ADVANCING THE DEVELOPMENT PIPELINE FOR THE TREATMENT OF INFLUENZA

Melissa Willis, Ph.D.
Chief, Influenza Therapeutics

Resilient People. Healthy Communities. A Nation Prepared.

Roadmap

- What is our goal?
- Where have we been?
- Where are we going?
- What strategies are we pursuing to achieve the goal?

Program Strategy & Goals

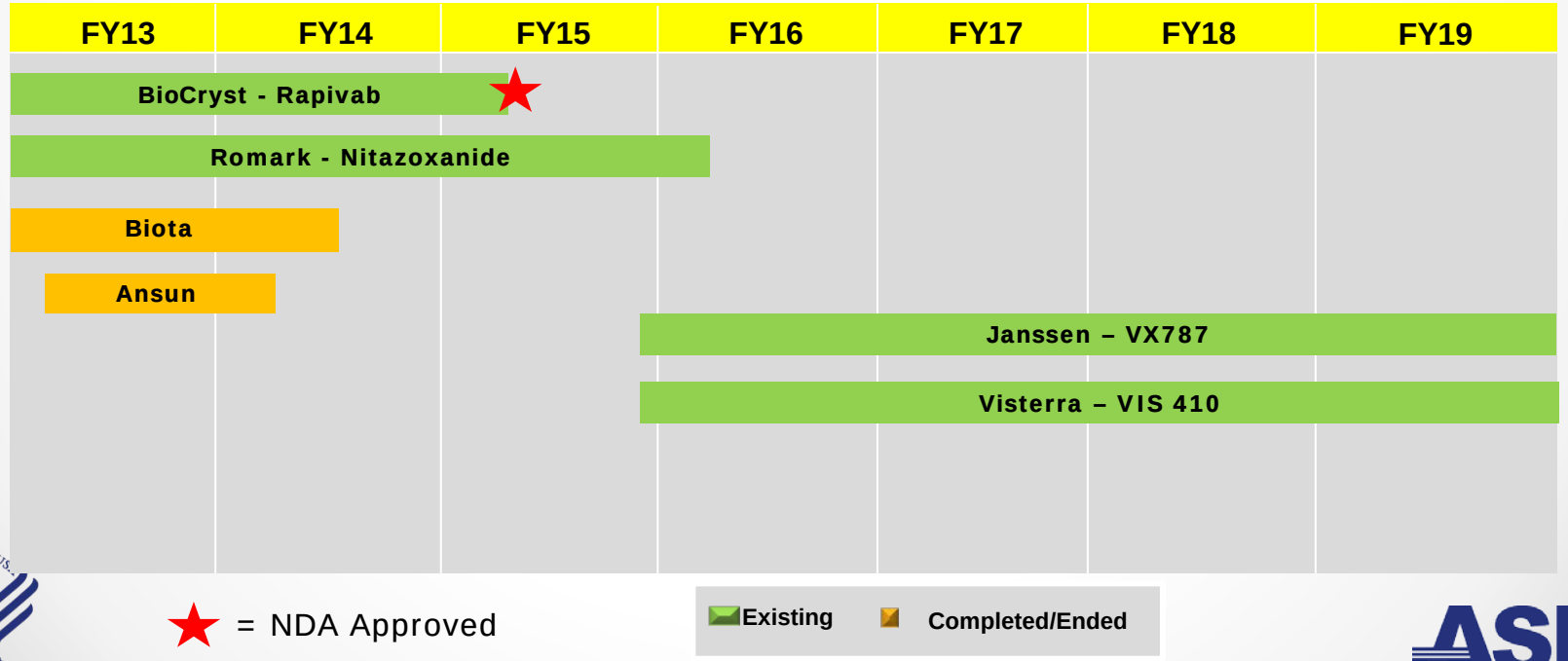
Program Goal
Reduce morbidity and mortality in all patient populations during an influenza pandemic by supporting advanced development, evaluation, and approval of new influenza antiviral drugs

- Mission established in the 2005 *National Strategy for Pandemic Influenza*, *HHS Pandemic Influenza Plan* and the 2006 *Implementation Plan for the National Strategy for Pandemic Influenza*

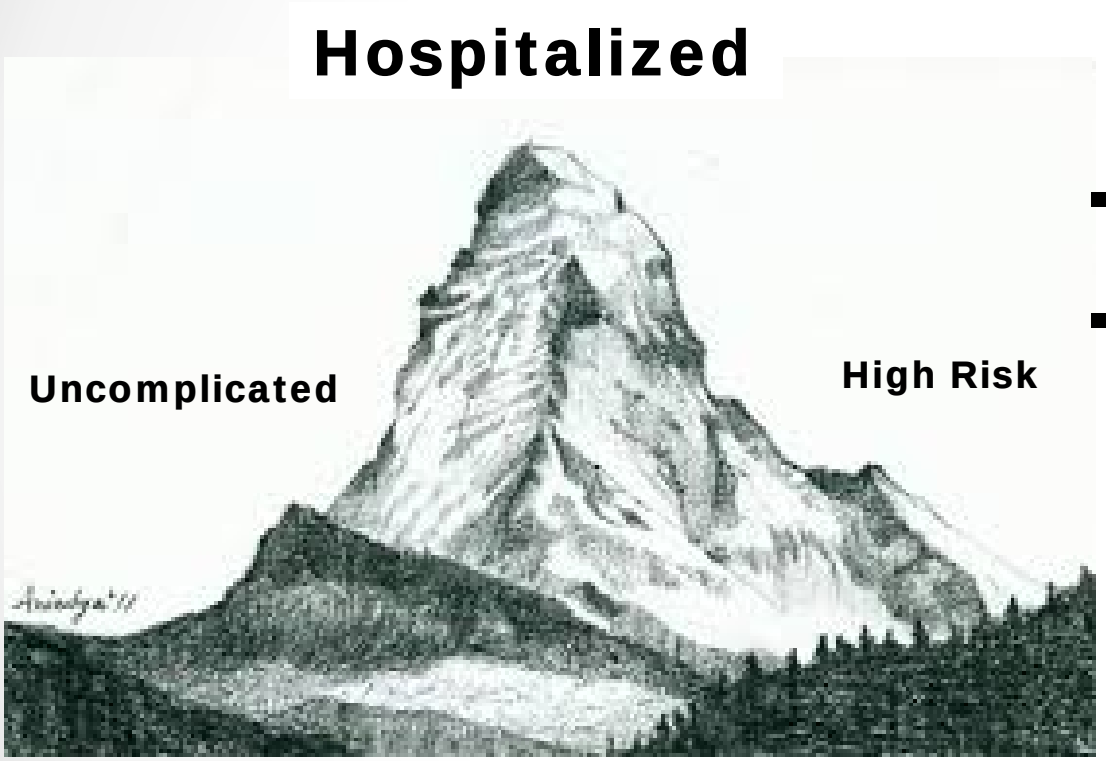
- Strategy to achieve the goal combines stockpiling existing antiviral drugs with development of new antivirals to address critical unmet medical needs for treating severely ill, hospitalized and pediatric populations
  - Stockpile total of 81M treatment courses of influenza antiviral drugs
  - Advanced development of new antivirals with novel mechanisms of action and/or combination therapy

Influenza Therapeutics Program Line-up

- 4 development programs
  - **BioCryst**— IV peramivir (Rapivab); approved in December 2014 for the treatment of influenza
  - **Romark**—Nitazoxanide; Phase 3 clinical trial completed, NDA submission in 2016
  - **Janssen** – VX787; Phase 3 development program for the hospitalized and high risk population
  - **Visterra** – VIS410 mAb; Phase 2 and 3 development program; hospitalized and pediatrics



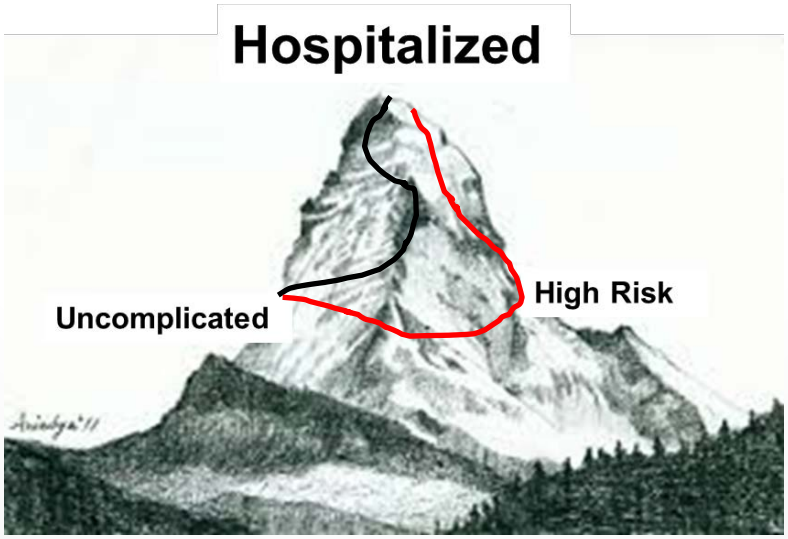
Trajectory for the Future: Challenges and Gaps



- Ability of a single drug or class of drugs to treat all stages of influenza infection and all populations unlikely.
- Historically limited pipeline of novel agents
- Leaves gaps in our preparedness:
  - Severely ill, hospitalized influenza patients
  - More effective treatment options, suitable for all populations including pediatrics

Areas of Emphasis in 2015

- Better define the target product profile for hospitalized indication
- Invest in drugs with novel MOA to reduce risk of resistance
  - mAb program launch
  - Small molecules and drugs in combination
- Using data to better inform decision making
  - Clinical Endpoints – evaluate existing datasets



Strategies to Address Unmet Needs

Critical unmet medical needs:

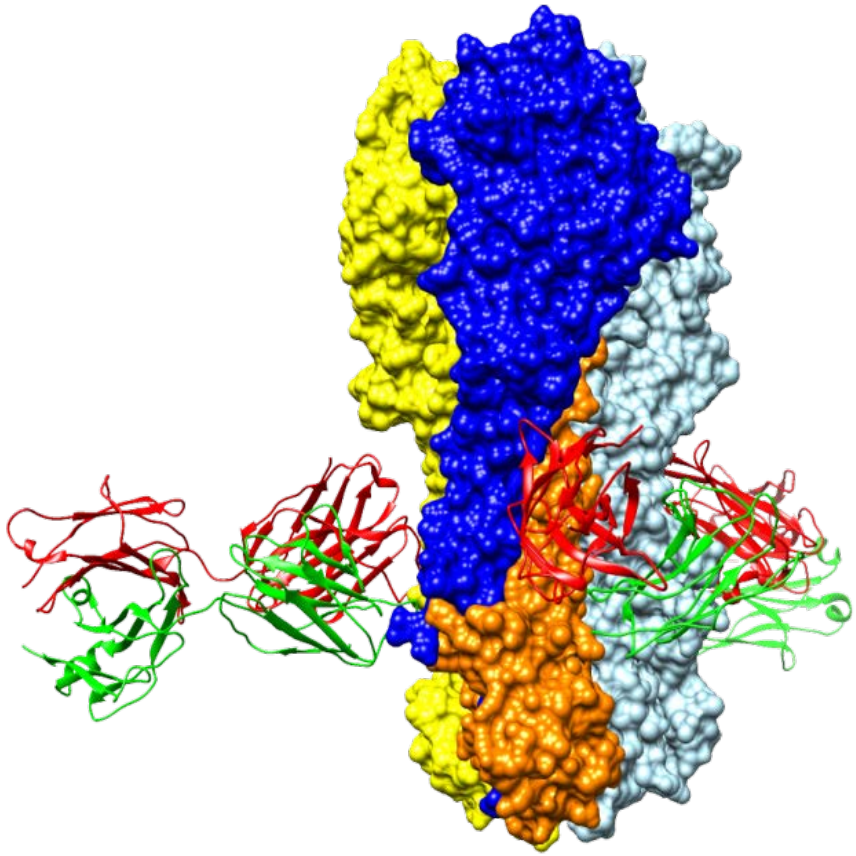
- **Severely ill, hospitalized influenza patients**
- **More effective treatment options, suitable for all populations**

- If the drug is a monoclonal antibody, then:
  - Broad spectrum = one or two mAbs cover all subgroups of Influenza A
  - IV formulation amenable to treatment of the severely ill
  - Expanded treatment window = must be effective more than 48 hours after symptom onset

- If the drug is a small molecule, then:
  - Needs to work better than neuraminidase inhibitors (NAIs)
    - Inhibits all Influenza A strains tested
    - Expanded treatment window beyond 48 hours
  - Suitable for combination therapy with existing NAI
  - Oral and IV formulations

Broad Spectrum Neutralizing Monoclonal Antibodies

- Target the HA stalk
  - Highly conserved
  - Novel target
  - Broad spectrum – Group 1 and 2, Influenza B
- Unique properties
  - Extended treatment window
  - Long half life likely resulting in single dose administration
  - Large binding surface reducing likelihood for resistance



Influenza mAb RFP

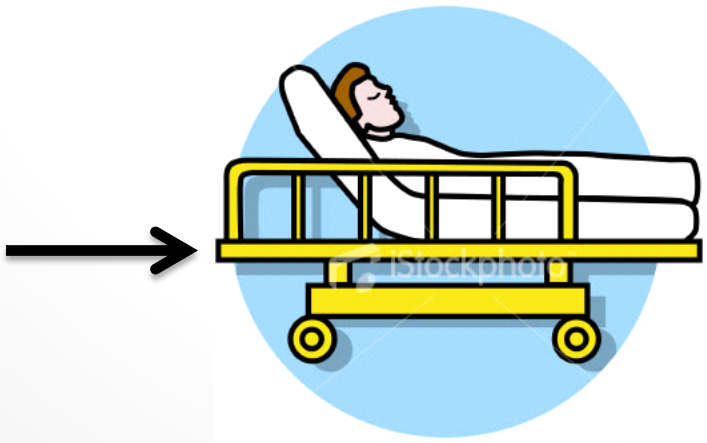
- Key Attributes for Influenza Broad-Spectrum mAbs
  - An indication for the treatment of seriously ill, hospitalized patients 6 months and older who are infected with influenza
  - Broad-spectrum neutralizing activity across multiple subtypes of influenza A viruses including, but not limited to, contemporary strains of H1N1, H2N2, H3N2, H5N1 and H7N9
  - Effective when treatment is initiated within 48-96 hours of influenza symptom onset (72-96 hours preferred)
  - Suitable for use in combination with other approved influenza therapeutics
  - Single dose treatment regimen with no more than three monoclonal antibodies

Clinical Endpoints

- Primary Goal: to develop improved clinical endpoints for better evaluation of clinical efficacy for severely ill, hospitalized population
- Secondary Goal: to evaluate other elements to increase likelihood of successful clinical trial in this population (i.e. large hospital/ERs, digital diary card reporting, better study design)
- Data-driven group comprised of HHS interagency, academia, and industry

Clinical Endpoints

- Using ordinal scale for initial evaluation of results from previous clinical trials in hospitalized patients
- Ordinal scale: death, ICU, mech. vent., supp. O2, length of hospitalization, return to normal activities
  - Developed from evaluation of ~1K hospitalized patients



Partnership Opportunities with BARDA

- Broad Agency Announcement (BAA)
- Request for Proposal (RFP) FY2015 – just closed
- We encourage frequent interactions prior to submission

What Types of Data?

- *In vitro* studies demonstrating broad-spectrum neutralizing activity across multiple subtypes of influenza A viruses including but not limited to modern strains of H1N1, H3N2, H5N1 and H7N9
- Pre-clinical animal studies demonstrating efficacy against multiple strains of influenza
- Data to support a wider therapeutic window (48-96 hours after infection with a preference for 72-96 hours after infection)
- Data to support combination therapy with other influenza drugs
- An active US Investigational New Drug (IND) application for an influenza indication, with appropriate pre-clinical GLP data
- A completed clinical study report documenting Phase 1 dose-escalation
- Evidence of adequate manufacturing capacity of final product(s)

Questions?

Thank you!

Melissa.Willis@hhs.gov