Where have all the inhaled biologics gone ?

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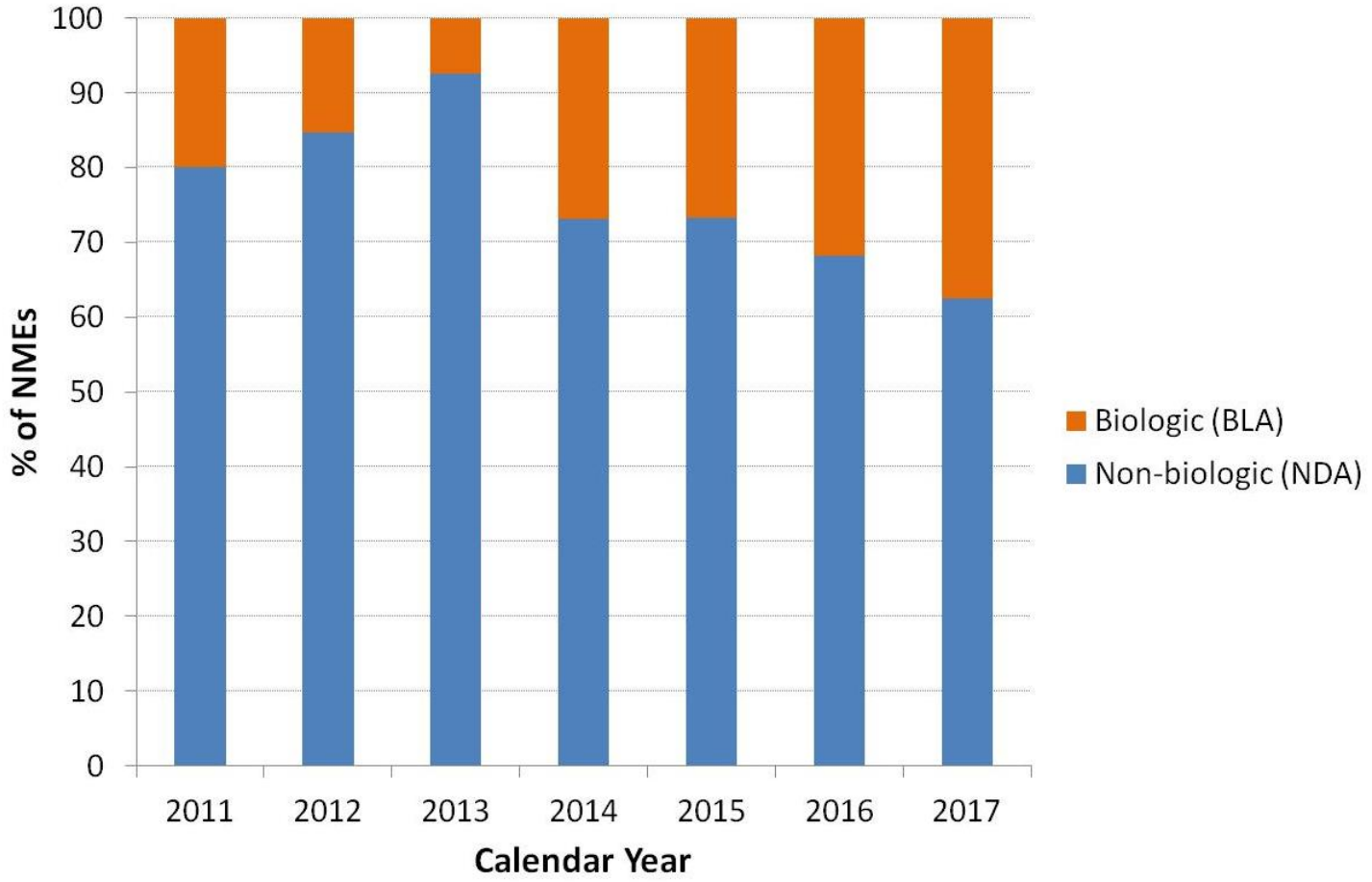
DDL2017
DRUG DELIVERY TO THE LUNGS

Overview

- Introduction
  - Trends in New Molecular Entity (NME) approvals
  - Emergence of biologics for treatment of asthma
  - Non-parenteral delivery routes for biologics
- Inhaled biologics
  - A historical perspective
  - Challenges
  - Pharmaceutical pipeline overview
  - Case Studies (dornase alfa, insulin)
  - Emerging opportunities (Nanobodies, oligonucleotides, vaccines)
- Conclusions

New Molecular Entity (NME) Approvals

2011-2017 trends[1]



Since approval of first medicine based on recombinant DNA product (Humulin®, 1982), increasing proportion of biologics-based NMEs relative to small molecules[2]

Refs: [1]CDER New Molecular Entity (NME) and Original Biologic Approvals Reports (http//:www.fda.gov) accessed 22 Jul 2017;
[2]Kinch M, Drug Discovery Today 2015; 20(4): pp393-398; [2]Pharmaprojects (data extract July 2017)

Biologics for asthma

Approved or in development

Mechanism of Action	Drug	Status	Administration
Binds free IgE	Omalizumab (Xolair®)	Approved	Subcutaneous injection (every 2-4 weeks; dosing frequency dependent on serum IgE levels)
IL-5 Antagonist	Mepoluzimab (Nucala®)	Approved	Subcutaneous injection (every 4 weeks)
	Reslizumab (Cinquair®)	Approved	Intravenous infusion (every 4 weeks; 20-50 minutes)
IL-5 receptor α antagonist	Benralizumab (Fasenra™)	Phase III	Subcutaneous injection (2 dosing regimens evaluated)
IL-13 antagonist	Lebrikizumab	Phase III	Subcutaneous injection (every 4 weeks)
	Tralokinumab	Phase III	Subcutaneous injection (every 2 weeks)
IL-13/IL-4 inhibition	Dupilumab	Phase III	Subcutaneous injection (every 2 weeks)

Refs: adapted from Tabatabaian, F., *et al,* Immunol Allergy Clin N Am 2017; 37: pp329-343; www.clinicaltrials.gov (accessed 21 Jul 2017)

Non-parenteral delivery of biologics

Oral delivery - The Holy Grail

- Oral route is preferred route of administration, but distinct challenges for biologics
  - Acidic pH in stomach
  - High content of proteolytic enzymes
  - Hepatic 1st pass effect
  - Permeability restrictions (Lipinski 'rule of 5') on bioavailability
  - GI transit time variability
- Significant area of study and some successes in late stage clinical studies
  - Octreotide for acromegaly (Mycapssa®)[1] - oral formulation of somatostatin analogue based on Chiasma's Transient Permeability Enhancer technology. Ongoing additional Phase III study versus parenteral somatostatin receptor ligands (octreotide, lanreotide)
  - Salmon calcitonin for postmenopausal osteoporosis (TBRIA™) [2] - proprietary technology to enable once a day oral delivery of sCT. Phase III data demonstrated superior effect on bone mineral density (lumbar spine) compared to placebo and nasal calcitonin with similar safety profile to nasal product and less immunogenicity. NDA filed 2015.

Refs: [1]http://www.chiasmapharma.com (accessed 22 Jul 2017), [2]http://www.tarsatherapeutics.com (accessed 22 Jul 2017)

Non-parenteral delivery of biologics

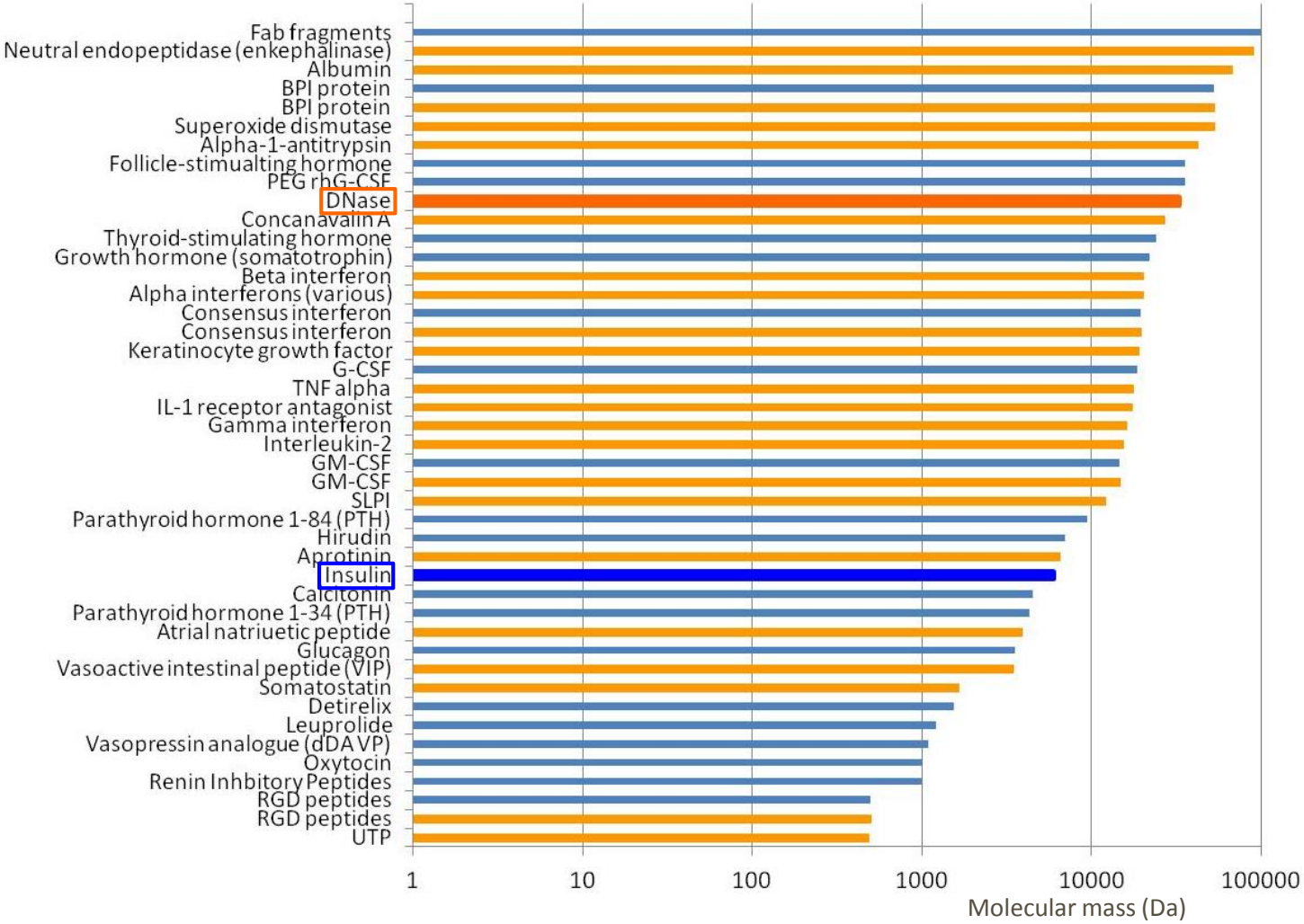
Transdermal delivery - microneedle patches[1]

Drug	Description of study	Sponsor	Clinical Phase	Identifier
Inactivated influenza vaccine	Inactivated Influenza Vaccine Delivered by Microneedle Patch or by Hypodermic Needle	Georgia Institute of Technology	Phase 1[2]	NCT02438423
Glucagon	Safety and Efficacy of ZP-Glucagon to Injectable Glucagon for Hypoglycaemia	Zosano Pharma	Phase 1	NCT02459938
Parathyroid hormone	A Study to Determine the Patient Preference Between Zosano Pharma Parathyroid Hormone (ZP-PTH) Patch and Forteo Pen	Zosano Pharma	Phase 1	NCT02478879
Abaloparatide	Phase 2 Study of BA058 (Abaloparatide) Transdermal Delivery in Postmenopausal Women With Osteoporosis	Radius Health, Inc.	Phase 2	NCT01674621
N/A	Glucose Measurement Using Microneedle Patches (GUMP)	Emory University	*Not described*	NCT02682056

Ref: [1]data sourced from CinicalTrials.gov (accessed 22 Jul 2017); [2]Rouphael NG *et al,* The Lancet 2017; 10095: pp649-658.

Inhaled biologics - a historical perspective

Biotherapeutics administered to the lung for local or systemic effect (circa. 1995)



Ref: Figure adapted from Niven, R., Crit Rev Ther Drug Carrier Syst 1995; 12 (2&3): pp151-231.

Challenges to Inhaled Delivery of Biologics

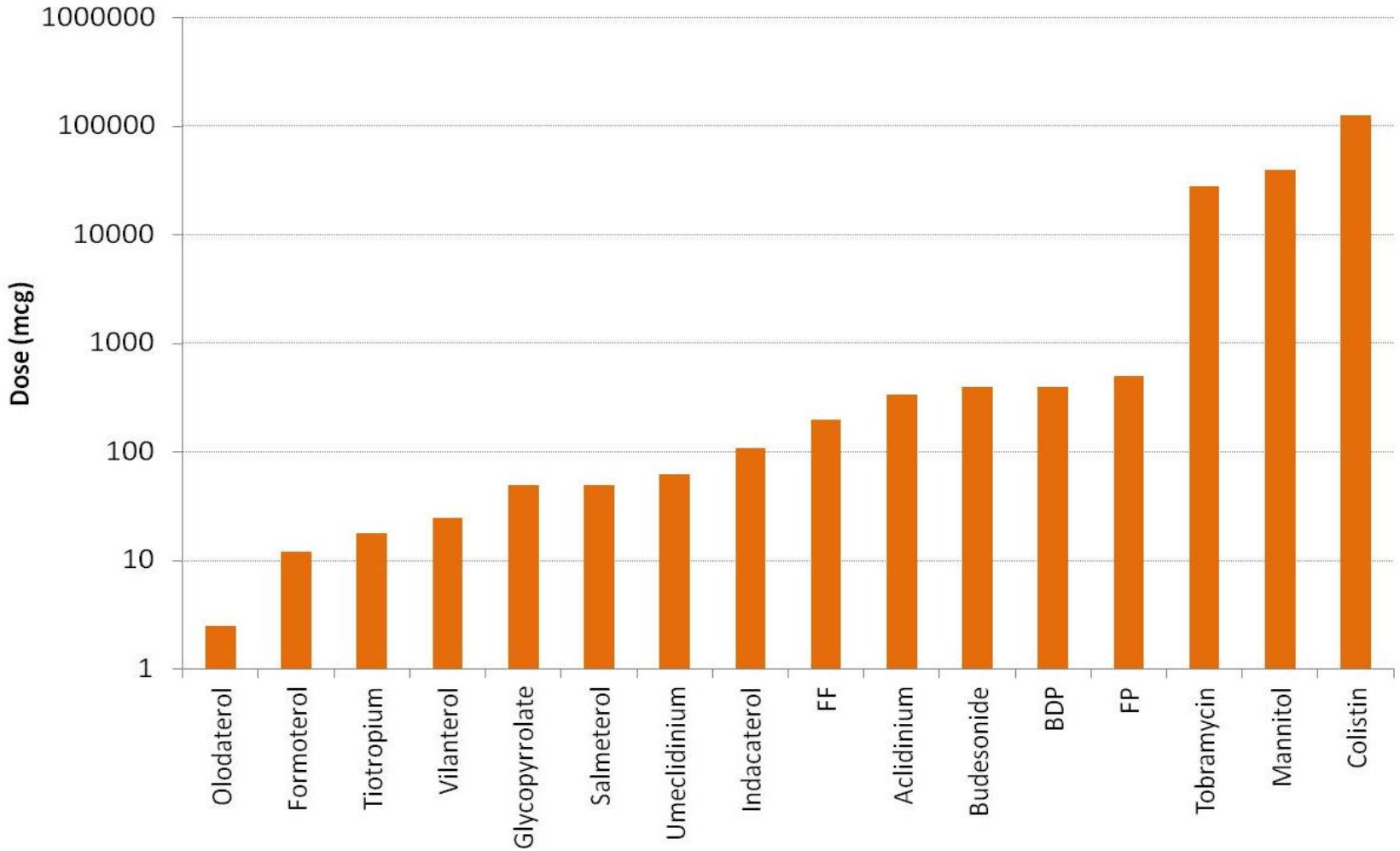
Meeting the needs of stakeholders

- Pharmaceutical Scientists (Technical)
  - High molecular mass = low mass potency and challenges ability to deliver efficacious dose
  - (Safely) overcoming biological barriers which protect the lung from physical, biological and chemical threats through mechanisms such as mucociliary clearance, macrophage surveillance, biotransformation enzymes
  - Maintenance of stability through formulation, manufacture and delivery process (pros/cons for standard liquid, powder and pressurised inhaled dose forms recently reviewed[1])
  - Manufacturing complexity for combination product
  - Advances in competing alternate dose forms (e.g. reduced needle gauge, auto injectors, microneedle patches, needleless injections)
- Prescribers
  - Confidence in delivery c.f. parenteral routes (e.g. compliance/adherence, role of caregiver, influence of lung disease etc.)
  - Contraindications (e.g. immunogenicity[2], co-morbidities)
- Patients
  - Does it control my disease ? Is it easy to use ? Does it fit my lifestyle ? Is it better than my existing treatment ?
- Payers
  - Inhaled treatment must be cost-effective vs. standard of care i.e. meets required cost/benefit threshold

Ref: [1]Fathe, K. *et al,* Current Pharmaceutical Design 2016; 22: pp2501-2521; [2]Baker MP *et al*, Self/Nonself 2017; 1(4): pp314-322.

Challenges to Inhaled Delivery of Biologics

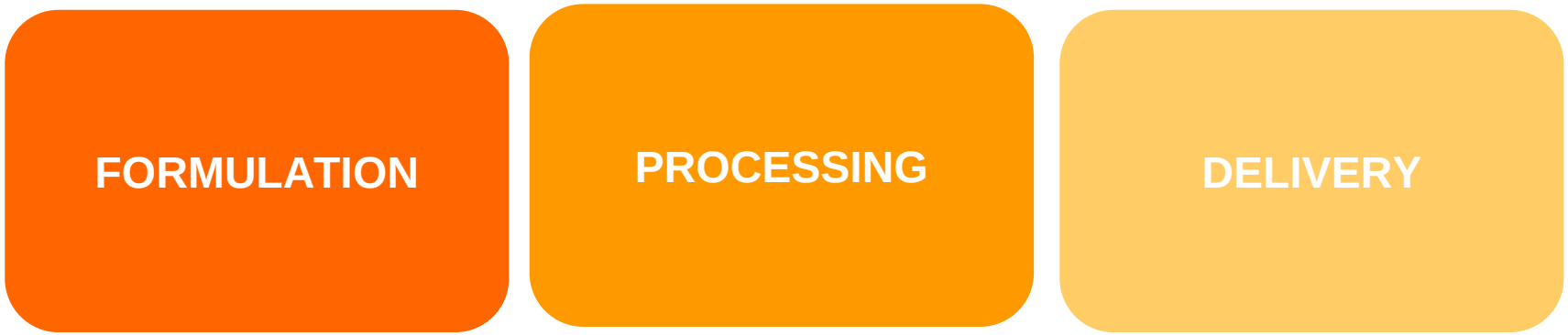
Dose



Ref: eMC (http://www.medicines.org.uk). Key: FF = fluticasone furoate, BDP = beclomethasone dipropionate, FP = fluticasone propionate

Challenges to Inhaled Delivery of Biologics

Stability



- Factors that can influence stability
  - Choice of dose form and Container Closure System
    - Liquid, DPI, pMDI
  - Choice of particle synthesis method
    - Impact of pH, heat, freezing, agitation
  - Choice of formulation
    - Limited range of approved excipients
  - Choice of delivery system
- Examples of approaches to optimise stability of biologics within inhalation dose forms subject of a recent review

Ref: Fathe, K. *et al,* Current Pharmaceutical Design 2016; 22: pp2501-2521.

Challenges to Inhaled Delivery of Biologics

Safety, efficacy, quality.....and cost effectiveness

- Incremental Cost-Effectiveness Ratio (ICER)
  - Ratio of the change in costs to incremental benefits of a therapeutic intervention or treatment and provides means of comparing projects or interventions across various disease states and treatments

    ICER = (C1 – C2) / (E1 – E2) = Cost/QALY

    C1 and E1 are the cost and effect in the intervention or treatment group
    C2 and E2 are the cost and effect in the control care group
    Costs usually described in monetary units while benefits/effect in health status is measured in terms of quality-adjusted life years (QALYs) gained or lost (adjustment for health utility)

- Example thresholds
  - UK - £20 000-£30 000 per QALY accepted as the threshold to decide whether or not NICE should recommend use of a new healthcare technology
  - US - $50 000-$100 000 per QALY often mentioned in medical literature, although no clear scientific evidence
  - Australia - Australian Pharmaceutical Benefits Advisory Committee unlikely to recommend a drug for listing if the ICER (cost per life-year) exceeded AU$ 76 000

Ref: Shiroiwa, T. *et al*, Health Econ 2010; 19: pp422–437; NICE Briefing Paper for Methods Working Party on the Cost Effectiveness Threshold (2007)

Challenges to Inhaled Delivery of Biologics

Safety, efficacy, quality.....and cost effectiveness: Health Utility

Dimensions/Score[1]	1	2	3
Mobility	No problems walking about.	Some problems walking about.	Confined to bed.
Pain/discomfort	No pain or discomfort.	Moderate pain or discomfort.	Extreme pain or discomfort
Self-care	No problems with self-care.	Some problems washing or dressing.	Unable to wash or dress self.
Anxiety/depression	Not anxious or depressed	Moderately anxious or depressed.	Extremely anxious or depressed.
Usual activities (work, study, housework, leisure activities)	No problems in performing usual activities.	Some problems in performing usual activities.	Unable to perform usual activities

Score = 1

Ref: [1]Phillips, C., What is a QALY ? 2nd edition NPR09/1265 from the What is ? Series 2009

Challenges to Inhaled Delivery of Biologics

Safety, efficacy, quality.....and cost effectiveness

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Score = 0.516

Ref: [1]Phillips, C., What is a QALY ? 2nd edition NPR09/1265 from the What is ? Series 2009

Challenges to Inhaled Delivery of Biologics

Safety, efficacy, quality.....and cost effectiveness

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Score = -0.429

Disease/Severity[2]	Intermittent	Mild	Moderate	Severe
Asthma	0.89	0.70	0.63	0.51
COPD	-	0.85	0.73	0.53

Refs: [1]Phillips, C., What is a QALY ? 2nd edition NPR09/1265 from the What is ? Series 2009
[2]Szende, A. *et al* , Quality of Life Research 2009; 18:2: pp 267-272.

Challenges to Inhaled Delivery of Biologics

Safety, efficacy, quality.....and cost effectiveness

Product & Indication	ICER	Eligibility
Omalizumab (Xolair) Severe persistent confirmed allergic IgE-mediated asthma	~£24,000	Add-on to optimised standard therapy in people aged 6 years and older: • who need continuous or frequent treatment with oral corticosteroids (defined as 4 or > courses in previous year) and • only if the manufacturer makes omalizumab available with the discount agreed in the patient access scheme. Optimised standard therapy is defined as a full trial of and, if tolerated, documented compliance with inhaled high-dose ICS, LABAs, leukotriene receptor antagonists, theophyllines, oral corticosteroids, and smoking cessation if clinically appropriate.

Ref: Omalizumab for treating severe persistent allergic asthma (TA278, 24 Apr 2013)

Challenges to Inhaled Delivery of Biologics

Safety, efficacy, quality.....and cost effectiveness

Product & Indication	ICER	Eligibility
Mepolizumab (Nucala) Severe refractory eosinophilic asthma in adults	£29,163	Add-on to optimised standard therapy only if: • blood eosinophil count is 300 cells/microlitre or more in the previous 12 months and • the person has agreed to and followed the optimised standard treatment plan and • has had 4 or more asthma exacerbations needing systemic corticosteroids in the previous 12 months or • has had continuous oral corticosteroids of at least the equivalent of prednisolone 5 mg per day over the previous 6 months and • the company provides the drug with the discount agreed in the patient access scheme At 12 months of treatment stop mepolizumab if the asthma has not responded adequately or continue if the asthma has responded adequately and assess response each year Adequate response means at least 50% fewer asthma exacerbations needing systemic corticosteroids in those people with 4 or more exacerbations in the previous 12 months or a clinically significant reduction in continuous oral corticosteroid use while maintaining or improving asthma control

Ref: Mepolizumab for treating severe refractory eosinophilic asthma (TA431, 25 Jan 2017)

Pharmaceutical pipeline statistics

Summary

- Current pharmaceutical pipeline[1]
  - ~60% small molecule
  - ~40% biologics

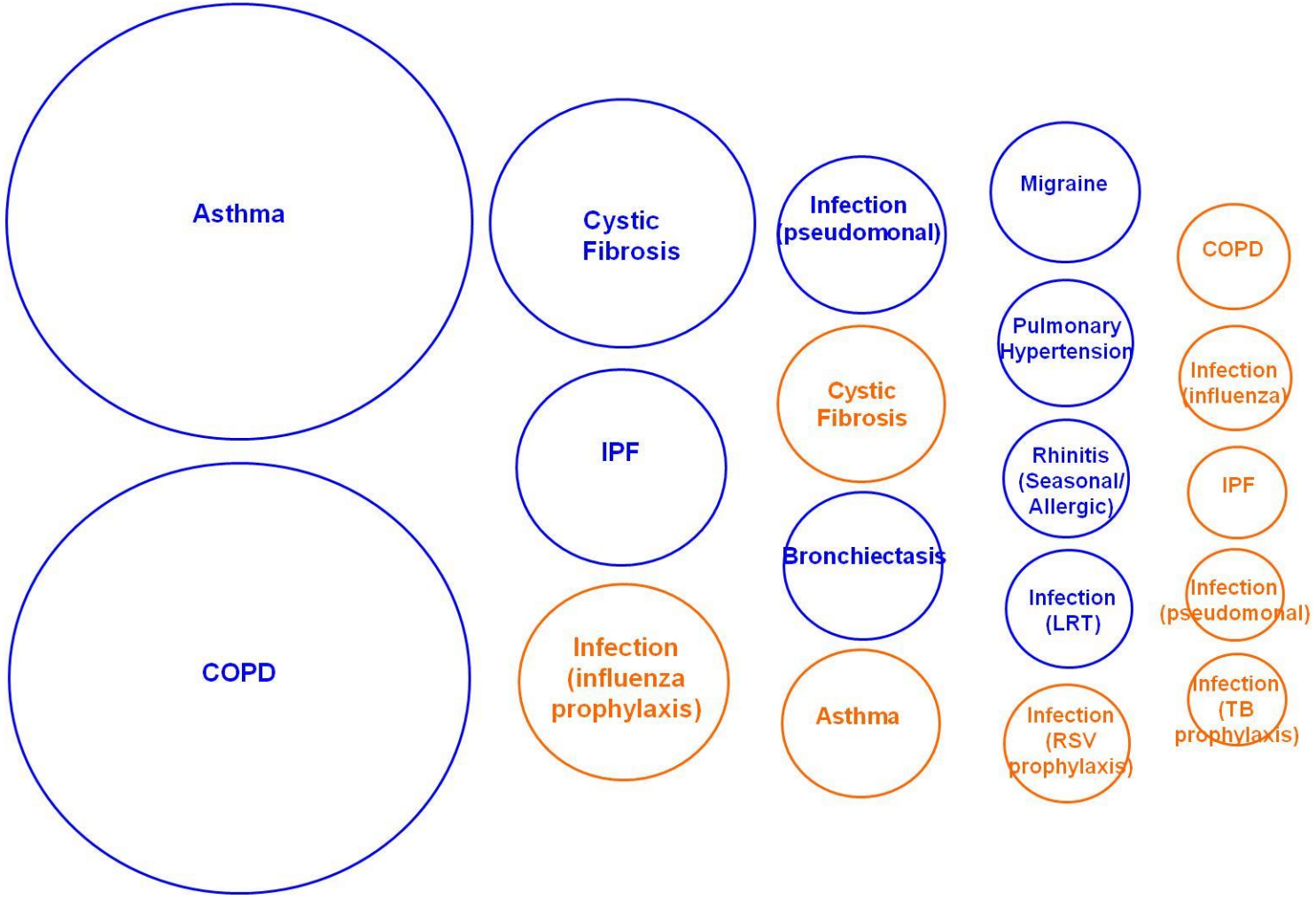
- Vast majority of biologics continue to be delivered by injection
  - Subcutaneous
  - Intravenous

- Inhaled delivery is niche delivery route
  - Small molecules (mostly oral)
  - Biologics (mostly injection)

Ref: [1]Pharmaprojects (data extract July 2017)

Pharmaceutical pipeline statistics

Indications for pipeline molecules delivered by inhaled (pulmonary & nasal) delivery (small molecule and biologic[1])



Area of circle indicates relative no. of drug candidates in comparison to Asthma and COPD for small molecules

Ref: [1]Based on Pharmaprojects (data extract July 2017)

Inhaled Biologics: Case Studies

Dornase alfa - background

- Pulmozyme was first recombinant protein (rhDNase) developed specifically for airway delivery and acts as mucolytic to decrease viscosity of lung secretions by cleaving extracellular DNA, a by-product of neutrophil degeneration (approved as orphan drug by FDA in Dec 1993)
- Indicated for daily administration along with standard therapies for the management of cystic fibrosis (CF) patients to improve pulmonary function. In CF patients with an FVC ≥ 40% of predicted, daily administration of Pulmozyme has also been shown to reduce the risk of respiratory tract infections requiring injectable antibiotics
- Recommended dosage is one 2.5 mg single-use ampoule inhaled once daily using a recommended nebulizer

Jet nebuliser/compressor	Nebuliser system
Hudson T Up-draft II® / Pulmo-Aide®	eRapid® (PARI) Nebulizer System
Marquest Acorn II® / Pulmo-Aide®	
PARI LC® Plus / PARI PRONEB®	
PARI BABY™ / PARI PRONEB®	
Durable Sidestream® / MOBILAIRE™ or Portaneb	

Ref: Pulmozyme Prescribing Information

Orphan Drug Designation Program

Inhaled therapies for lung infections

Drug	Designation (Date)	Status*	Sponsor
Tobramycin for inhalation	Bronchopulmonary infections of Ps. aeruginosa in CF patients (10/13/1994)	Approved (TOBI™)	Novartis
Liposomal ciprofloxacin for inhalation	Bronchiectasis (12/27/2006)	Linhaliq™ NDA filed 27 Jul 2017	Aradigm
Ciprofloxacin dry powder inhaler	Non-cystic fibrosis bronchiectasis (04/17/2014)	Phase III	Bayer
Alpha1-Proteinase Inhibitor, alpha1-PI (human)	Inhalation therapy for treatment of congenital alpha$_1$-PI deficiency(12/22/2004)	Phase III	Kamada
Vancomycin hydrochloride (inhalational)	Persistent MRSA lung infection in CF patients (09/20/2012)	Phase II	Savara
Itraconazole inhalation powder	Pulmonary fungal infections in CF patients (08/16/2016)	Pre-clinical	Pulmatrix
Amphotericin B inhalation powder	Prevention of pulmonary fungal infections in patients at risk patients due to immunosuppressive therapy (12/15/2005)	No development reported	Novartis

Ref: www.fda.gov (accessed 28 Jul 2017) and Pharmaprojects

Inhaled Biologics: Case Studies

Dornase alfa - updated NICE guidance on cystic fibrosis: diagnosis and management

- Efficacy
  - Dornase alfa continues to be recommended as first choice mucolytic agent with hypertonic saline as add-on if lung function testing indicates inadequate response.
  - Use of mannitol dry powder for inhalation is recommended as an option for treating cystic fibrosis in adults who cannot use dornase alfa and whose lung function is rapidly declining and or whom other osmotic agents are not considered appropriate (as per NICE Technology appraisal 266)
- Pharmacoeconomics
  - "*What is the most clinical and cost effectiveness dose of dornase alfa in people with cystic fibrosis?"*
  - Annual cost of dornase alfa treatment (nebule and nebuliser) estimated as £6-7k and whilst extant economic evaluations do not report cost per QALY ICER, some evidence that alternate day dosing could give large cost savings with small decrease in effectiveness. Would also reduce treatment burden on cystic fibrosis patients who already have complex treatment schedules (including multiple nebulised treatments)

Ref: NICE Guideline on *Cystic fibrosis: diagnosis and management* [NG78]

Inhaled Biologics: Case Studies

Dornase alfa - combination formulations?

- Polypharmacy is the standard for cystic fibrosis patients - mucolytics, bronchodilators, antibiotics
- Combination approaches common for asthma and COPD therapy would help reduce treatment burden
- In absence of commercially available combination formulations, surveys of home-nebuliser practice have noted practice of extemporaneous preparation of medication mixtures in large no of patients[1]
- Studies of physico-chemical compatibility of drug nebuliser solutions[2] have reported that whilst preservative-free solutions were likely compatible with dornase alfa, an excipient-driven loss of activity was noted in specific cases

Product	Implicated excipient
Atrovent (ipratropium) and Sultanol (albuterol)	Benzalkonium chloride
Atrovent (ipratropium)	Disodium edetate
Gernebcin (tobramycin)	Sodium metabisulfite

Refs: [1]Rosenfeld, M. *et al*, J Pediatr 1998; 132: pp125-131; [2]Kamin, W. *et al*, Journal of Cystic Fibrosis 2014; 13:3 : pp243-250.

Inhaled Biologics: Case Studies

Dornase alfa - approval of alternate delivery systems

- Originally approved with range of jet nebuliser/compressor combinations. More recently approved with eRapid Nebuliser System (Jan 2015)
- Results from a randomised crossover study where cystic fibrosis (CF) patients (n=87) received dornase alfa 2.5mg/d in 2 week periods with Pari eRapid and Pari LC Plus

	Pari eRapid	Pari LC Plus
Comparable efficacy Primary end point FEV1, % predicted, mean [SD]	98.1 [22.1]	97.2 [20.7]
	Mean ratio (90% CI) 100.9 (99.5,102.3)	
Comparable safety – Most common AEs (>5% incidence)	**Similar no. of AEs for both systems** 40% of patients experienced at least 1 AE while on study	
• Upper respiratory infection	3.5%	2.4%
• Cough	2.4%	4.7%
• Nasal congestion	2.4%	4.7%
Shorter nebulisation time (patient reported)	**2.7 min**	10.2 min
	Difference between devices [95% CI], 7.5 min [6.8 min, 8.2 min]	
Higher patient preference - key factors informing preference • 6-13 yrs - shorter nebulisation time, size of device, ease of use • 14 yrs - device portability and convenience for use away from home	**89.4%** **90.5%**	8.5% 4.8%

Ref: adapted from Sawicki. G.S. *et al*, Journal of Cystic Fibrosis 2015; 14 : pp777-783.

Inhaled Biologics: Case Studies

Dornase alfa - Alidornase alfa (PRX-110): Rationale and Phase 2 study results

- Rationale
  - DNase activity is compromised by actin found in high concentration in the sputum of CF patients
  - Postulated that actin may potentially interfere with the effectiveness of inhaled DNase I in the lungs of CF patients.
  - Alidornase alfa (PRX-110) is a proprietary plant cell-expressed recombinant form of DNase chemically modified to form an actin inhibition resistant DNase.
- Phase II Study design
  - 28-day switchover study in 16 patients to evaluate the safety and efficacy of alidornase alfa in CF patients previously treated with Pulmozyme® (two-week washout period from Pulmozyme® before treatment with alidornase alfa)
- Phase II Study Results
  - Safety - well tolerated and safe
  - Pharmacokinetics - not absorbed into systemic circulation and active alidornase measured in patient's sputa
  - Efficacy - Improved lung function (ppFEV1) and sputa analyses demonstrated
    - Mean reduction of ~70% in DNA content from baseline
    - Mean reduction of >90% in sputa viscoelasticity from baseline
    - Reduction in over 70% in presence of pseudomonas (leading cause of infections and morbidity in CF patients)

Ref: Keram, E. *et al*, Presentation at European Cystic Fibrosis Society, Seville (http://protalix.com (accessed 15 Jul 2017)

Inhaled Biologics: Case Studies

Inhaled insulin - the rationale and the challenges

- Ideal candidate biologic for non-invasive delivery as need for life-long treatment
  - "*[with inhaled insulin a]..physiological mode of action is achieved and the risk of a hypoglycaemic reaction is eliminated...*" [1]
- Multiple development programmes delivered elegant technical solutions (novel powder and liquid based delivery systems) to overcome technical challenges associated with product performance, stability and manufacturability and achieve comparable clinical effectiveness to other prandial insulin products
- But.....
  - Competitive delivery systems - inhaled delivery represented conversion from a well-established and continually improving parenteral dose form (small gauge needles, insulin pens etc.)
  - Long term safety - approved inhaled insulin product[2] has boxed warning re: use in patients with extant respiratory disease (asthma and COPD) and smokers due to risk of acute bronchospasm as well as a post-marketing commitment to evaluate, through a randomised clinical trial, the potential risk of pulmonary malignancy, cardiovascular risk and long term effect on pulmonary function
  - Commercial performance - low sales revenue for Exubera[3] and Afrezza[4] (Safety concerns ? Product Awareness ? Patient Acceptance?)
  - Cost effectiveness - e.g. NICE assessment in UK restricted use to a specific patient demographic
  - No inhaled equivalent for basal insulin which still needed injection

Refs: [1]Gänsslen M, Klin Wochenschr 1925; 4; p71; [2]FDA Approval letter: Afrezza (insulin human) Inhalation Powder (NDA 022472), 27 Jun 2014; [3]Mack GS, Nature Biotechnology 2007; 25,: pp1331 - 1332; [4]Ratner M, Nature Biotechnology 2016; 34: p224

Inhaled Biologics: Case Studies

Inhaled insulin - cost effectiveness (NICE technology appraisal)

- Inhaled insulin as effective in controlling HbA1c levels as short-acting sc insulin (RCTs)
- Inhaled insulin more expensive but not more clinically effective than sc insulin
- Inhaled insulin does not replace need for injections as only a substitute for pre-prandial insulin i.e. no equivalent inhaled for basal insulin element of daily insulin regimen
- Cost effectiveness of inhaled insulin dependent on magnitude of utility gain, which across entire population of diabetics was judged as NMT >0.02. Calculated ICERs thus >£30 000 threshold (note different models, assumptions used by manufacturer and assessors)
- Inhaled insulin not recommended for routine use but as a treatment option where evidence of poor glycaemic control despite other therapeutic interventions and for patients unable to initiate or intensify preprandial sc insulin therapy due to diagnosed marked, persistent fear of injections or severe, persistent problems with injection sites e.g. lipohypertrophy
- If treatment initiated (specialist diabetes centre)
  - Should only not be continued >6 months if sustained improvement in HbA1c clinically relevant to individual patient's overall risk of developing long-term complications of diabetes.
  - Data on inhaled insulin use (individual patient outcomes, adverse events, lung function measurements) should be collected as part of a coordinated prospective observational study.

Ref: National Institute for Health and Clinical Excellence (NICE): Inhaled insulin for the treatment of diabetes (types 1 and 2), Technology appraisal guidance 13 Dec 2006; TA113 (withdrawn)

Inhaled nanobodies

ALX-0171 - anti-RSV Nanobody to treat Respiratory Syncytial Virus (RSV)

- Background
  - Nanobodies® are therapeutic proteins derived from naturally occurring heavy chain only antibodies (VHH) found in *camelidae.*
  - Represent smallest functional fragment of naturally occurring immunoglobulin.
  - Recombinant Nanobodies® can be produced in bacterial, yeast or mammalian hosts. Multimerisation of monomer can be used to enhanced potency
  - Nanobodies® have Ideal properties for inhaled delivery
    - Small size (12-15 kDa = 10x increase in mass potency c.f. standard immunoglobulin)
    - Good physicochemical properties (high solubility and stability)
    - Short systemic half life (minimises exposure)

Ref: Van Heeke, G. *et al* , Pharmacology & Therapeutics 2017; 169: pp 47-56; http://www.ablynx.com (accessed 18 Jul 2017)

Inhaled nanobodies

ALX-0171 - anti-RSV Nanobody to treat Respiratory Syncytial Virus (RSV)

- ALX-0171 is a trivalent Nanobody (42 kDa) to treat RSV in children (high unmet need for effective therapeutic). Mechanism of action is binding to RSV fusion protein which interferes with viral penetration of respiratory epithelial cells
- Developed as solution for delivery via vibrating mesh nebuliser (air jet nebuliser showed greater (40%) propensity for protein aggregation). Pharmaceutical development studies demonstrated storage stability (36 months) at long term storage condition of 5°C:
  - Maintenance of aerosol delivery performance (laser diffraction)
  - Limited aggregation (SE-HPLC) (pre/post aerosolisation)
  - Limited loss of potency (ELISA)
- Pre-clinical
  - PoC study in RSV infected-lambs - ALX-0171 delivery at peak viral loads reduced viral titers and lung viral antigen expression
- Clinical
  - Phase I/IIa in infants - good safety and tolerability. Anti-drug antibodies did not effect PK and no apparent relation to adverse events. Demonstrated anti-viral effect (based on nasal swab analysis) and encouraging trends in disease severity (NCT02309320)
  - Phase IIb dose ranging efficacy study in infants - started in Q1 2017 (NCT02979431)

Ref: Van Heeke, G. *et al* , Pharmacology & Therapeutics 2017; 169: pp 47-56; http://www.ablynx.com (accessed 18 Jul 2017)

Inhaled siRNA

Opportunities for pulmonary administration

- Strong rationale for pulmonary administration of siRNA as many lung diseases typified by over expression of genes
- siRNA is a highly specific approach (single gene target) and achieves post-transcriptional gene silencing through RNA interference within cytoplasm (degradation or stabilisation of mRNA) and thus therapeutic effect does not require nuclear transport
- siRNA has short systemic half-life due to enzymatic degradation (nucleases) and rapid renal clearance (molecular mass ~7 kDa) and thus local delivery to site of action would be advantageous
- Recent review[1] of pre-clinical studies concludes that pulmonary delivery of siRNA has promise, but highlights no. of challenges/areas of for further study:
  - Can successful delivery of siRNA to intracellular targets be achieved without need for vectors (toxicity concerns)?
  - Can siRNA be localised in lungs and avoid bio distribution to other tissues?
  - Need for improved predictive capability of pre-clinical models (species differences in lung in lung anatomy and physiology impact fidelity of extrapolation to humans)
  - Need to understand long term effects of siRNA administration
  - Paucity of knowledge on inhalable formulations as majority of pre-clinical studies have used liquid formulations

Ref: [1]Ruigrok, M.J.R. *et al,* Journal of Controlled Release 2016; 235: pp 14-23.

Inhaled vaccines

WHO Global Vaccine Action Plan 2011-2020

- Global Vaccine Action Plan[1] is a “framework to prevent millions of deaths by 2020 through more equitable access to existing vaccines for people in all communities” i.e. vaccines that are more effective, less expensive and easier to manufacture and deliver
- Developed by Decade of Vaccines collaboration lead by Bill & Melinda Gates Foundation, GAVI Alliance, UNICEF, United States National Institute of Allergies and Infectious Diseases and WHO working with partners in government, academia, health care professionals and manufacturers
- Priority research areas include:
  - Non-syringe delivery mechanisms and vaccine packaging that best suit the needs and constraints of countries
  - Thermostable vaccines (avoid ‘cold chain’)
  - New bioprocessing & manufacturing technologies
  - Microneedle patches for mass vaccination?[2]
    - Offer advantages of ease of (painless) administration and simplifies storage (thermostability) and waste disposal (no sharps)

Ref: [1]http://www.who.int/immunization/global_vaccine_action_plan; [2]Arya, J. and Prausnitz, M.R, Journal Control Rel 2016; 240: pp135-141.

Inhaled vaccines

- Pros
  - Vaccination via inhalation has advantages over injection for mass vaccination campaigns (no need for disposal strategies for needles, avoids risk of spread of blood-borne infections etc.) especially if can avoid ‘cold chain’.
  - Number of examples in literature where in pre-clinical models and early clinical studies, an effective mucosal (IgA) and systemic immune response (IgG) has been invoked through delivery of vaccine to the lungs (natural route of infection for many viruses) with acceptable safety profile
- Cons
  - Most vaccines now based on recombinant proteins which need adjuvants to boost immune response - safety in lung especially with concurrent disease ?
  - Need to demonstrate improved cost-effectiveness over needle & syringe
  - Studies generally supported by academic groups/philanthropic organisations and needs industry input to provide necessary scale for manufacturing capacity
  - FluMist - only non-injection-based flu vaccine (intranasal live attenuated influenza vaccine approved by FDA in 2003). Not recommended by CDC for use during the 2016-2017 season because of “concerns about its effectiveness”
    - Data from U.S. Influenza Vaccine Effectiveness Network (children 2 years through 17 years during 2015-2016 season) showed a vaccine effectiveness against any flu virus of 3% (95%CI -49%- 37%) versus 63 % (95%CI, 52 percent to 72 percent) for standard flu shots

Ref: https://www.cdc.gov/

Inhaled vaccines

Drug	Description of study	Sponsor	Clinical Phase	Identifier
Dry Powdered Measles Vaccine (PMV)	A Clinical Trial to Assess the Safety of a Measles Vaccine (Dry Powder) Administered by Two Different Devices (PMV-001)	Serum Institute of India Pvt. Ltd.	Phase 1	NCT01557699
Tuberculosis Vaccine, MVA85A	MVA85A Aerosol vs Intramuscular Vaccination in Adults With Latent Mycobacterium Tuberculosis (M. tb) Infection	University of Oxford	Phase 1	NCT02532036
Sendai virus vaccine	A Study to Assess the Safety of Live Intranasal Sendai Virus Vaccine in Children and Toddlers	St. Jude Children's Research Hospital	Phase 1	NCT00186927
Adenovirus-based TB Vaccine (Ad5Ag85A)	Phase 1 Clinical Trial of the Safety and Immunogenicity of an Adenovirus-based TB Vaccine Administered by Aerosol	McMaster University	Phase 1	NCT02337270

Ref: clincialtrials.gov (accessed 22 Jul 2017)

Conclusions

- Biologics represent a growing share of global pharmaceutical market and a growing proportion of the pharma pipeline
- Despite advances in non-parenteral delivery systems (e.g. oral, transdermal, pulmonary), 'needle & syringe' remains the predominant delivery system for biologics
  - Simple
  - Cost-effective
  - Confidence in delivery
- Resolving technical challenges alone will not guarantee success for an inhaled biologic
  - Patients: acceptance and adherence
  - Prescribers: established efficacy and long term safety
  - Payers: demonstration of cost-effectiveness vs. standard of care
- Reason to be optimistic for right drug, right disease !
  - Potent, safe, stable candidate with a disease target amenable to local lung delivery

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