NATIONAL PRIORITIES:
CONTINUOUS MANUFACTURING OF MEDICAL COUNTERMEASURES

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Manufacturing, Facilities, and Engineering
HHS/ASPR/BARDA
June 27, 2016
PCAST reports in 2011, 2012, and 2014 highlighted the need for U.S. to innovate in the manufacturing sector, and continuous manufacturing of pharmaceuticals has been identified as a Priority Technology Area.
Pandemic and All-Hazards Preparedness Act

Public Law 113–5
113th Congress

An Act

To reauthorize certain programs under the Public Health Service Act and the Federal Food, Drug, and Cosmetic Act with respect to public health security and all-hazards preparedness and response, and for other purposes.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

SECTION 1. SHORT TITLE; TABLE OF CONTENTS.
(a) SHORT TITLE.—This Act may be cited as the “Pandemic and All-Hazards Preparedness Reauthorization Act of 2013”.

(b) TABLE OF CONTENTS.—The table of contents of this Act is as follows:

TITLE I—STRENGTHENING NATIONAL PREPAREDNESS AND RESPONSE FOR PUBLIC HEALTH EMERGENCIES

Sec. 102. Assistant Secretary for Preparedness and Response.
Sec. 103. National Advisory Committee on Children and Disasters.
Sec. 104. Modernization of the National Disaster Medical System.
Sec. 105. Continuing the role of the Department of Veterans Affairs.

TITLE II—OPTIMIZING STATE AND LOCAL ALL-HAZARDS PREPAREDNESS AND RESPONSE

Sec. 201. Temporary reassignment of State and local personnel during a public health emergency.
Sec. 202. Improving State and local public health security.
Sec. 203. Hospital preparedness and medical surge capacity.
Sec. 204. Enhancing situational awareness and biosurveillance.
Sec. 205. Eliminating duplicative Project BioShield reports.

TITLE III—ENHANCING MEDICAL COUNTERMEASURE REVIEW

Sec. 301. Special protocol assessment.
Sec. 303. Definitions.
Sec. 304. Enhancing medical countermeasure activities.
Sec. 305. Regulatory management plans.
Sec. 306. Report.
Sec. 307. Pediatric medical countermeasures.

TITLE IV—ACCELERATING MEDICAL COUNTERMEASURE ADVANCED RESEARCH AND DEVELOPMENT

Sec. 401. BioShield.
Sec. 402. Biomedical Advanced Research and Development Authority.
Sec. 403. Strategic National Stockpile.
Sec. 404. National Biodefense Science Board.

Mar. 13, 2013
[H.R. 307]

Pandemic and All-Hazards Preparedness Reauthorization Act of 2013.
42 USC 201 note.

National Security:
Advanced development of medical countermeasures for public health emergencies needed for an Effective Public Health Response

inextricably linked

U.S. manufacturing sector and its ability to innovate
BARDA's vision: A NATION with the capability to respond quickly and effectively to deliberate, natural, and emerging threats so as to minimize their impact and recover promptly by supporting the development of a comprehensive portfolio of medical countermeasures, needed manufacturing infrastructure, and countermeasure production platforms.

BARDA explores innovative solutions to meet our Vision.
BARDA’s Mission

Support advanced development of and make available medical countermeasures for CBRN threats, pandemic influenza, and emerging infectious diseases by transitioning medical countermeasure (MCM) candidates from early development across the “Valley of Death” into advanced development towards regulatory approval.
Drug Development Pipeline

**PHASES**
- **Discovery**
- **Preclinical Development**
- **Phase I**
- **Phase II**
- **Phase III**
- **Licensure**
- **Production & Delivery**

**PRODUCT PIPELINE**
- NIH & DoD
- BARDA ARD
- Project BioShield

**PROBABILITY OF SUCCESS TO LICENSURE**
- 1-3%
- 5-17%
- 10-25%
- 18-35%
- 45-70%
- 90%

**TIME**
- 3-7 yr
- 0.5-2 yr
- 1-2 yr
- 2-3.5 yr
- 2.5-4 yr
- 1-2 yrs

**PIPELINE PHASE COST**
- $100M - $130M
- $60-70M
- $70M-100M
- $130M-160M
- $190M-220M
- $18M-20M
BARDA’s View of Manufacturing

- Medical countermeasures against CBRN/EID threats have reduced investment interest by pharma
  - Increased costs for drug development due to complex regulatory pathway
  - Small commercial market; profits not commensurate with increased development cost
  - Production facilities that need to be maintained, although not in use

- Scale-up of pilot to commercial production processes may affect product quality

- Commercial production moving outside US due to reduced capital and operating costs and practices have become increasingly routine
Public-private partnerships provide advanced development and manufacturing capabilities as core service assistance to Medical Countermeasure (MCM) developers

Contribute to U.S. emergency preparedness by providing vaccine and biological product manufacturing surge capacity
Continuous Manufacturing: Paradigm shift

- Production could be implemented upon market demand as opposed to forecast and associated warehousing
- Smaller “footprint” facility can be used for development and commercial production
  - no “scale-up” necessary; efficient use of facilities; potential for more sustainable multiproduct facilities
- Efficiencies may lead to cost savings
- Technology transfer to ex-US facilities may not be necessary

BARDA envisions funding may drive Industry investment and make technologies more accessible in the market for pharma adoption
BARDA ↔ FDA
Continuous Manufacturing Partnership

Vision:
- Consistent with the Pandemic and All-Hazards Preparedness Act (PAHPA) to support innovations that lead to more cost-effective and faster production of high quality MCMs
  - foster development of continuous manufacturing technologies
  - facilitate commercial adoption in the private sector
  - transfer technology to CIADMs to increase capabilities for domestic resilience and national security

Scope:
- Support enabling technologies for continuous manufacturing
- Advance continuous manufacturing innovations for existing and new products
- Transition realized technologies to increase domestic MCM response core capabilities
Complimentary Partnership Goals

BARDA
- Speed the process for MCM advanced development and manufacturing
- Increase efficiency and sustainability of MCM production
- Improve overall quality of MCMs
- Reduce total lifecycle development and operational costs
- Transfer technology to CIADMs to increase capabilities for domestic resilience, response capabilities and national security

FDA
- Fund regulatory science research that addresses scientific, technical, operational continuous manufacturing challenges to evolve future regulatory practices
- Facilitate development of broadly-generalizable, product independent, continuous manufacturing enabling technologies and platforms that are interoperable
Continuous Manufacturing Innovation Initiative

- Initiated BARDA – industry intel through private communications, targeted Tech Watch presentations
- BARDA/FDA established a joint working group and issued an RFI on April 21, 2015 entitled “Innovations in Medical Countermeasure Continuous Manufacturing” for conducting formal market research
- BARDA publically addressed interest in initiative and started funding projects in September 2015
- BARDA is engaging other USG Agencies to encourage federal coordination of Continuous Manufacturing
BARDA BAAs

BARDA Advanced Research and Development BAAs for MCM products (October 14, 2015)

- Chemical, Biological, Radiological, and Nuclear (CBRN) Medical Countermeasures, BAA-16-100-SOL-00001
- Pandemic Influenza, BAA-16-100-SOL-00002

Development of existing and new product candidates using continuous manufacturing technologies

- Include continuous manufacturing technology development or improvements
- Preliminary steps to evaluate the feasibility of continuous manufacturing as compared to traditional batch processes

Special Instructions (April 2016): Expanded scope to include translational science, integration of innovative CM technologies into current process development, and/or demonstration of a phase 3 /commercial process POC with CM technologies

https://www.medicalcountermeasures.gov/newsroom/2015/broad-agency-announcements/
Janssen for the advanced development of an influenza antiviral, JNJ-872 (also known as VX787)

- Developing commercial continuous manufacturing capacity (focused on fill of solid dosage forms)
- Determine potential to implement continuous manufacturing for high volume pharmaceuticals

Rempex for the advanced development of Carbavance (meropenem/RPX7009)

- Rempex is using continuous processing technologies to achieve larger scale of production of Carbavance for projected commercial demand
- If steps were conducted as traditional batch processes, future scale-up would be limited
- As a result, Rempex will use sequential continuous manufacturing processing to create efficiencies and improve quality in the process
Why BARDA is interested in working with you

- Promote public-private partnerships
- Foster continuous manufacturing development in pharma
  - Support transition and adoption of technology development from academia/industry to Pharma
- Interested in creating novel solutions for difficult technical hurdles in MCM manufacturing
- BARDA can provide subject matter expertise and proven successful history in bringing MCM to licensure/approval and supply for the US stockpile
- Leverage partnership with FDA to help support regulatory guidance for continuous manufacturing
How to Contact BARDA

- www.medicalcountermeasures.gov
  - Announcements, solicitations

- BARDA BAAs
  - Special Instructions for CM issued April 2016
    [https://www.fbo.gov/index?tab=documents&tabmode=form&subtab=core&tabid=2ccbf50f176293cf3f624b36be58b736]
    - Technical Point of Contact for each Area of Interest

- Request a Tech Watch meeting
  - Contact Jonathan Seals, Director Strategic Science and Technology Division, jonathan.seals@hhs.gov

- Additional BARDA CM questions
  - Contact Kim Sciarretta, kimberly.sciarretta@hhs.gov
NATIONAL PRIORITIES:
CONTINUOUS MANUFACTURING
OF MEDICAL COUNTERMEASURES

Jean Hu-Primmer
Sr Advisor for CBRN and Pandemic Influenza
FDA/OC/OCET
Jan 31, 2017

www.fda.gov/medicalcountermeasures
FDA BAA
Advanced Research and Development of Regulatory Science
Priority Area #3

Support New Approaches to Improve Product Manufacturing and Quality

https://www.fbo.gov/?s=opportunity&mode=form&id=19f4a4e1745fe86550731f1fcd0dcdde&tab=core&_cview=1
FDA BAA
Advanced Research and Development of Regulatory Science
Priority Area #7

Facilitate Development of Medical Countermeasures

https://www.fbo.gov/?s=opportunity&mode=form&id=19f4a4e1745fe86550731f1fcd0dcdde&tab=core&_cview=1
Review

Emerging technology: A key enabler for modernizing pharmaceutical manufacturing and advancing product quality

Thomas F. O’Connor, Lawrence X. Yu, Sau L. Lee*
Office of Pharmaceutical Quality, CDER, FDA, United States

Modernizing Pharmaceutical Manufacturing: from Batch to Continuous Production

Sau L. Lee · Thomas F. O’Connor · Xiaochuan Yang · Celia N. Cruz · Sharmini Chatterjee · Rapti D. Madarawe · Christine M. V. Moore · Lawrence X. Yu · Janet Woodcock

Advancement of Emerging Technology Applications to Modernize the Pharmaceutical Manufacturing Base 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 http://www.regulations.gov. Submit written comments to the Division of Dockets Management (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 (CDER) Sau L. Lee 240-506-9136.
Vertex Orkambi
July 2015

Continuous DS to DP

Photo Credit: Vertex
Aprecia Spritam
August 2015

First FDA-approved drug using Additive Manufacturing (3D printing)
Janssen Prezista
April 2016

Batch-to-Continuous Conversion

Photo Credit: Fierce Pharma (at Janssen)
FDA-funded Regulatory Science Research

Since 2013: FDA has funded 6 projects related to CM

1. Univ of Conn: Continuous Manufacturing of Liposomal Drug Formulations
4. Rutgers C-SOPS: Continuous Direct Compression for Final Dosage Form Manufacturing
5. NJIT: Continuous Thin Film Manufacturing
6. Continuus: Continuous End-to-End Manufacturing
Innovations in Advanced Manufacturing is a National Priority!

ADVANCED MANUFACTURING:

A Snapshot of Priority Technology Areas Across the Federal Government

PRODUCT OF THE Subcommittee for Advanced Manufacturing OF THE NATIONAL SCIENCE AND TECHNOLOGY COUNCIL

April 2016

The National Network for Manufacturing Innovation

An interagency team building partnerships with U.S. Industry and Academia
Our Mission

The NIIMBL mission is to accelerate biopharmaceutical manufacturing innovation, support the development of standards that enable more efficient and rapid manufacturing capabilities, and educate and train a world-leading biopharmaceutical manufacturing workforce, fundamentally advancing U.S. competitiveness in this industry.
NIIMBL National Map

NIIMBL ECOSYSTEM
140+ Partners, 60 Industry Members,
35+ Academic Members, 35+ Non-profits
PARTNERS NOTIONAL PENDING SIGNED MEMBERSHIP AGREEMENT
The NIIMBL Impact

- **Economic Growth**: Foster the national growth through a highly skilled best-in-class workforce.
- **Advance U.S. Security**: Rapid and effective response to public health threats (natural and intentional).
- **Patient Health**: Improve quality of life for the patients it serves.
- **Collaborative Technology Development**: Accelerate medical progress by fostering collaborative technology development.
- **Industry Standards**: Support industry-wide manufacturing standards and harmonize regulations.

853,818
Direct Jobs
(33% are STEM Occupations)

4,446,365
Total U.S. Jobs

$1.2 Trillion
U.S. Economic Output

U.S. economic output represents the value of goods and services produced by the sector.

NIIMBL Regional Meetings

NIIMBL is hosting a series of regional meetings:

1. February 13, 2017: Cambridge, MA
2. February 15, 2017: Chicago, IL
3. February 20, 2017: Raleigh, NC
4. February 23, 2017: Newark, DE
5. February 24, 2017: Cambridge, MA
6. February 27, 2017: Berkeley, CA

Please visit: http://www.niimbl.us/
For additional information, please visit our website:
www.fda.gov/MedicalCountermeasures

Questions RE CM? jean.hu-primmer@fda.hhs.gov