Overview of Regulatory Landscape for Inhaled Biologics

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Inhaled Biologics: Preparing for a Future Beyond Small Molecules

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Outline

1. Diversity of regulatory pathways for inhaled biologics
2. Inhalation biologics are complex products
3. Regulatory guidance specific to inhaled biologics is limited
4. Points to consider for inhaled biologic products
5. Take aways

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Diversity of regulatory pathways for inhaled biologics

Regulatory Definition of a Biologic

- FDA: PHS Act, A virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, **protein**, or analogous product…applicable to the prevention, treatment, or cure of a disease or condition of human beings.
- EMA: A biological medicinal product is a medicinal product whose active substance is made by or derived from a living organism
- WHO: Class of medicines which are grown and then purified from large scale cell cultures which includes vaccines, growth factors, immune modulators, monoclonal antibodies, blood- and plasma-derived products. Biological therapeutics are regulated, tested, and controlled differently than other medicines
- Canada: Class of drugs derived through the metabolism of living organisms rather than being synthesized by chemical reactions
- Japan: Under Pharmaceutical affairs Law: Products including ingredients derived from human or biological (excluding plants) source materials (cell, tissue, blood, etc)
- China: Products derived from biotechnology to prevent, treat and diagnose human disease from microorganism, cells, animals or human derived tissues and bodily fluids

Inhaled biologic format can add to regulatory complexity

- Drug product can be protein, gene, peptide, cell, virus
- A delivery system is necessary: nebulizer, metered propellant, dry powder inhaler (DPI)
- Drug product format may be powder, liquid
- Inhalation device types may come in many flavors: MDI, PMDI, IDP, SMI
- Depending on the drug/device interface chosen, different regulatory pathways may be indicated (a drug/device combination product may be regulated separately or as a combination)
- Regional regulatory requirements can add to complexities in global regulatory strategy (e.g., protein review outcomes from Germany BfArM and PEI can differ significantly, Europe requires a 3rd party Notified Opinion outcome for devices)

FDA: size-dependent regulatory pathway on protein/peptide

As of 2020, the Biologics Price Competition and Innovation (BPCI) Act requires that all biological products, including synthetic proteins made of more than 40 amino acids be submitted for marketing approval through a BLA under Section 351 of the PHS Act.

Responsibilities for Quality Assessments of Products Containing Peptide or Protein Drug Substances

Size (Expressed in Number of Amino Acids)	Submission Type[a]	Responsible OPQ Suboffice[b]
≤40	IND	ONDP
	Treatment IND or treatment protocol	ONDP and OPMA
	Original NDA	ONDP and OPMA
	Supplement to approved NDA	OLDP and OPMA
	EUA	ONDP and OPMA
≥41	IND	OBP
	Treatment IND or treatment protocol	OBP and OPMA/DBM
	Original BLA	OBP and OPMA/DBM
	Supplement to approved BLA	OBP and OPMA/DBM
	EUA	OBP and OPMA/DBM

[a] Submission types include amendments.
[b] Assignments also apply to meetings that occur under respective submission types.

MAPP 5016.3 Rev.1

OBP has been reorganized as OPQ III since 2024

Regulation differences for product and device

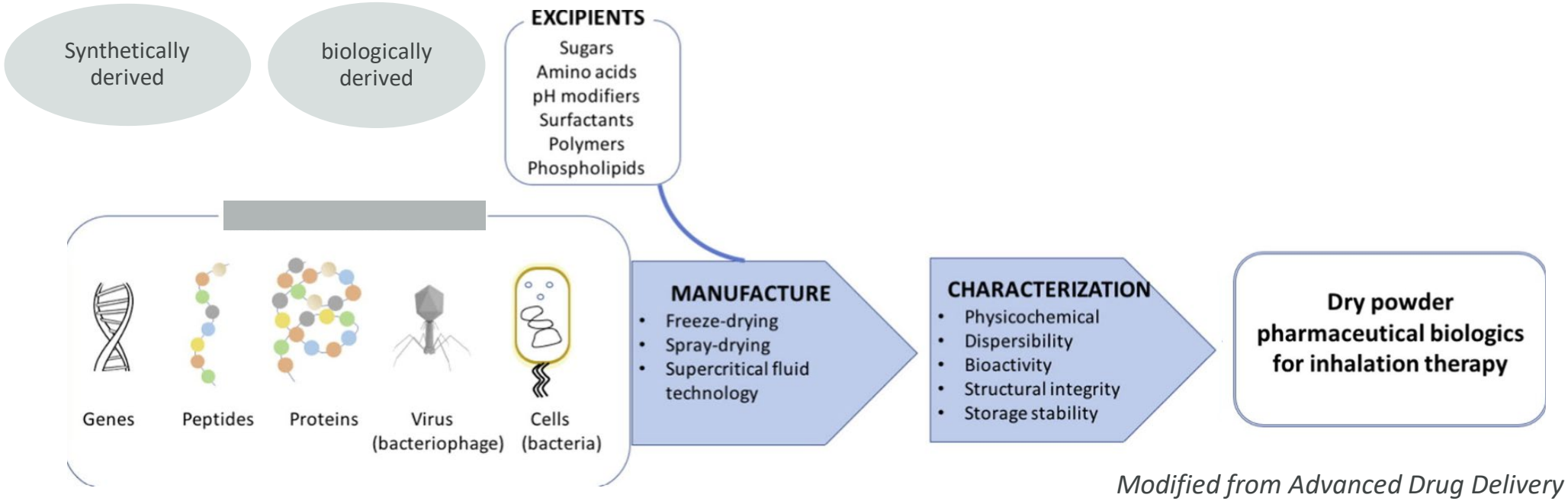
Drug product integral within device

- Nearly all health authorities regulate primarily as drug product
- Single investigational and marketing applications permitted

Drug product and device are not integral

- Nearly all health authorities regulate as two separate components (device and drug)
- Some regions require separate investigational and marketing applications

Inhaled proteins may be regulated/reviewed by different review groups in US



Modified from Advanced Drug Delivery Reviews 2021 vol 172

CBER BLA
CDER BLA
CDRH 510(k)

CDER NDA
CDRH 510(k)

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Inhaled biologics are complex products

Biologics require complex control strategies

- Proteins are more labile. Their quality profile can be impacted by the manufacturing process (both DS and DP), the storage conditions, transport, device and user handling.
- Extensive characterization studies are required to identify potential critical quality attributes (CQA)
- Safety (e.g., immunogenicity) and efficacy (e.g., clearance) can be specific to the route of administration, indication and patient population (e.g., immunocompromised)
- A global supply chain requires a robust stability program to support storage and transport conditions (e.g., zone temperatures)
- Immunogenicity is one key concern for biologics. Some routes of administration may lead to increased immunogenicity for a given product. In general, the inhalation route is considered more immunogenic: IV < SC < inhalation.

The quality of an inhaled biologic can be impacted by multiple factors

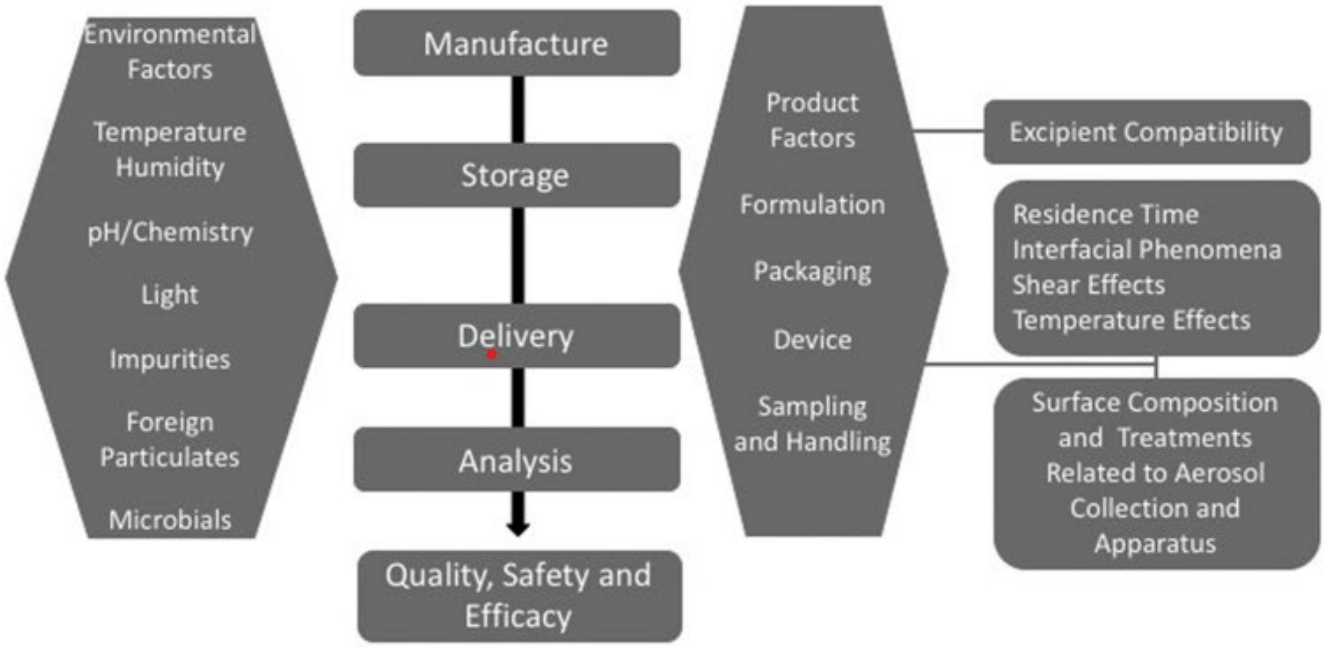
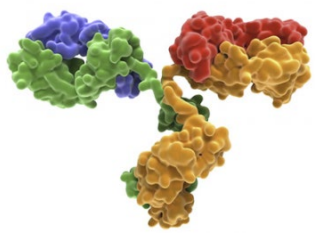


Figure 2. Environmental and product factors that contribute to the quality and performance of inhaled monoclonal antibodies that are uses to assure efficacy and safety outcomes.

Human Vaccines & Immunotherapeutics 2022 Vol18 (2)

A holistic approach should be used to the establishment of the desired product quality- Powder filled capsules example

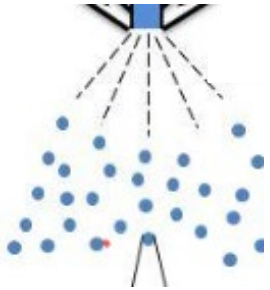
Liquid/Frozen



- 1º structure
- 2º structure
- 3º/4º structure
- Glycosylation
- Activity
- Effector function

- Purity
- Impurities
- Potency
- Microbiology
- Stability

Spray dried powder



- Fine particle mass
- Delivered dose uniformity
- Particle size distribution
- Moisture

- Performance
- Moisture content
- Purity
- Impurities
- Potency
- Microbiology
- Stability

Encapsulated powder

- Physical attributes
- Content uniformity
- Foreign particulate matter

- Appearance
- Performance
- Moisture content
- Purity
- Impurities
- Potency
- Microbiology
- Stability

Device as powder propellant

- Physical attributes
- Average delivered dose
- Delivered dose uniformity
- Aerodynamic particle size distribution

- Appearance
- Performance
- Moisture content
- Purity
- Impurities
- Potency
- Microbiology
- Stability
- L/E

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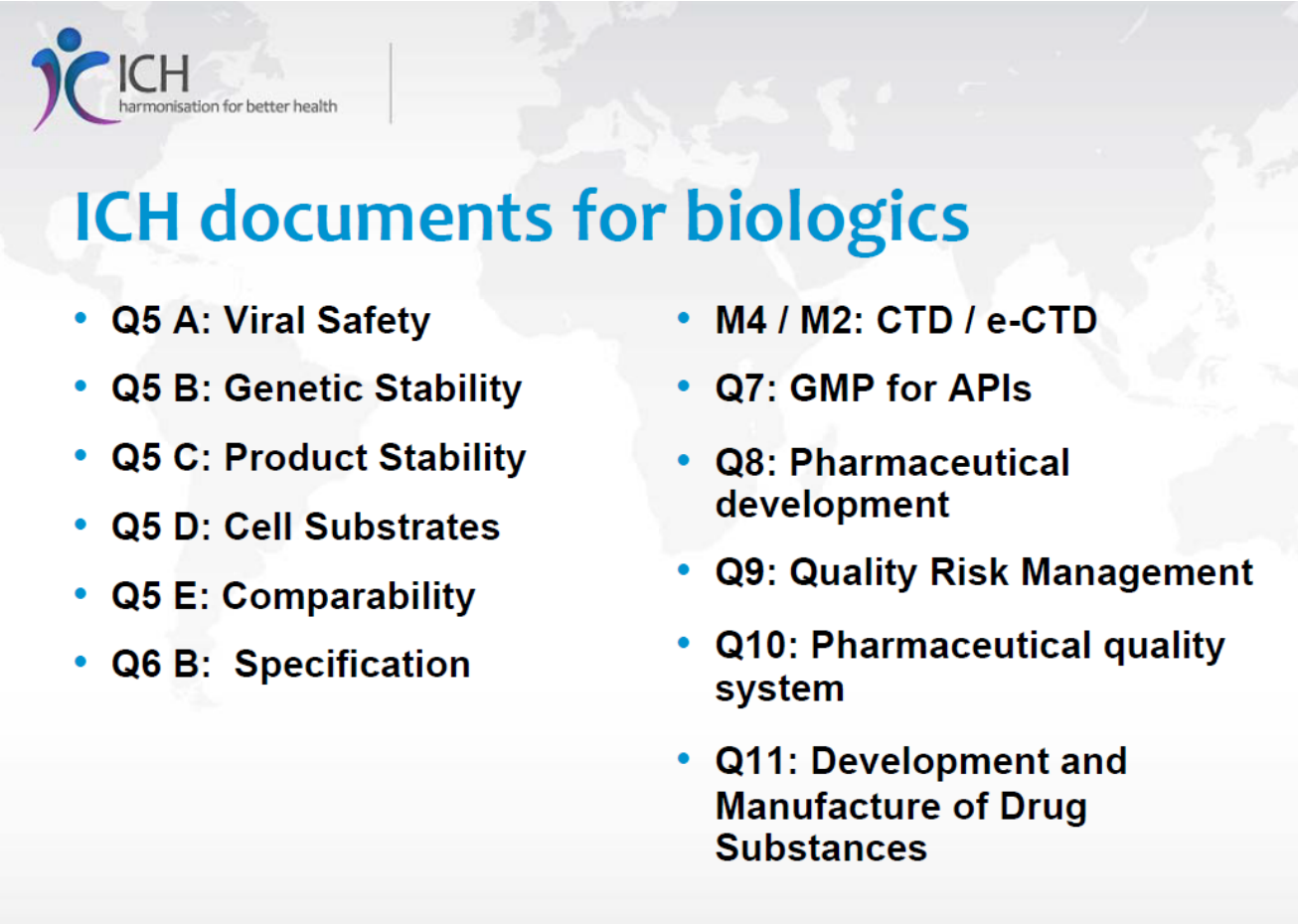
Regulatory guidance specific to inhaled biologics is limited

Guidance specific to inhaled biologics is limited

ICH Quality Documents



Development

- 2022 EMA/CHMP/BWP/534898/2008 rev.2 corr. Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials

Guidance specific to inhaled biologics is limited

Drug/Device/Inhalation

- EMEA/CHMP/QWP/Corr: Guideline on the pharmaceutical quality of inhalation and nasal products 2006 (*in review*)
- FDA Draft Guidance April 2018: Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Products - Quality Considerations
- FDA Draft Guidance June 2024 Essential drug delivery outputs for devices intended to deliver drugs and biological products

Drug/Device/Inhalation

- CPMP/EWP/4151/00 rev 1 Requirements for clinical documentation for orally inhaled products (OIP) including the requirements for demonstration of therapeutic equivalence between two inhaled products for use in the treatment of Asthma and Chronic Obstructive Pulmonary Disease (COPD)
- Draft guideline on the requirements for demonstrating therapeutic equivalence between orally inhaled products (OIP) for asthma and chronic obstructive pulmonary disease (COPD)

Drug/Device/Inhalation

- FDA Draft Guidance Bridging for Drug-Device and Biologic-Device Combination Products 2019
- Quality documentation for medicinal products when used with a medical device (2/07/2021) EMA/CHMP/QWP/BWP/259 165/2019

Guidance specific to inhaled biologics is limited

- Inhaled biologics combine additional considerations during development to support commercialization (e.g., spray dried powder and device performance) that are not specifically addressed in current guidance
  - Aggregation is a common phenomenon in liquid protein preparations. Protein aggregation has been extensively studied for IV and SC administrations because of the potential for immunogenicity. Yet, there is limited experience on aggregate characterization for powders using the inhalation route. Guidance on acceptable levels of protein aggregates and particles is lacking.
- Drug product formulation (e.g., to enhance powder performance) can provide exceptional stability to the inhaled biologic.
  - Such product formulation may require the use of novel excipients. Approaches to the qualification of novel excipients may warrant consultation with regulatory agencies to obtain specific guidance.

The inhaled biologics space in clinical development is growing

Inhaled biologics in the clinic

Table 1
Overview of clinical trials with inhaled biologics (A, active; I, enrollment by invitation; NR, not yet recruiting; R, recruiting).

Type of biologic	NCT Number	Title	Status	Condition(s)	Intervention(s)	Phase	Start Date
Antibodies	NCT03574805	Study of Multiple Doses of PRS-060 Administered by Oral Inhalation in Subjects With Mild Asthma	R	Asthma	Drug: PRS-060|Drug: Placebo	I	2018, Jun 26
	NCT03574805	Study of Multiple Doses of PRS-060 Administered by Oral Inhalation in Subjects With Mild Asthma	R	Asthma	Drug: PRS-060|Drug: Placebo	I	2018, Jun 26
	NCT04410523	Study of Efficacy and Safety of CSJ117 in Patients With Severe Uncontrolled Asthma	R	Asthma	Drug: CSJ117 Drug: Placebo	II	2020, Sep 9
Cytokines	NCT04569877	GM-CSF Inhalation to Prevent ARDS in COVID-19 Pneumonia	R	Severe Acute Respiratory Syndrome (SARS) Pneumonia COVID-19 Pneumonia	Drug: Molgramostim nebuliser solution Other: Placebo nebuliser solution	II	2020, Sep 24
	NCT03421743	Pilot Trial of Inhaled Molgramostim in Nontuberculous Mycobacterial (NTM) Infection	A	Mycobacterium Infections, Nontuberculous	Drug: Inhaled molgramostim	II	2018, Mar 1
	NCT03482752	Safety Extension Trial of Inhaled Molgramostim in Autoimmune Pulmonary Alveolar Proteinosis	I	Autoimmune Pulmonary Alveolar Proteinosis	Drug: Molgramostim	III	2018, Apr 16
	NCT02595060	Granulocyte Macrophage-Colony Stimulating Factor (GM-CSF) Inhalation to Improve Host Defense and Pulmonary Barrier Restoration	R	ARDS	Drug: inhaled molgramostim (rhGM-CSF)|Drug: inhaled placebo	II	2016, Jan
	NCT04707664	Sargramostim Use in COVID-19 to Recover Patient Health	NR	Covid19|SARS-CoV Infection	Sargramostim|Drug: Placebo	II	2021, Mar
	NCT04642950	A Phase II/III Study of Sargramostim	R	COVID-19	Sargramostim|Drug: Placebo	II/III	2020, Dec 20
	NCT04569877	GM-CSF Inhalation to Prevent ARDS in COVID-19 Pneumonia	R	Severe Acute Respiratory Syndrome (SARS) Pneumonia| COVID-19 Pneumonia	Molgramostim nebuliser solution|Other: Placebo nebuliser solution	II	2020, Sep 24
	NCT04411680	Study of Sargramostim in Patients With COVID-19	A	COVID-19|Sars-CoV2	Sargramostim|Drug: Standard of care	II	2020, Aug 18
	NCT03570359	A Study to Test a Potential New Treatment for COPD Patients Suffering From the Common Cold or Influenza	R	Chronic Obstructive Pulmonary Disease (COPD)	Drug: Interferon Beta-1A| Other: Placebo	II	2018, Jan 29
Enzymes	NCT03994380	Use of DNase in Neutrophilic Asthma	A	Neutrophilic Asthma	Drug: RhDNAse Inhalation Solution	I, II	2019, Sep
	NCT03368092	Inhaled Dornase Alpha to Reduce Respiratory Failure After Severe Trauma	R	Multiple Trauma|Respiratory Distress Syndrome, Adult	Drug: Dornase Alfa Inhalant Solution [Pulmozyme]|Drug: Placebos	III	2019, Mar 4
	NCT03808922	STOP PIV - Phase III DAS181 Lower Tract PIV Infection in Immunocompromised Subjects	R	Lower Respiratory Tract Infection|Parainfluenza| Immunocompromised	Drug: DAS181|Drug: Placebo	III	2019, May 23
	NCT04298060	DAS181 for Patients With Severe Hospitalized Flu and SAD-RVs (COVID-19)	NR	Influenza Infection|SAD-RV Infection and COVID-19	Drug: DAS181|Drug: Placebo	III	2020, Apr
	NCT02315898	Inhaled Tissue Plasminogen Activator for Acute Plastic Bronchitis	R	Plastic Bronchitis|Protein-Losing Enteropathies|Healthy	Drug: Treatment-inhaled tPA	II	2018, Mar 19
Proteins	NCT04204252	Evaluate Efficacy and Safety of "Kamada-AAT for Inhalation" in Patients With AATD	R	Alpha 1-Antitrypsin Deficiency	Drug: Alpha 1-Antitryp-sin|Drug: Placebos	III	2019, Nov 25
	NCT02598999	Dose Escalation Study of ALX-009 in Healthy Men and Cystic Fibrosis (CF) and Non-CF Bronchiectasis Patients	R	Cystic Fibrosis|Bronchiectasis	Drug: ALX-009|Drug: OSCN-|Drug: bLF|Drug: Placebo	I	2015, Nov
	NCT04183062	BIO-11006 for Osteosarcoma and Ewing's Sarcoma Lung Metastases	R	Osteosarcoma Metastatic|Ewing's Sarcoma Metastatic	Drug: Chemotherapy (gemcitabine & docetaxel) plus BIO-11006	II	2019, Oct 4
	NCT03472053	A Study of BIO-11006 in the Treatment of Advanced Non-Small Cell Lung Cancer	A	Non Small Cell Lung Cancer Stage IIIB	Drug: BIO-11006 plus standard of care|Drug: Standard of Care	II	2018, Feb 1
	NCT03202394	Evaluation of Safety & Efficacy of BIO-11006 Inhalation Solution in Patients With ARDS	R	Respiratory Distress Syndrome, Adult	Drug: BIO-11006|Drug: Placebo	II	2017, Aug 5
	NCT02337270	Phase 1 Clinical Trial of the Safety and Immunogenicity of an Adenovirus-based TB Vaccine Administered by Aerosol	R	Tuberculosis	Biological: Ad5Ag85A	I	2017, Sep 5
	NCT04121494	ChAdOx1 85A Aerosol Versus Intramuscular Vaccination in Healthy Adults (TB039)	R	Mycobacterium Tuberculosis, Protection Against|Tuberculosis	Biological: ChadOx1 85A - aerosol|Biological: ChadOx1 85A - IM	I	2019, Jan 22
	NCT03912207	Investigating Immune Responses to Aerosol BCG Challenge in Healthy UK Adults	R	Tuberculosis	Biological: BCG Danish| Other: Saline placebo	I	2019, Apr 19
	NCT04545541	Nebulised Heparin in Patients With Severe COVID-19	NR	Covid19 Respiratory Failure	Drug: Nebulised unfractionated heparin (UFH)	II/III	2020, Oct

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Licensed inhaled biologics

- Pulmozyme (dornase alfa enzyme)
- Exubera (insulin)
- Afrezza (insulin)

Indications

- Asthma
- COPD
- Respiratory infections
- Cystic fibrosis
- Diabetes
- Parkinson's disease
- Schizofrenia

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Points to consider for inhaled biologic products

Points to Consider: know your product/process

- Characterization of powder presentations (DPI) to understand protein activity/purity during and after dissolution in the lung- can be challenging (e.g., dissolution in airway)- The use of models may help.
- Protein preparations commonly present aggregates and particles with potential for immunogenicity. While available guidance for parenteral administration aids in the establishment of control strategies, guidance is limited for inhalation routes.
- Inhalation powders may require multiple product strengths to support clinical development. Bracketing stability approaches may help streamline material need for stability studies.
- During CMC development, manufacturing changes are a common occurrence (e.g., formulation, scale-up, site transfers). Science-based risk assessments are necessary to determine if and how extensive a comparability exercise between pre- and post-change material is required. ICH Q5E provides guidance on general criteria to determine the need for pre-clinical and/or clinical studies in addition to analytical comparability.

Points to Consider: know your product/process

- Direct characterization of the protein in powder for inhalation is challenging as protein testing technology generally requires reconstitution into liquid samples.
- While inhalation products do not require to be sterile, biologics preparations may facilitate microbial growth. Risk assessment of the inhaled biologic potential for microbial growth (e.g., endotoxins, water activity) should be made to support appropriate controls
- Drug product formulations that provide better powder performance may include excipients considered novel: *"Sponsoring"* the safety assessment of novel excipients: 2017(FDA) & 2020 (Merck) insulin case study on novel excipients talk about the manufacturer of the product to be the sponsor of the novel excipient that is being used in the product formulation…"*The sponsor is encouraged to contact the appropriate review division to receive specific guidance*". On a US FDA Note for Guidance…"*the inclusion of an excipient in a USP/NF monograph or other non-FDA document is not an indication that the substance has been reviewed by the FDA and found safe for use*". "*It is incumbent upon the biopharmaceutical manufacturer to build the case for fit-for-function as a human medicinal excipient*."

Points to Consider: Regulatory Challenge/Opportunity

- While parenteral biologics are expected to use the 'commercial' material by pivotal (Ph3) studies, inhalation products may need to do it earlier in development (e.g., Ph2)- "Dose-ranging studies are considered pivotal trials, and the to-be-marketed MDI should be used during dose-ranging studies to avoid potential therapeutic differences." *2018 FDA Draft Guidance on DPIs and Metered Products for Inhalation*.
- Long manufacturing processes for biologics for inhalation present challenges to establish stability programs that support a long shelf life. Biologics generally show non-Arrhenius behavior leading to limited predictability on stability. Regulatory acceptance of stability modeling and predictive stability programs would support better management of the storage of inhaled biologics.

Points to Consider: Regulatory Challenge/Opportunity

- Device development should be carefully considered from the perspective of filing globally during clinical studies as majority of regions require separate clinical applications for non-approved devices. For marketing applications, additional registration process need to be considered (e.g., EU Notified Body, FDA 510(k))
- Pediatric formulations may be challenging depending on the type of device for inhalation that is being developed for the adult population (a different inhaler may be needed for children under 6)
- Agencies may have discrepant views on aspects of inhaled biologics (nominal dose, pre-metered dose, delivery dose)
- Agencies have put in place programs in support of novel technologies and approaches that can help inhaled biologics advance their CMC programs while opening more effective communications with regulatory agencies on CMC issues (e.g., FDA ETP, EMA ITF, EMA QIG)

4

Take Aways

Take aways

- Inhaled biologics require a significant science and technology uplift in CMC. “Novel” and “specialized” are common themes during development.
- Global regulatory pathways for inhaled biologics can be complex. Understanding how product and device are regulated in each region is key to develop regulatory strategy and support CMC development
- Regulatory strategy ‘adaptability’ is key to navigate the gaps in regulatory guidance and support CMC development challenges. When not explicitly stated in guidance, a conservative approach may need to be used to support uncertainties during development

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