

US – EU Mutual Recognition Agreement

Pharmaceutical Quality Congress
June 16, 2017

Presentation and Panel Discussion



PANEL

- I. **Howard Sklamberg, Esq.**, Principal, Sklamberg Strategies LLC
 - **FDA, 2010-2017**
 - Last position: Deputy Commissioner, Global Regulatory Operations and Policy
 - **Department of Justice, 1998-2010**

- II. **Cynthia Schnedar, Esq.**, EVP, Greenleaf Health
 - **FDA, 2014-2016**
 - Last position: Director, CDER, Office of Compliance
 - **Department of Justice, 1989-2004**

- III. **David Elder, EVP**, Greenleaf Health
 - **FDA, 1988-2012**
 - Last position: Director, Office of Regional Operations, ORA

AGENDA

- I. Background (History and Operational Reality)
- II. The Agreement
- III. Discussion Questions

ATTRIBUTION: Significant content of this presentation was pulled from, “The Mutual Reliance Initiative: A New World For Pharmaceutical Inspections,” Dara Corrigan, Acting Deputy Commissioner For Global Regulatory Operations And Policy

I. BACKGROUND

-HISTORY

HISTORY

- 1998 Mutual Recognition Agreement
 - Pharmaceutical Annex to US – EU trade agreement
 - US and EU agreed in principle to recognize each other’s GMP inspections
 - Agreement never fully implemented
- 2012 Food and Drug Administration Safety and Innovation Act
 - Section 712 created a specific statutory foundation:
 - “...may enter into arrangements and agreements with a foreign government... that the Secretary has determined as having the capability...”
 - “...shall perform such reviews and audits...of a foreign government...to determine that...the foreign government is capable of conducting inspections that meet the applicable requirements of this Act...”
 - “...The results of inspections performed by a foreign government...may be used as evidence of compliance with section 501(a)(2)(B) [*GMP*] or section 801(r) [*standards for admission of imported drugs*] or for any other purposes”

HISTORY

- 2014 Mutual Reliance Initiative
 - Rapid increase in imported drugs from nations where FDA devotes limited inspection resources (Ex. India, China) → Need for an expanded inspectorate
 - Teams from FDA and EU assessed the risks and benefits of an agreement
 - FDA invited to observe EU's Joint Audit Program
 - EU to conduct an audit assessment of FDA

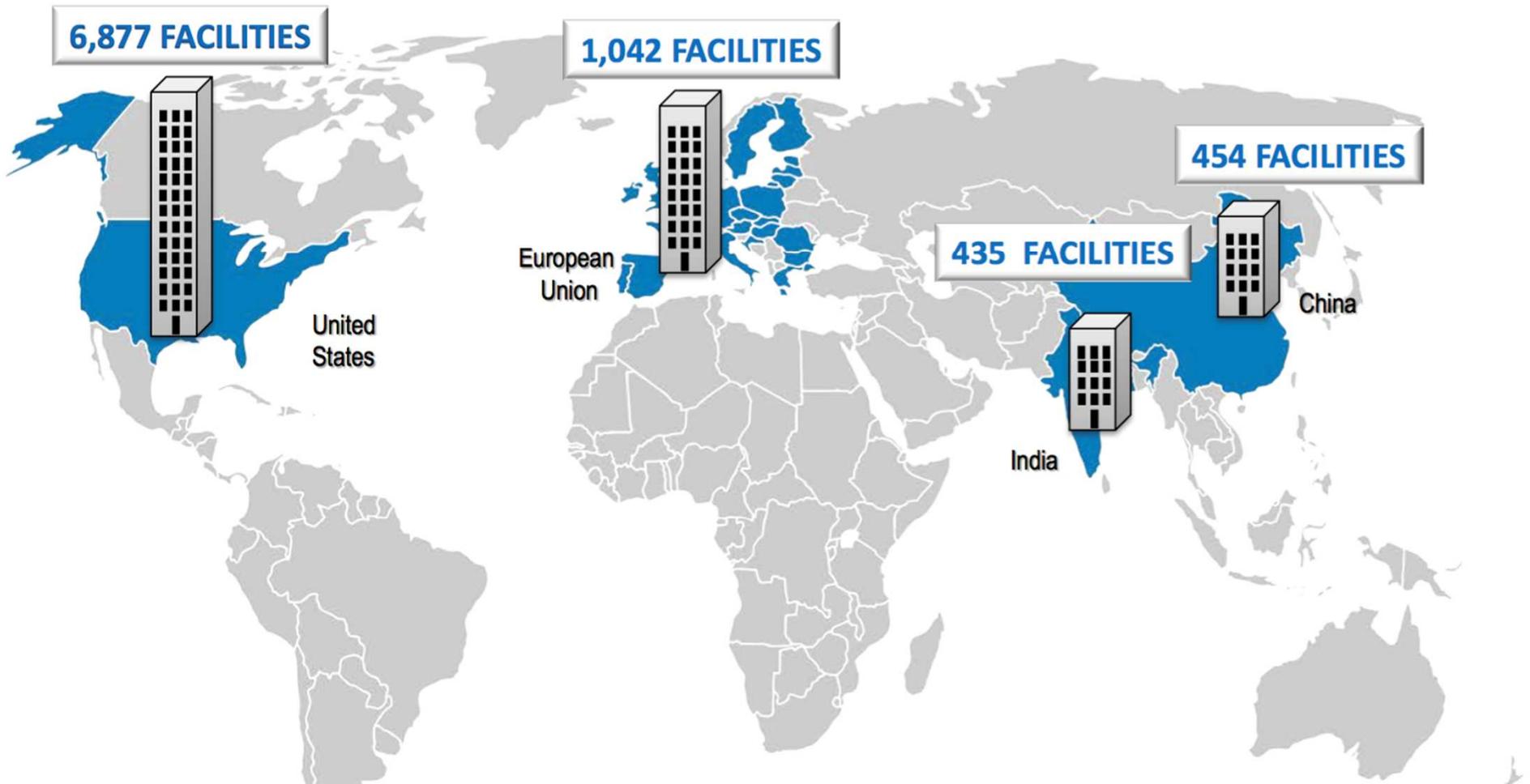
Goal: Reach an agreement with the European Union where each entity would be able to rely on each other's good manufacturing practice drug inspections

- EU inspectors inspect in their respective countries
- FDA inspects facilities in the U.S.
- Rely on each other's inspections

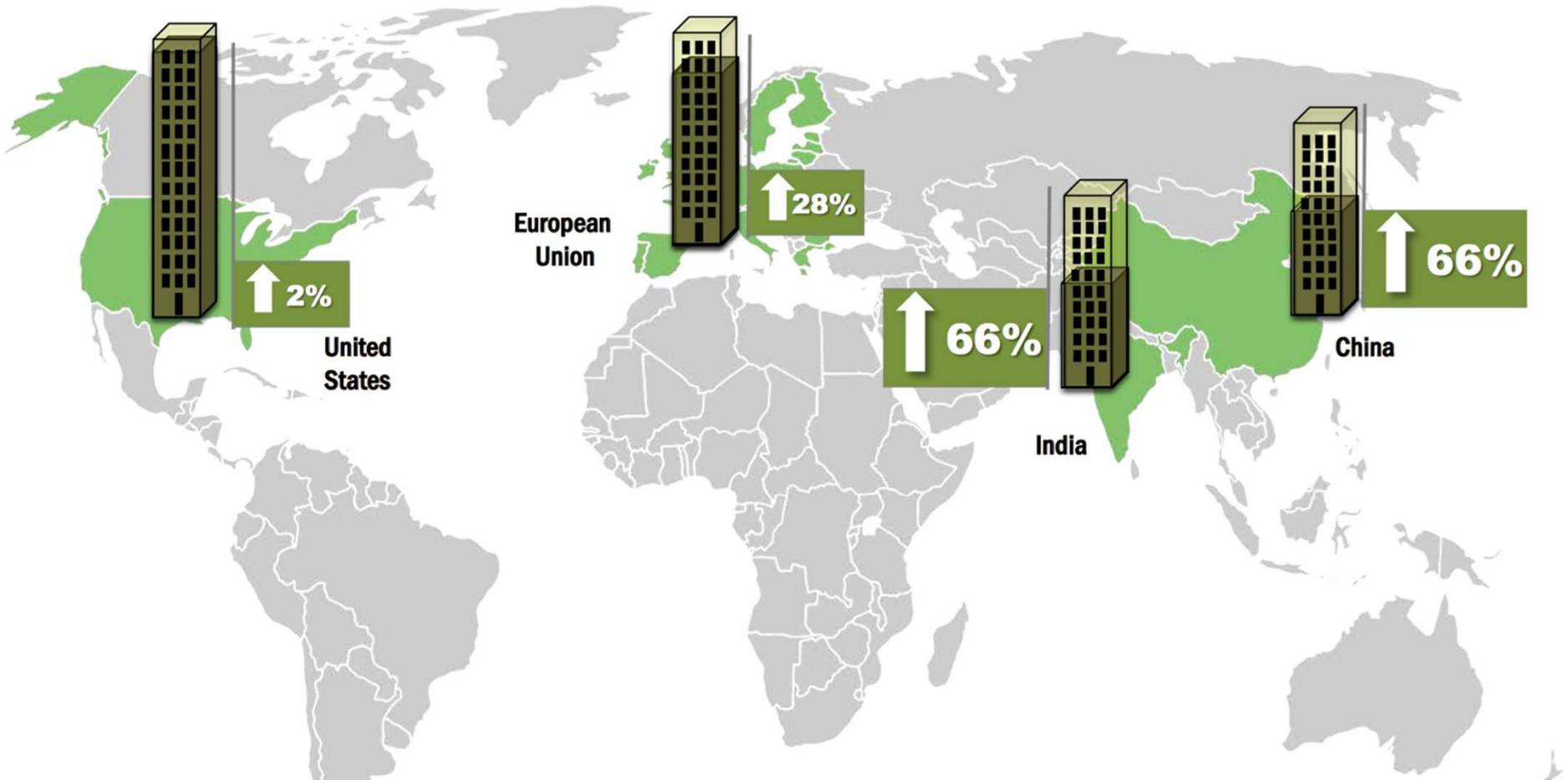
I. BACKGROUND

-“CHANGING OPERATIONAL REALITY”

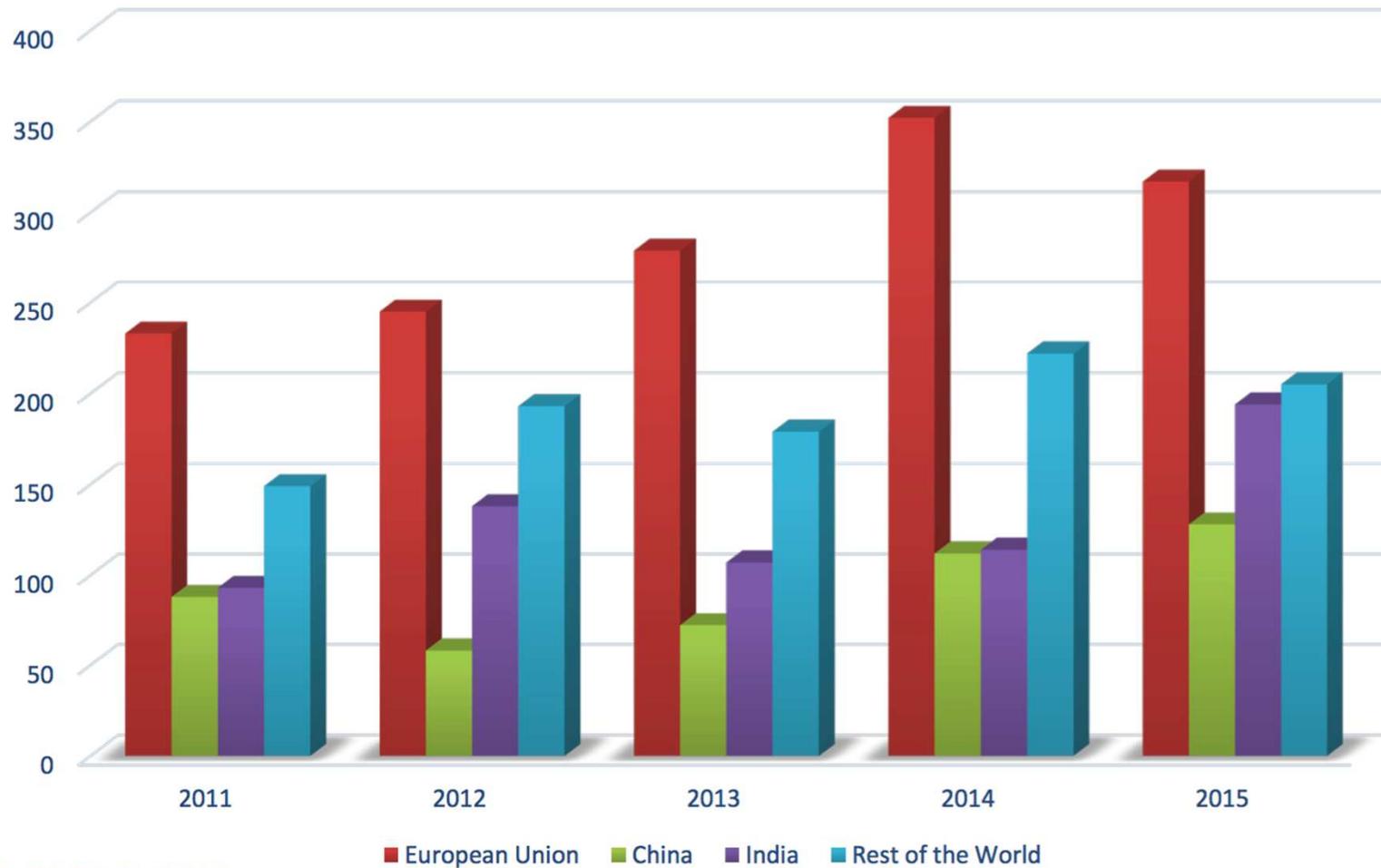
FDA REGISTERED DRUG FACILITIES 2011



FDA REGISTERED DRUG FACILITIES 2016



FDA INSPECTIONS THROUGHOUT THE WORLD



FDA INSPECTIONS IN THE EU

- In 2016, there were 1224 drug facilities in EU
- FDA inspected 32% of the drug facilities in EU
- 5% of inspected facilities in EU led to an Official Action Indicated classification
- EU countries account for 11% of the sites on #66-40 (GMP) and 5% of the sites on #99-32 (DDLRL)
- **CONCLUSION: High coverage, violation rate on par with domestic rate**



FDA INSPECTIONS IN CHINA

- In 2016, there were 754 drug facilities in China
- FDA inspected 21% of the drug facilities in China
- 22% of inspected facilities in China led to an Official Action Indicated classification
- China accounts for 36% of the sites on #66-40 (GMP) and 44% of the sites on #99-32 (DDLRL)
- **CONCLUSION: Lower coverage, violation rate >3X EU/Domestic US rate**



FDA INSPECTIONS IN INDIA

- In 2016, there were 722 drug facilities in India
- FDA inspected 23% of the drug facilities in India
- 14% of inspected facilities in India led to an Official Action Indicated classification
- India accounts for 27% of the sites on #66-40 (GMP) and 44% of the sites on #99-32 (DDLRL)
- **CONCLUSION: Lower coverage, violation rate >2X EU/Domestic US rate**



DOES THIS OPERATIONAL REALITY SUPPORT ENTERING INTO THE MRA?

- Does inspection of 32% of the registered drug facilities in the EU with a 5% OAI rate indicate that FDA is prioritizing and expending its limited inspection resources in the area of highest risk?
- Are the regulatory systems (laws, regulations, operations, actions) in the EU member states sufficiently mature and aligned with FDA requirements and expectations to support leveraging of resources? That is, are systems and health authorities ‘capable?’
- Can FDA better rely upon the work of other capable health authorities to extend coverage to sites in China and India, areas that represent significant manufacturing growth and origin of products for the US market and together account for 63% of the sites on IA #66-40 (GMP) and 88% of the sites on IA #99-32 (DDLRL)?

II. THE AGREEMENT

NEGOTIATION OF THE US-EU MUTUAL RECOGNITION AGREEMENT

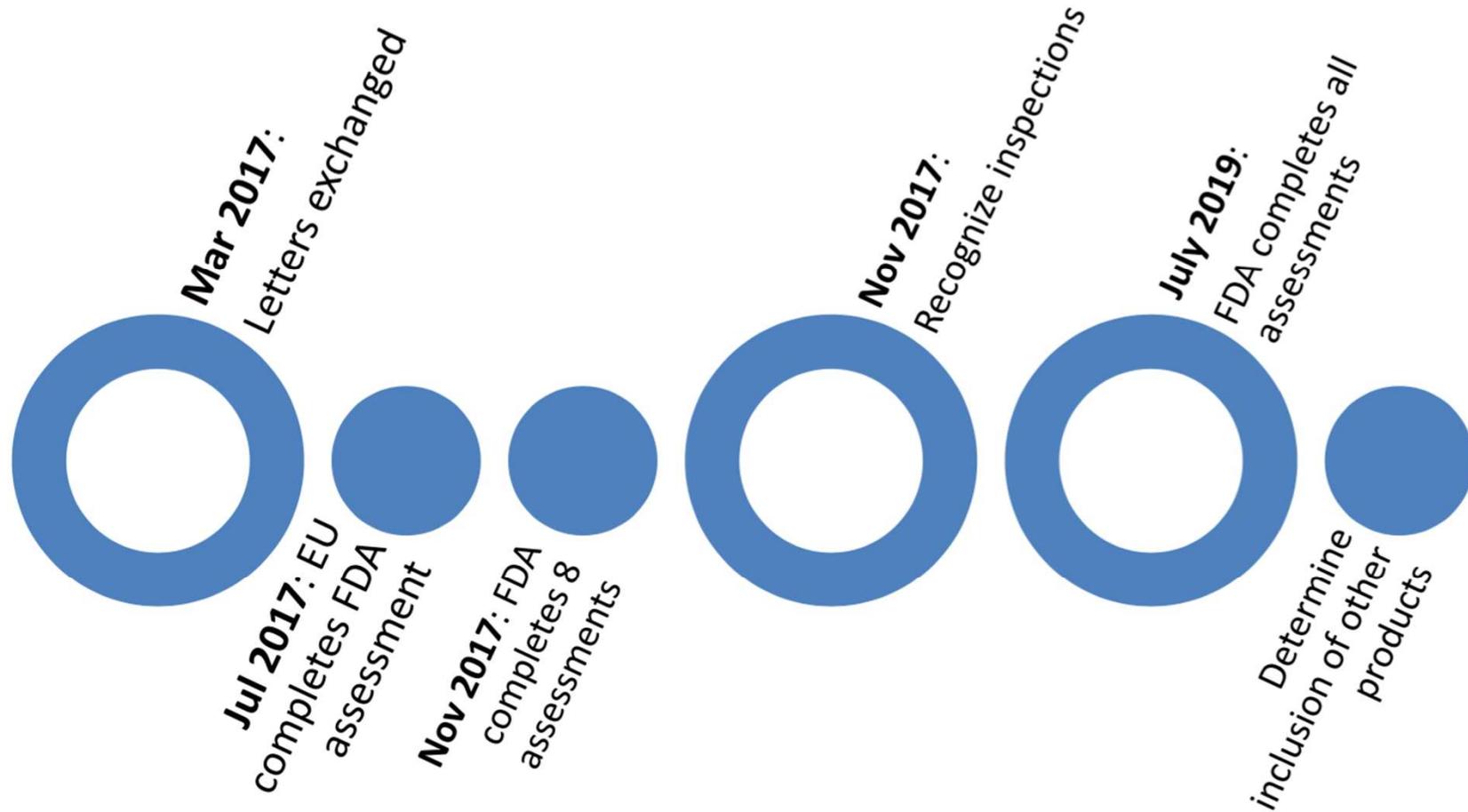
- Exchanged and analyzed ideas
- Developed Capability Assessment Process
- Sectoral Annex to the 1998 Mutual Recognition Agreement - Finalized in March 2017
- Expected Outcomes:
 - Reduce duplication
 - Lower costs (gov't & industry)
 - Improve allocation of resources
 - Increase public health protection



SCOPE

- Includes a vast majority of drugs
- Certain products will be reevaluated in the future, such as vaccines and veterinary products
- Surveillance and, under certain conditions, pre-approval inspections of marketed human drug facilities located within the US and EU

MAJOR DELIVERABLES



WORLDWIDE IMPACT

- Apart from the direct impact of drug facilities physically located in Europe and the U.S., the Agreement will:
 - Significantly expand inspectional coverage of drug facilities in the Rest of World (ROW)
 - Almost double the inspectional coverage of drug facilities located in China and India



III. DISCUSSION QUESTIONS FOR THE PANEL

A DOZEN QUESTIONS FOR THE PANEL

1. How will this apply to sites in the UK post Brexit?
2. Why couldn't FDA create an agreement that included all of Europe rather than just specific member states?
3. What is the most significant practical impact to the industry related to this new MRA?
4. Can you anticipate the agency ever accepting OUS product approvals in lieu of full FDA submission and approval (i.e. NDA, ANDA)?
5. If an inspection finds violations, what next steps can be expected?
6. Do you anticipate any changes to the inspection approach? Will the "home" agency consider issues of interest to the "away" agency (like adverse event reporting or products only intended for export)?
7. Will the inspection reports become standardized or will each health authority continue to issue reports in their own format and native language?
8. Will sites in Europe be able to stop translating procedures to English in anticipation of FDA inspection?
9. Does FDA anticipate in engaging in similar MRA arrangements with other countries or areas, such as Australia, Brazil, Canada, or China?
10. What's not included in the MRA (that is, any particular types of inspections?)
11. What are the likely next steps in order to move forward with the MRA?
12. For inspections conducted by US or EU health authorities in other areas, like China and India, how will the agencies use those inspection results? Will they be automatically shared among the agencies?

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