

Step three: Execute a large pivotal study

Once the sponsor confirms its combination product's safety and finalizes its eligibility criteria, it should be ready to perform the third step, a pivotal study that enables it to observe a larger population over a longer period.

A sponsor Should base its Pivotal trial's size on the properties of the Combination Product itself

- The sponsor needs to consider the PMOA,
- The intended use,
- The adverse effects it produces and the frequency at which they occur, and
- Its efficacy compared to the standard of care.

If a sponsor's only intention is to demonstrate its product's BE, it will only need to run a small, non-inferiority study. A standard non-inferiority trial for combination products requires a double-blind, two-arm study design, similar to the initial pilot study. A study like this would be used to show that the combination product is as safe, and no less efficacious, than the standard of care.

Superiority studies are not typically necessary, as FDA usually only requires a product demonstrate "substantial equivalence," or non-inferiority, to the standard of care. But unlike FDA, the Centers for Medicare & Medicaid Services (CMS), which is the agency responsible for issuing new reimbursement codes, requires that sponsors run superiority trials on combination products. If the sponsor intends to demonstrate that its product is superior to predicate products, it must run a much larger study.

A superiority trial requires a larger, two- or three-arm design, aimed at demonstrating the combination product's superior efficacy versus a competitor product or standard of care. These trials are larger because the difference needs to be substantial, which requires more statistical power.

Superiority studies are also more complex; CMS not only demands a stronger effect, but also needs to see that the product has a positive impact on the healthcare market. More specifically, CMS requires that the combination product's safety and efficacy are both superior to the standard of care, and that the product use will reduce the overall cost of care.
These trials are typically more expensive due to larger patient numbers and the need to collect more data than the typical non-inferiority trial. These data make it easier to compare costs between the use of the combination product and the competitor.

Superiority trials also take longer to complete, as sponsors need to demonstrate the long-term safety and effectiveness of combination products on patients' health. Sponsors usually seek regulatory clearance from FDA, the European Medicines Agency, or both, and then use patient registries to perform the long-term safety and effectiveness research that CMS requires. For these studies, sponsors should seek coordinated CMS and FDA approval for their combination products.

Many sponsors run their pivotal trials outside of the United States, but these trials require additional oversight. Most importantly, sponsors must ensure that their trials all conform to FDA regulations. FDA will accept data collected in Europe as part of an evidence package for approval; however, sponsors must ensure that, for their product's specific treatment indication, its trials meet the FDA's rigorous standards for clinical practice. Therefore, sponsors should understand the details of each country's and region's clinical practices and choose sites that will operate in accordance with FDA standards.

Regulatory Approval Pathway

Depending upon the type of drug, whether it is to be considered under the New Drug(ND) or Abbreviated New Drug application (AND) –Form 356h is filed with the detailed information to suffice the application.[32]

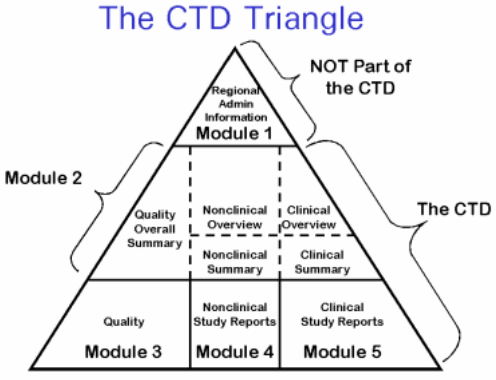
In the US, a generic drug product should be shown therapeutic equivalent to a designated Reference Listed Drug (RLD). To obtain approval of generic drug products we should have to file Abbreviated New Drug Application (ANDA) which is submitted to the US Food and Drug Administrations (FDA) Office of Generic Drugs (OGD) should contain data pharmaceutical equivalence [per 21 CFR 320.1 (c)] and bioequivalence [per 21 CFR] and bio-equivalence [per 21 CFR 320.1 (E)] of the proposed generic products to the designated RLD.[33]

FDA developed an *aggregate weight-of-evidence* approach, which utilizes

1) *in vitro* studies, 2) pharmacokinetic studies, and 3) pharmaco-dynamic or clinical endpoint studies . FDA publish its first product- specific recommendation for a pMDIand a DPI in April and September 2013

Along with the above detailed guidelines, complete documents are to be submitted for approval through electronic submission in a format of Common Technical Dossier (CTD) as per the ICH – CTD guidelines including all of the modules in format, and proper fees submission as per Generic Drug User Fees Act, GDUFA. [34]

Proper application is filed through form 356 h – with proper trail of administrative documents is prepared and maintained, which might be inspected by the FDA surprise visit with their cGMP records and practices.



The top selling products in USA

Product Name	Company	Sales (Mn $)
Xolair	Roche	1748
Dupixent	Sanofi	844
Fasevra	Astra Zenica	808
Nucala	GSK	605
QAW039	Novartis	486
BreoEllipta	GSK	389
Ventrolin HFA	GSK	356
Tezepelumab	Astra Zenica	326
Flovent	GSK	308
Aerospan	MYLAN	285

Regulatory System in India

Thelegislation of the India governing drug registration, import, manufacture, distribution and sale in India is contained in the Drug and cosmetic Act of 1940 and Drug and Cosmetic of 1945. Central Drug Standard Control Organization (CDSCO), and the office of its controller, the Drug Control General of India (DCGI) is also established by this body of legislation. The CDSCO has six zonal, four sub zonal and eleven port/airport offices, and six laboratories to carry out its activity. DCGI has not specifically issued guidelines to assess the efficacy and safety of orally inhaled product.

Generic drug application must adhere to the "Guidelines for bioavailability and bioequivalence studies" issued by the CDSCO. In India all trial are regulated by guidelines/rules such as Rule 122 A to E of Drug and Cosmetic Act, Schedule'y' of Drug and Cosmetic and rules there under (Amended in 2005). The Union Ministry for Health and Family Welfare has notified the Drugs and Clinical Trials Rules, 2019 with an aim to promote clinical research in the country. CDSCO also issued guidelines for Good Clinical Practice and Ethical Guidelines for Biomedical Research on Human Subjects. This following category is very much relevant when determining the regulatory path for registering a second-entry orally inhaled product in India.[35,36]

Similarly, approval process is much in compliance with electronic submission, eCTD format processed online through regional office Portal, i.e. SUGAM with proper tracking of the status making it more align with global standards.[34]

Top Selling Products in India

Products	Company	Price In Rs
Budecort	CIPLA	321
Asthalin	CIPLA	129
Duolin	CIPLA	173
Levolin	CIPLA	300
Foracort	CIPLA	52
SeretideEvohaler	GSK	500

The Oral Tablets Which are mostly used in India are

1. Deriphylline
2. Monteleukast
3. Asthalin
4. Montair

Challenges

Nebulizer

All of the nebulizers performance available in the marketvaries from manufacturer to manufacturer. Drug delivery is largely dependent on the rate of nebulization and greatly affected by particle size. The physicochemical properties of the formulation such as viscosity, ionic strength, osmolality, pH, and surface tension affect the performance of nebulizer. Inhalation through nebulization may induce bronchoconstriction, coughing and irritation of the lung mucosa at low pH, or at hyper- or hypo-osmolality of the formulation. High drug concentrations can affect the drug output with some nebulizers, e.g. colomycin at concentrations >75 mg/ml foams in all nebulizers, making aerosolization of the drug very inefficient. [37]

pMDI

The effectiveness and efficiency of an MDI depend on a patient's breathing pattern, inspiratory flow rate and hand-mouth coordination. For an effective delivery of drug and prevention of oropharyngeal loss through pMDI, it requires spacers or holding chambers or valve holding chambers (VHC) in clinical practice. Use of improper technique can decrease drug delivery eventually loss of dose. The reasons for decreased drug delivery through pMDI can be due to electrostatic charge, inhalation before actuation, multiple actuations into the device, or delay between actuation and inhaling the dose. Lack of a proper mask fit, a spacer volume greater than tidal volume is considered problematic for children.[38]

DPI

The delivery efficiency of a DPI depends on the intrinsic resistance of patients breathing pattern, exposure of powder material to moisture and the particle size. Intrinsic resistance - as they are inspiratory flow-driven inhalers, patient's inspiratory effort plays a crucial role in deaggregation of powder into finer particles. This type of delivery may not be suitable for very young population and patients suffering from chronic obstructive pulmonary disease as they may not be able to generate an adequate inspiratory flow.

Exposure to humidity - the flow properties of aerosolized powders in a DPI system are affected by humidity and moisture. This can cause powder clogging and problem in fine-particle development during inhalation, so they must be kept dry.

Particle engineering - most important factor involved in evaluating DPI performance is the engineering of particle size. In a review, Staniforth explained the Pascal system. This is an example of improved DPI system with carrier formulation technology. It uses a novel single step process called as Corrasion. In this process, mixing and surface modifications of mixtures of αLactose monohydrate and amino acid L-leucine take place simultaneously, and thereby produces a powder formulation that delivers accurate, uniform and efficient doses of the drug .[39]

Medspray's inhalers and sprays are the next generation inhalers, under clinical study, aims to generate aerosols with a narrow distributed particle size of micro and nanotechnology. It is designed to aim for more efficacious and simple aerosol delivery of drugs to the specific targeted sites with improved patient compliance.

Importance of Patient's Breathing Pattern in Inhalation Therapy

The design of inhalation system and patient respiratory effort play a key role to maximize drug uptake into lungs. Incorrect inhaler technique and poor device technology lead to inhaler misuse. Age and illness of the patient are the determinants of affectivity of inhalation system. The variation in deposition varies from 20% to 95% with a standard inhalation device. Long period of treatment increases the chances of patient's noncompliance and dose-related toxicity. Hence, breathing pattern should be controlled to ensure adequate, effective and quick therapy.[40]

Medical personnel should train the patient at the time of initiation of therapy. For the aerosol system patients are

advised to take an initial deep breath and holding of breath for 10 s to allow the settlement of the particles in the deep pulmonary region. In case of pMDIs addition of spacer can help in coordination between actuation of the device and patient inhalation by slowing the velocity and reduction in particle size. Similarly, a VHC for pMDI system opens easily with patient's inspiratory effort through one-way opening of the valve. However, improper techniques, multiple actuations, inhaling before actuating the pMDI system may decrease drug delivery through spacer and VHC.

Recent development of AKITA technology aims in individualization and controlled inhalation with popular nebulizers using a smart card to ensure consistent and optimal dosing.

CONCLUSION

Pulmonary administration through inhalation technique has become an attractive route of drug delivery to treat chronic and severe disease conditions with target specificity, economic utilization of drug and toxicity-limiting point of view. It also avoids problems associated with intravenous delivery. To maximize drug concentration at the site of action and to improve the drug efficacy, the therapeutic agent is made to localize in the airways during the inhalation therapy. Hence, the particle diameter and its aerodynamic velocity play a crucial role. It has been reported that targeting drug through nanoparticles reduces chances of resistance of antibiotics. [41–45]

To achieve success in inhalation therapy through a harmonic interaction with breathing and inhaler mechanism patient should be trained properly. Recent advancement in pulmonary drug delivery has been achieved by introduction of new particle engineering technologies through spray drying, freeze drying, spray freeze drying, use of biodegradable polymers and binding of drug formulations with specific ligands for effective site-specific lung targeting.[46–48]

The structure and design of inhaler play a major role on the aerosol deposition to the lungs. An ideal inhaler should deliver precise and consistent doses to the targeted region of the lungs keeping the stability of the formulation throughout its shelf-life. In the development of new inhalation medications, consideration must be given to the formulation ingredients to ensure chemically stability, non-irritability with improved bioavailability of the formulation. It should also be compatible with a suitable metering system to produce a convenient device that is comfortable and easy to use by the patient.

Hence, the inhaler drug combination should serve as a one in all, compact, single medication for effective use, of which the in vitro performance and in vivo efficacy must be demonstrated.

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