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# Drug Development in Cystic Fibrosis: Successes and Challenges

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# Topics For Consideration

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- Therapeutics for CF Today
- Bringing a drug to patients
  - Clinical trial process
  - Clinical trial design
  - Clinical trial endpoints
  - Regulatory environment
- Unique challenges of CF
  - Orphan disease population
  - Multisystem disease
  - High number of variables (e.g. comorbidities, infections, concomitant medications)
  - Life-shortening disease
  - Rapid adoption of new therapies
  - Evolving treatment regimens

# Therapeutics for CF Today

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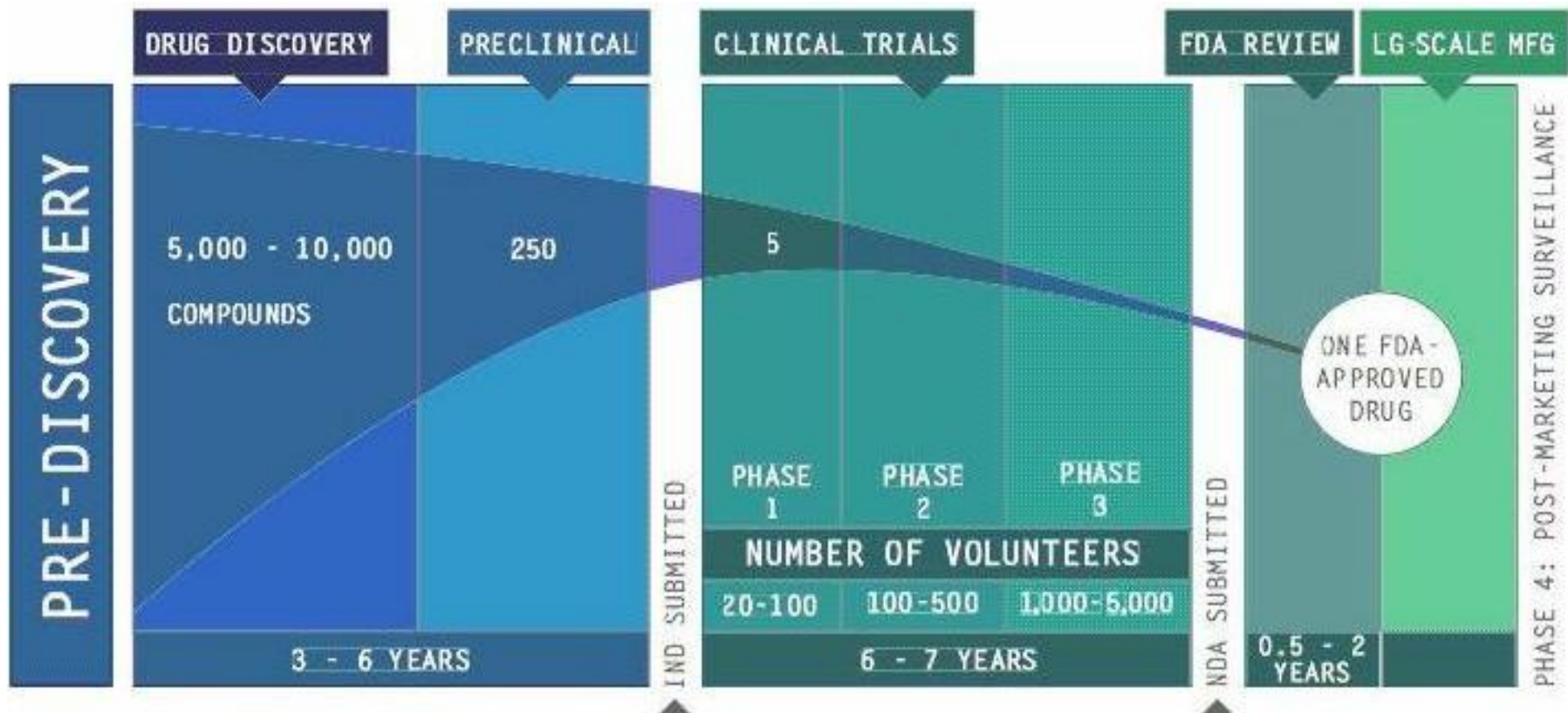
- To target gene function
  - Ivacaftor for G551D mutations (Kalydeco)
- To target obstruction
  - Mechanical airway clearance
  - Mucolytics
    - Dornase alpha (Pulmozyme)
    - Hypertonic saline
    - Inhaled mannitol (Bronchitol)
- To target inflammation
  - High-dose ibuprofen
  - Inhaled corticosteroids [????]
  - Leukotriene receptor antagonists (e.g. montelukast)
  - Azithromycin

# Therapeutics for CF Today

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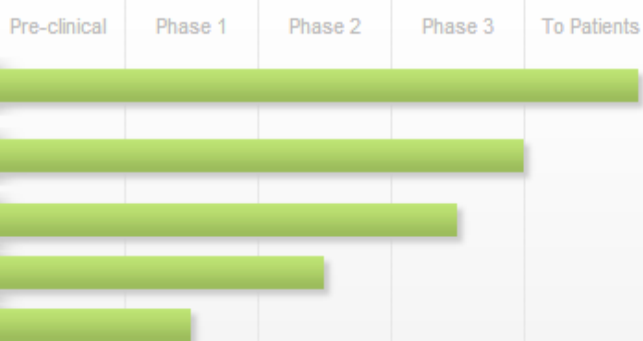
- To target airway infection
  - Inhaled tobramycin (TOBI, Bramitob, Podhaler)
  - Inhaled colistin (Colomycin, Colobreathe)
  - Inhaled aztreonam lysine (Cayston)
  - Systemic antibiotics
- To improve nutrition and weight
  - Pancreatic enzyme supplements
  - Vitamin replacement
  - Diabetes management

# Drug Development Process



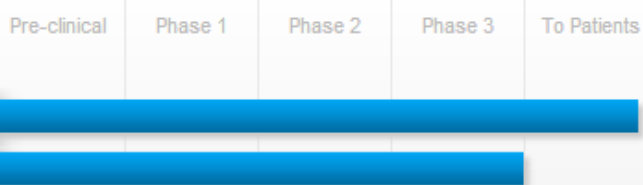
## CFTR Modulation

Kalydeco™ (formerly known as VX-770)  
Ataluren (formerly known as PTC124)  
VX-809 + Kalydeco™  
VX-661 + Kalydeco™  
N6022



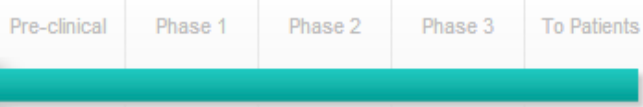
## Restore Airway Surface Liquid

Hypertonic Saline  
Bronchitol



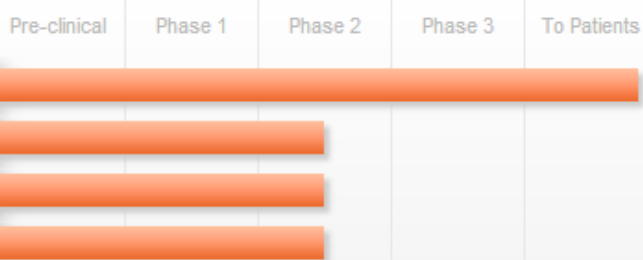
## Mucus Alteration

Pulmozyme®



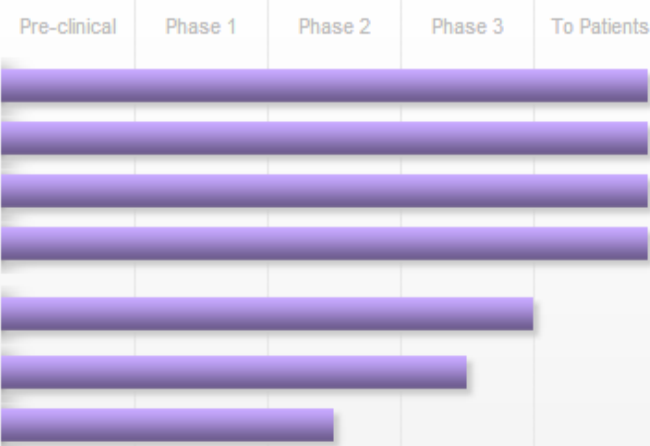
## Anti-Inflammatory

Ibuprofen  
Alpha 1 Anti-trypsin  
KB001A  
Sildenafil



## Anti-Infective

Inhaled Tobramycin  
Azithromycin  
Cayston®  
TIP (TOBI Inhaled Powder)  
Levofloxacin (Inhaled)  
Arikace™  
AeroVanc™



## Nutrition

AquADEKs  
Pancrelipase Enzyme Products  
Liprotamase



# Clinical Trial Endpoints in CF

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- Outcome measures
  - Death
  - Time to event
  - Symptom improvement
- Surrogate measures
  - FEV<sub>1</sub> (or any other pulmonary function parameter)
  - Weight
- Biomarkers
  - Density of bacteria in sputum
  - Sweat chloride
  - CT scans
  - S<sub>p</sub>O<sub>2</sub>
  - Serum levels (e.g. vitamins, WBC, IL-8)

# Regulatory Environment

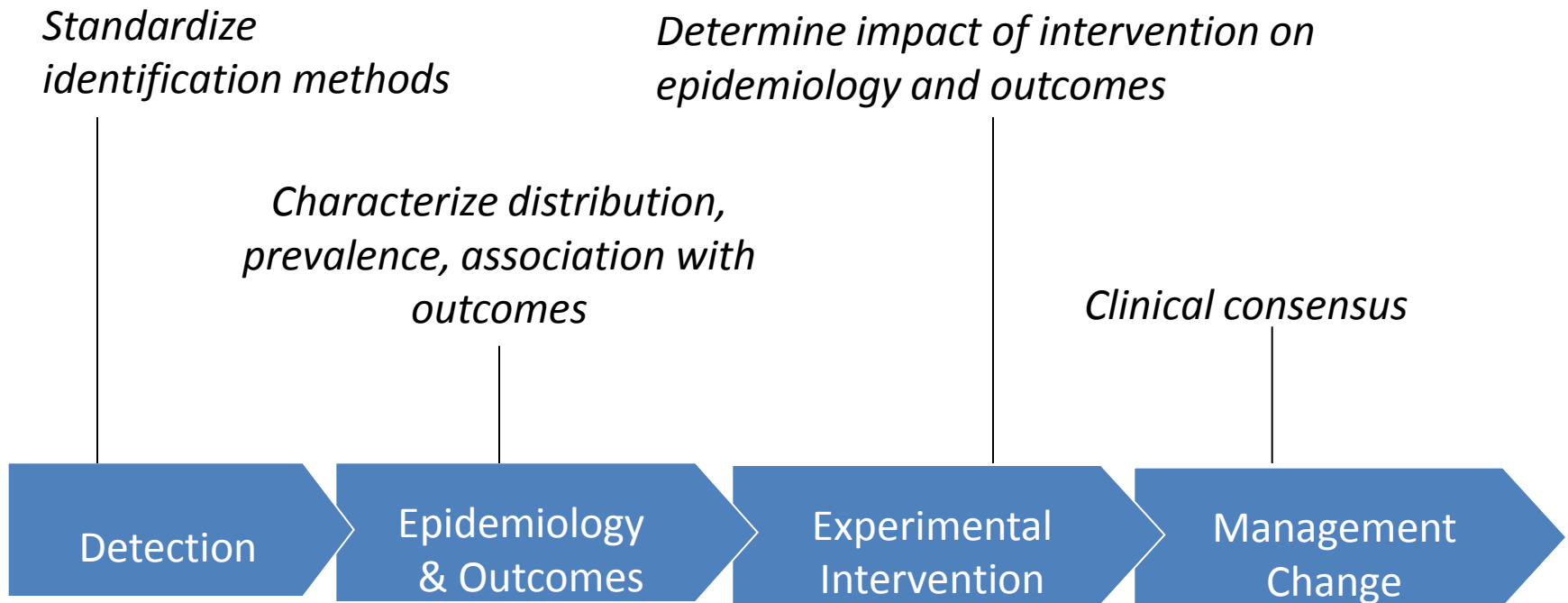
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- Wide variation amongst countries
- Safety first
- Statistics rule
- Variety of reviewer experience in CF or orphan disease
- Conflicting advice is not uncommon
- Wide variation in timelines for review and approval
- Medical community often evolves care beyond clinical trial experience (e.g. “on/off” inhaled antibiotics)

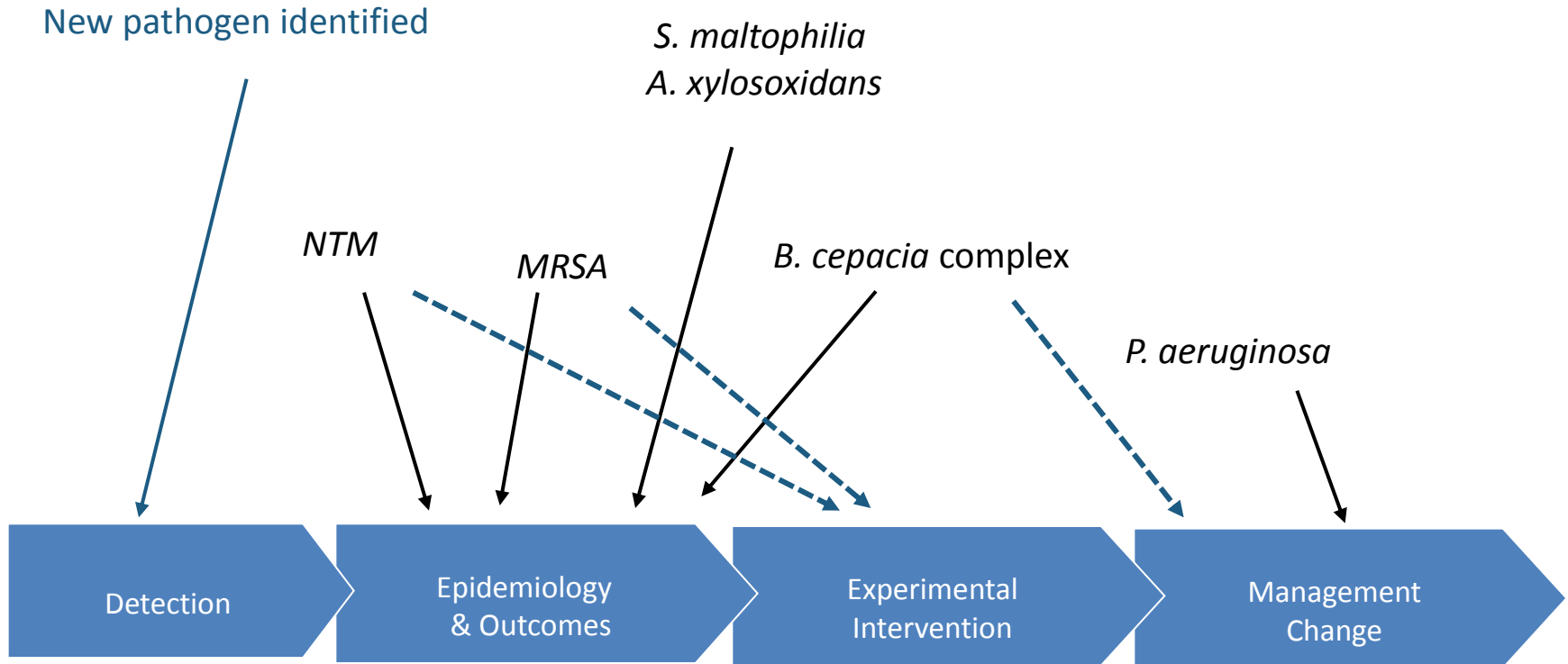


# Evolution of Clinical Care in CF

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# Clinical Knowledge of CF Bacterial Species



# CF: Inhaled Antibiotic Pipeline

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Pipeline Drug	2010	2011	2012	2013
DPI colistin (Colobreathe ~ Forest)	Ph 3	Ph 3	Ph 3 (EU approval 2/2012)	
DPI tobramycin (PODHALER ~ Novartis)	Ph 3	Ph 3 (EU approval 7/2011)	Ph 3	Ph 3 (FDA approval 3/2013)
DPI ciprofloxacin (Bayer)	Ph 2	Ph 2		
DPI vancomycin (AeroVanc ~ Savara)			Ph 1	Ph 2
Inhaled levofloxacin (Aeroquin ~ MPEX → Aptalis)	Ph 2	Ph 3	Ph 3 (NS vs PBO)	Ph 3 (Non-inferior to TIS)
Liposomal amikacin (Arikace ~ Transave → Insmed)	Ph 2	Ph 3	Ph 3 (EU & Canada only)	Ph 3 (EU & Canada only)
Liposomal ciprofloxacin (Aradigm)	Ph2	Ph 2	Development on hold	
Liposomal tobramycin (Axentis)	Ph 2			

# Physician, Patient and Family Expectations

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- Variation in practice patterns impacts uptake or feasibility of any given clinical trial
- Patients participate “as long as they are going to get the good stuff”
  - Placebo-controlled trials
  - Open-label extension trials
- Trials of long duration can negatively impact enrollment and/or need for standard of care can impact interpretability of the trial

# Challenges of Drug Development in CF

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- Small population
  - Newborn screening
  - ~30% of patients participate in clinical trials
  - Heterogeneous
- Multisystem disease
- High number of variables (e.g. comorbidities, infections, concomitant medications)
- Life-shortening disease – therapy is good, but not good enough
- Rapid adoption of new therapies
- Evolving treatment regimens
- Little known about endpoints and predicted behavior within a given clinical trial
- Meeting and managing expectations of patients, families, and health care professionals