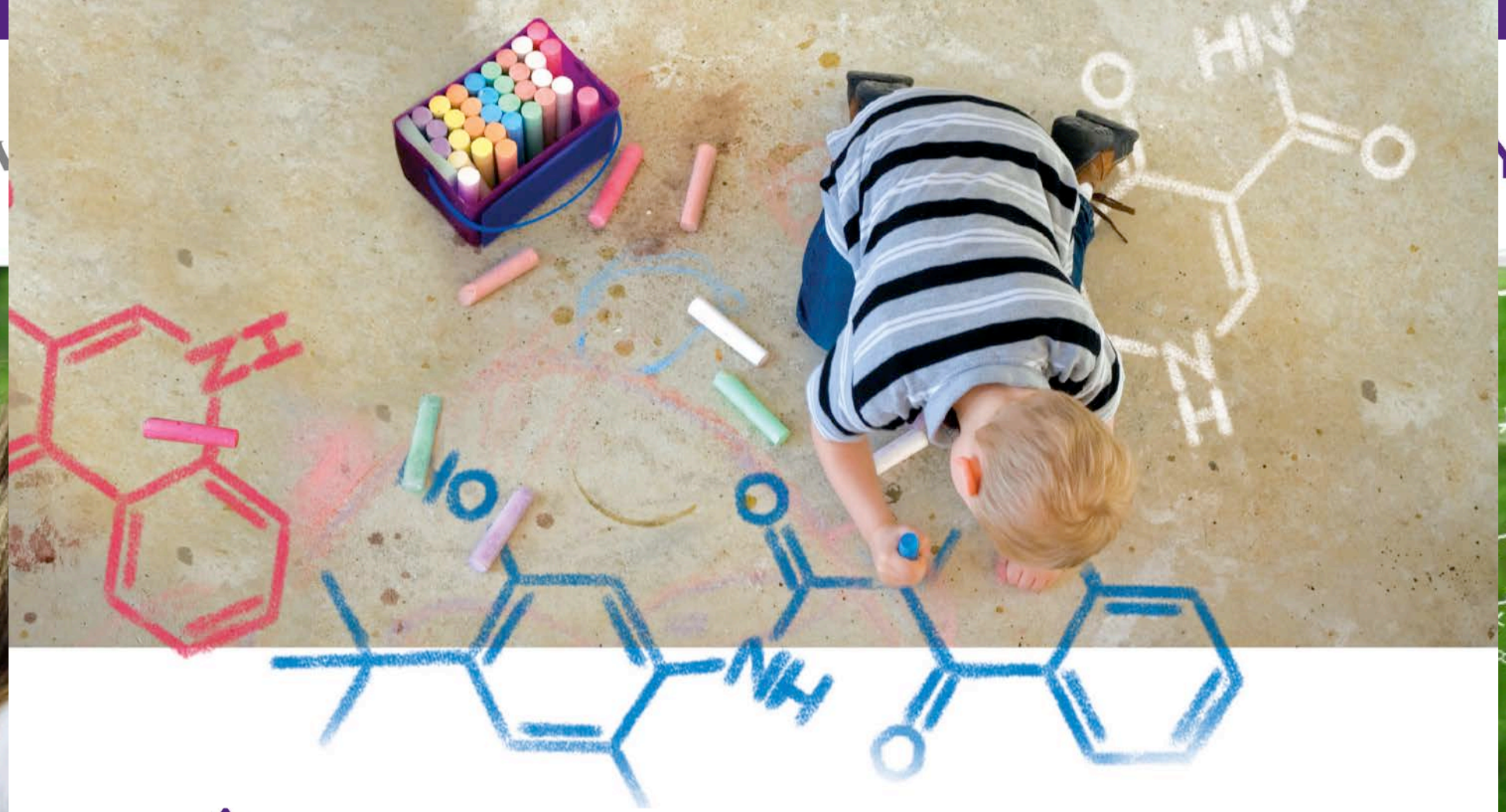


VERTEX™

THE SCIENCE *of* POSSIBILITY

Innovative Approaches for Rare Disease: Cystic Fibrosis Case Study

Annetta Beauregard, MS, MBA,
Vice President, Regulatory Policy & Operations, Vertex

A Little Bit About Vertex…

APPROVED MEDICINES
DEVELOPMENT-STAGE MEDICINES
OUTLICENSED DEVELOPMENT-STAGE MEDICINES

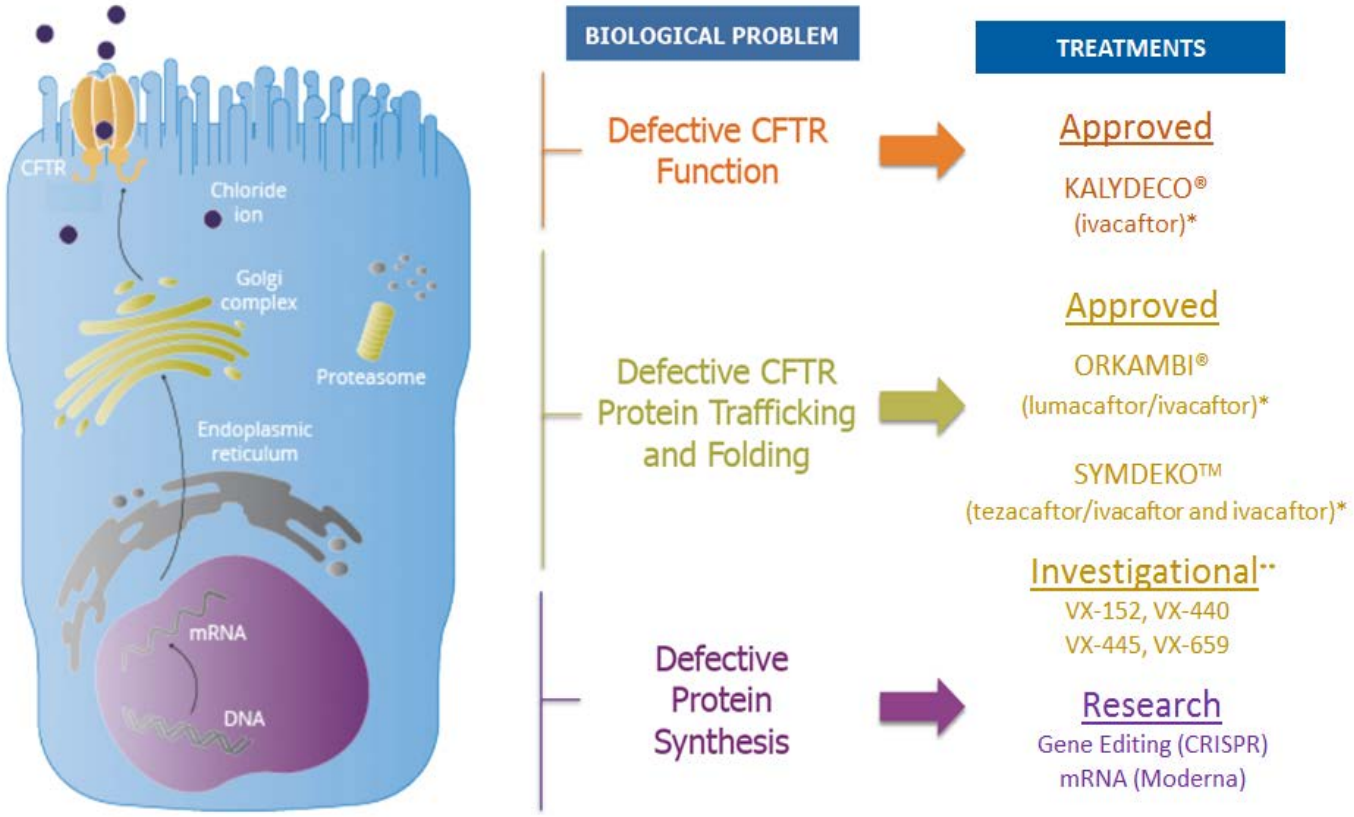
RESEARCH ENGINE

A Little Bit about Cystic Fibrosis…

- CF is a rare, lethal disease affecting ~**75,000** people worldwide. ~**30,000** in US
- CF is an autosomal recessive genetic disease
- Mutations, or errors, in the cystic fibrosis transmembrane conductance regulator (CFTR) gene lead to absence/reduced amounts of or inadequate function of CFTR chloride channel at the surface of epithelial cells
- If the CFTR protein does not function properly, the balance of chloride and fluids is disrupted, causing mucus in various organs to become thick and sticky leading to lung infections, respiratory failure, poor digestion, and problems in the reproductive system.
- High burden of therapy, mostly focused on treatment of symptoms
- Median age of death is 30

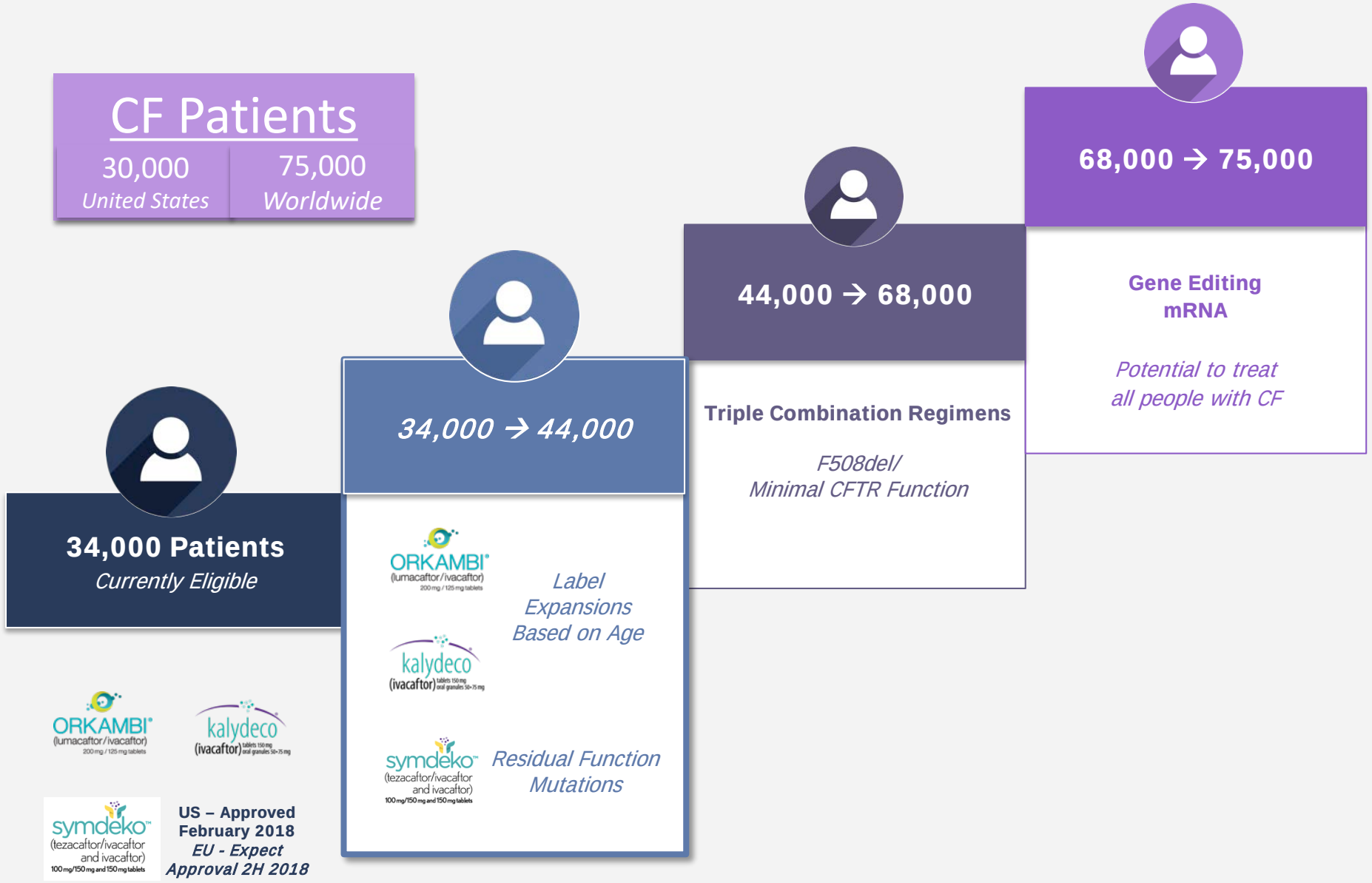
The Genetics of Cystic Fibrosis

- ~2,000 mutations have been identified, with ~300 known to result in CF
  - **>1,200 CFTR mutations carried by 5 or fewer people in the world**



* Approved for use in patients with cystic fibrosis and specific CFTR gene mutations.
** Compounds under investigation in combination with other therapies.

Developing Medicines for All People With CF



Original US Approval of Kalydeco and Initial Expansions Based on Clinical Trial Data

- **January 30, 2012** - Approved for patients 6 and older carrying at least one copy of G551D mutation
  - Approximately 1,200 people in the US
  - **First medicine to treat the underlying cause of cystic fibrosis**

- **February 21, 2014** – Approved for patients 6 and older carrying one of eight additional mutations (G128R, S529N, S549R, G551S, G1244E, S1251N, S1255P, G1349D)
  - Expands to approximately 150 people age 6 and older in the US who carry one of the eight additional mutations

- **December 29, 2014** – Approved for patients 6 and older carrying R117H mutation
  - Approximately 500 patients in the US 6 and older

Challenges of further expansion

- Initial approval/Expansions were based on clinical trials
  - Adequate numbers of patients available for study

- Additional mutations where ivacaftor might be effective, but difficult/infeasible to assess
  - **>1,500 mutations carried by 5 or fewer patients worldwide**

- Innovative approach required to license KLD for patients where direct clinical study may not be feasible

Innovative Regulatory Approach – use of in vitro data

Novel Approach Allows Expansion of Indication for Cystic Fibrosis Drug

SHARE | TWEET | LINKEDIN | PIN IT | EMAIL | PRINT

Tony Durmowicz, M.D., Lead Medical Officer, Division of Pulmonary, Allergy and Rheumatology Products, Office of Drug Evaluation II, CDER
Mike Pacanowski, Pharm.D., MPH, Associate Director for Genomics and Targeted Therapy, Office of Translational Sciences, CDER

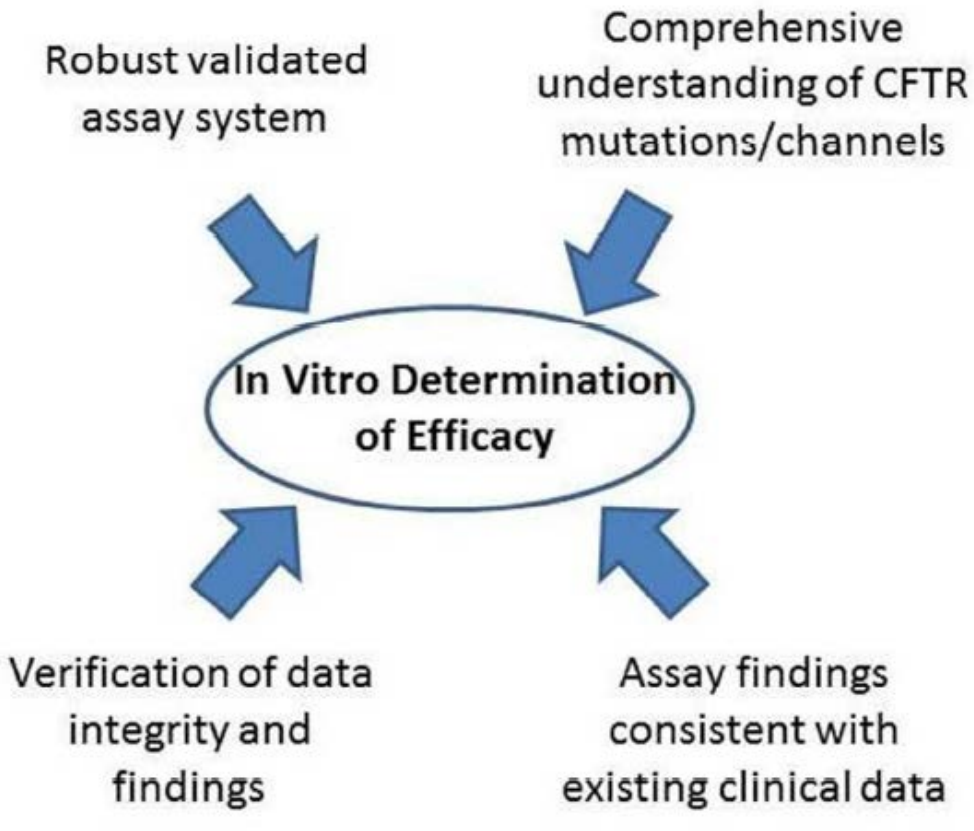
Typically, when FDA approves an expansion of the indication for a drug, it means that additional clinical data have shown the drug can safely and effectively treat patient populations other than those for which it was originally intended. But collecting additional clinical data is sometimes very difficult, especially with rare diseases. Patient populations are small and are often scattered throughout the country or the world, and therefore hard to access.

In the case of the drug Kalydeco (ivacaftor)—a drug that works in patients with specific mutations of the cystic fibrosis transmembrane conductance regulator (*CFTR)* gene that cause cystic fibrosis (CF)—expansion of the indication was possible, thereby offering a disease-modifying treatment option to hundreds of patients living with CF, despite not having additional clinical data. To approve the indication expansion, a novel approach was used that relied on evidence from laboratory-based in vitro assay data. These data gave us sufficient information to determine whether certain populations with CF would likely respond to the drug.

"Many rare cystic fibrosis mutations have such small patient populations that clinical trial studies are not feasible. This challenge led us to using an alternative approach based on precision medicine, which made it possible to identify certain gene mutations that are likely to respond to Kalydeco." – ***Janet Woodcock***

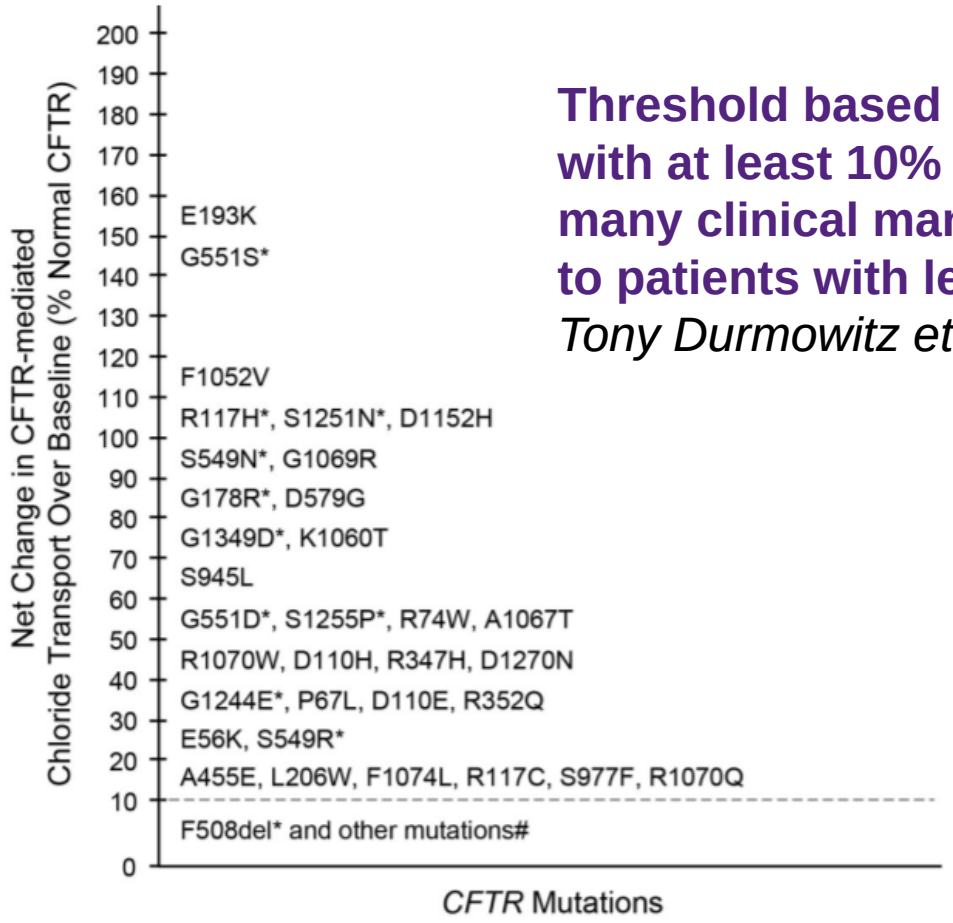
Innovative Regulatory Approach – use of in vitro data

4 pillars for evaluating use of in vitro data to expand indication in absence of clinical data



In Vitro Data Supports Expansion of Kalydeco Indication to Include 23 Addl. Responsive Mutations

Figure 1: Net Change Over Baseline (% of Normal) in CFTR-Mediated Chloride Transport Following Addition of Ivacaftor in FRT Cells Expressing Mutant CFTR (Ussing Chamber Electrophysiology Data)



*Clinical data exist for these mutations *[see Clinical Studies (14)]*.
#A46D, G85E, E92K, P205S, R334W,R347P, T338I, S492F, I507del, V520F, A559T, R560S, R560T, A561E, L927P, H1054D, G1061R, L1065P, R1066C, R1066H, R1066M, L1077P, H1085R, M1101K, W1282X, N1303K mutations in the *CFTR* gene do not meet the threshold of change in CFTR mediated chloride transport of at least 10% of normal over baseline.

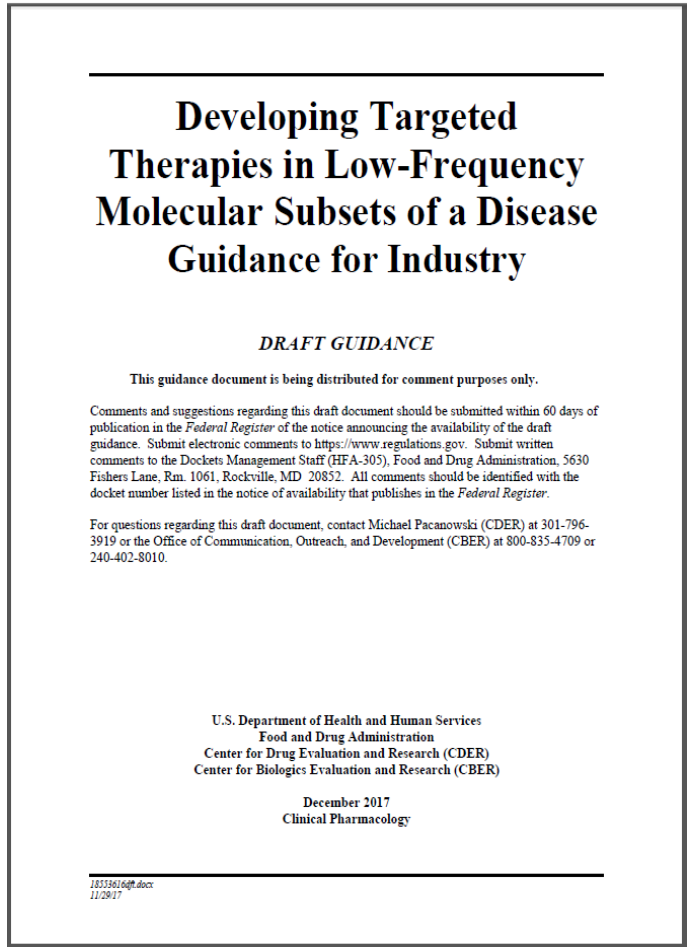
Threshold based on data showing patients with at least 10% of normal CFTR activity lack many clinical manifestations of CF compared to patients with less CFTR activity

Tony Durmowitz et al. Annals of ATS.Oct 11, 2017

Source: Kalydeco (ivacator) tablets. Boston, MA: Vertex, May 2017 (package insert).

FDA Targeted Therapies Draft Guidance (Dec 2017)

- Provides recommendations on **grouping patients with different genetic mutations** of eligibility in clinical trials
- Agency will accept patient groupings if **reasonable to expect grouped patients will have similar pharmacological responses** based on a strong scientific rationale
- Agency **will generally approve drug for all subsets included in the grouping irrespective of whether subsets were represented in the clinical trial(s)**
  - Sponsor should include mutation-by-mutation data in the label



Developing Targeted Therapies in Low-Frequency Molecular Subsets of a Disease Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact Michael Pacanowski (CDER) at 301-796-3919 or the Office of Communication, Outreach, and Development (CBER) at 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

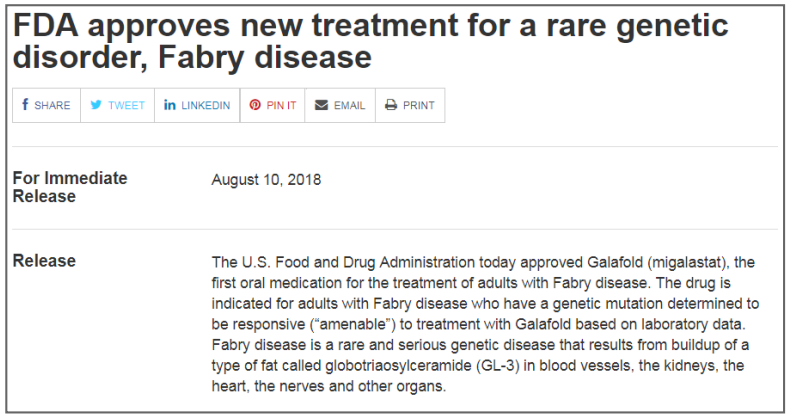
December 2017
Clinical Pharmacology

1833616dft.docx
11/29/17

Recent Approvals Reinforce Viability of In Vitro Data-Based Approach

- **Fabry Disease** - rare X-linked lysosomal disorder caused by mutated GLA gene; leads to functional impairment of multiple organs and premature death
  - More than 3,000 patients in the US

- Aug 2018 - **Galafold (migalastat) granted Accelerated Approval for adults with Fabry disease with one of 348 "amenable" mutations based on in vitro data**
  - Review package not yet available



FDA approves new treatment for a rare genetic disorder, Fabry disease

SHARE | TWEET | LINKEDIN | PIN IT | EMAIL | PRINT

For Immediate Release	August 10, 2018
Release	The U.S. Food and Drug Administration today approved Galafold (migalastat), the first oral medication for the treatment of adults with Fabry disease. The drug is indicated for adults with Fabry disease who have a genetic mutation determined to be responsive ("amenable") to treatment with Galafold based on laboratory data. Fabry disease is a rare and serious genetic disease that results from buildup of a type of fat called globotriaosylceramide (GL-3) in blood vessels, the kidneys, the heart, the nerves and other organs.

- **Limited clinical data**
  - Efficacy demonstrated in 45-patient PBO-controlled study
    - Specific mutations studied clinically not included in FDA-approved labeling

- **In vitro assay used to identify responsive mutations on the basis of relative and absolute increases in alpha-Gal A activity**

VERTEX

Questions