

The InBios logo features the word "In" in a red, italicized serif font, followed by "Bios" in a blue, italicized serif font. A red swoosh underline is positioned beneath the "In" and extends slightly under the "Bios".

InBios

Innovative Diagnostics for Infectious Diseases

Case Study: From EUA through direct *de novo* marketing authorization

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February 3, 2020

Case Study: ZIKV *Detect*[™] 2.0 IgM Capture ELISA

- Overview of InBios
- The Regulatory Pathway – a Dual Approach
- EUA Process and Amendments
- Clinical and Bench Study Challenges
- *De Novo* Submission and Marketing Authorization (DEN180069)
- Revocation of EUA
- Lessons Learned
- Opportunities for Improvement?
- Incorporation of RWE in 510(k)?

Innovative Diagnostics for Public Health

What we do:

InBios International develops and manufactures highly sensitive and specific immunodiagnosics for infectious diseases.

Our Mission:

Our mission is to serve the global marketplace with accurate, superior quality products that are easy to use and cost effective. InBios' products are backed by 20+ years of experience.

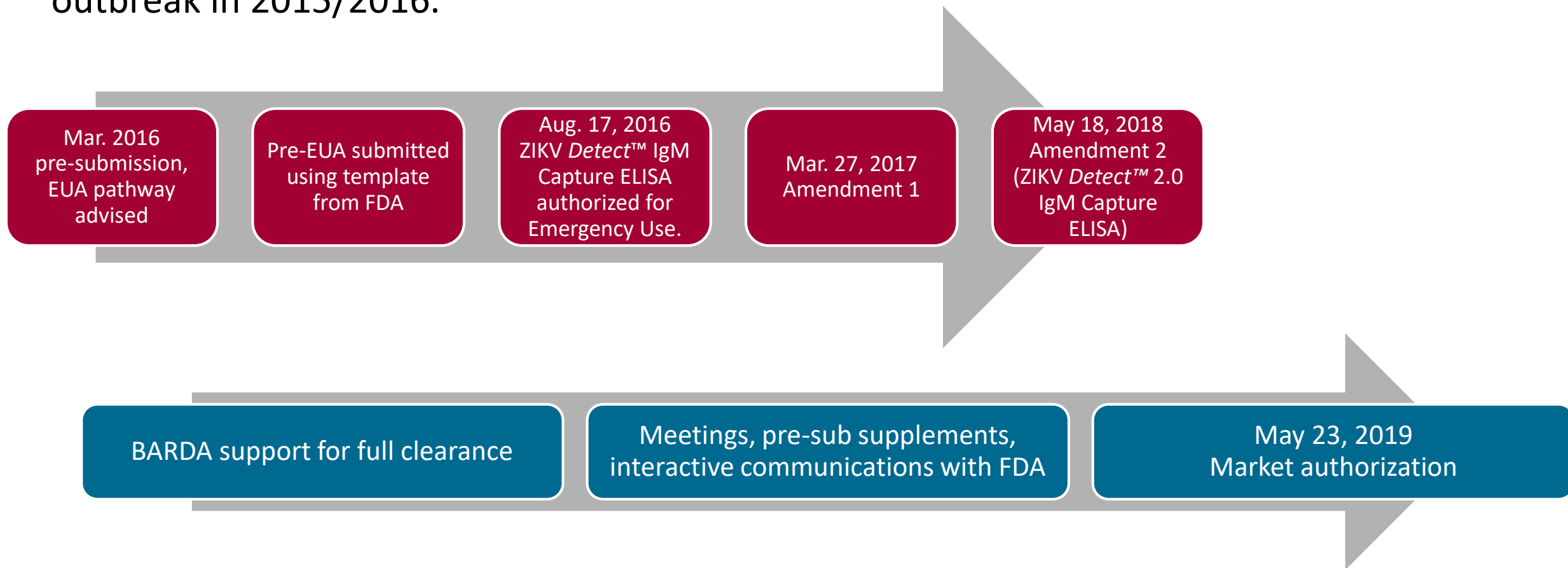
Organization:

- Staff of 77 committed scientists, engineers and associates
- Fully validated GMP facility, ISO 13485:2016 certified
- Strong presence in the 'flavivirus space'
 - FDA clearance for Dengue NS1 and IgM, West Nile IgM and Zika IgM IVDs
- Distribute product worldwide



Regulatory Pathway – A Dual Approach

Objective: Obtain an EUA with concurrent goal of full market clearance following Zika outbreak in 2015/2016.



EUA Process and Amendments

The Process:

- FDA template and interactive communication resulted in a smooth EUA process.
- Amendment #1: Customer feedback on assay identified the need for an amendment to the EUA device. Product insert updated for clarity.
- Amendment #2: 2nd Generation assay developed to increase sensitivity and specificity of the EUA device.
- **Note:** The name of the 2nd generation device changed. Amended version market authorized May 23, 2019.

Clinical and Bench Study Challenges

- Zika cases decrease in 2017 creating a challenge to obtain prospectively collected samples.
- Initially, FDA was still trying to collect sufficient information about Zika to give informed guidance to industry. Zika was not classified and guidance on clinical studies was delayed. Understandable, but did present a challenge to plan studies in advance, i.e., site selection, IRB approvals, etc.
- Reference standard not established. Gold standard did not exist.
- FDA required 'serial draws'. Created a major challenge as there was only one available commercial source that InBios could identify and extremely expensive.
- Collection of 'cross-reactive' samples that were well characterized was a challenge. Certain specimens extremely difficult to obtain such as Yellow Fever, Ross River virus.
- FDA's requirement that the specimen be confirmed by an FDA cleared or validated assay was extremely challenging. Most cross-reactive specimens could not be confirmed with a 'cleared' FDA assay.
- CDC and BARDA helped mitigate the above challenges. FDA also understood the challenges.



Direct *De Novo* Submission & Authorization

- Direct *De Novo* submission for the ZIKV *Detect*[™] 2.0 IgM Capture ELISA submitted to FDA Dec. 21, 2018.
 - Bench studies: Cut-off evaluation, Reproducibility, Cross-reactivity, Interference, Carryover, Freeze-Thaw
 - Clinical Studies: Sensitivity and Specificity studies at 3 sites – endemic and non-endemic
- Market Authorization received May 23, 2019.

NOTE: ZIKV *Detect*[™] 2.0 IgM Capture ELISA marketed from May 18, 2018 under EUA. Thousands of kits sold with only 1 field complaint. Sites were required to report positive results.



Revocation of EUA

- Revocation of InBios' EUA was done the same day as market authorization.
- Created a challenge at customer sites due to labeling changes.
- Labs were concerned with validation issues.
- FDA invited InBios to write a report as to whether InBios' newly authorized kit was adequate and available alternative to the EUA authorized kits.
- InBios had 30 days to submit a report as a 3rd Amendment to its EUA.

Lessons Learned

- Interaction with FDA key to a smooth process especially during an emergency.
- Mindset that full FDA clearance is the goal.
- With minimal clinical data available when EUA is granted, it is important to continue to evaluate the assay with customer feedback and seek ways to improve it prior to full clearance.
- Collaborators – very key in sourcing samples, external evaluations, site selection. CDC and BARDA played an important role.
- Prepare customers in advance of market authorization so that validation planning can occur.



Opportunities For Improvement?

- Well-characterized development panel available to industry during the pre-EUA phase will be helpful when industry strives to design an assay quickly during an emergency.
- Blinded well-characterized panel for external assessment of assay.
- Early consensus on reference standard.
- Repository of well-characterized cross-reactivity test samples.
- How to provide incentive to move past EUA? Small companies with limited resources to afford the cost of clinical studies, *De Novo* fees if market is perceived to be low.

How To Incorporate RWE Into 510(k)?

Real World Evidence (RWE) – possible things to consider:

- Public Health and commercial reference labs were the key purchasers of this assay. CLIA labs validate the assay even with an EUA. Can that data be used such that the need for reproducibility studies during 510(k) submission process be streamlined?
- Labs were required to submit to companies the number of positive specimens identified. Difficult to get data on whether the positive specimens were confirmed by CDC.
- The number of negative specimens were not known. If this data could be gathered, RWD (Real World Data) could perhaps be incorporated and clinical study data requirements could be streamlined.