Biodosimetry: An HHS Priority for Radiological Public Health Emergencies

Biomedical Advanced Research and Development Authority (BARDA)

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HHS/ASPR/BARDA

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Assistant Secretary for Preparedness and Response (ASPR)

Mission
Lead the nation in preventing, preparing for, and responding to the adverse health effects of public health emergencies and disasters.
The Biomedical Advanced Research and Development Authority (BARDA)

Project Bioshield Act of 2004
- Special Reserve Fund (~$5.6 B)

The Pandemic and All-Hazards Preparedness Act
(Public Law 109 – 417, December 2006)
- Established BARDA
- Provides authority to invest in advanced research and development of MCM
- Annual appropriations from Congress

Programs are supported by:
Advanced Research and Development
Project BioShield Special Reserve Fund
Pandemic Influenza appropriations
BARDA Mission

Ensure the availability of countermeasures to address public health emergencies

- Three threat areas: Chem/Bio/Rad/Nuc, Pandemic Influenza, Emerging Infectious Diseases
- Comprehensive, integrated portfolio approach to development and acquisition of medical countermeasures (MCM)
- BARDA manages and supports advanced development and procurement of products to diagnose, treat, and prevent the adverse health effects resulting from public health emergencies
Public Health Emergency Medical Countermeasures Enterprise (PHEMCE)

National Biodefense Science Board

NIH | BARDA | BARDA and CDC | CDC | CDC | CDC and OPEO

FDA

Research and Development | Advanced Development | Acquisition | Storage/Maintenance | Biosurveillance/Detection | Deployment | Utilization

PHEMCE Coordinated Planning & Execution
Defining and Prioritizing Medical Countermeasure Development and Acquisition

Address a diverse set of threats: CBRN* and Influenza/Emerging Diseases

Face product development challenges: lengthy, risky, and expensive

Prioritize advanced development, acquisition, & mfg infrastructure building programs

Consider the needs of a large, diverse population

Develop medical countermeasures that are deployable and readily dispensable

*Chemical, Biological, Radiological, Nuclear
### The Government Acquisition Model for Medical Countermeasures & Devices

<table>
<thead>
<tr>
<th>Concept Refinement</th>
<th>Technology Development 4-8 years</th>
<th>System Development and Demonstration 3-4 years</th>
<th>Production and Deployment</th>
<th>Operations and Support</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prototype scale production</td>
<td></td>
<td>Pre-IDE/IND Submission</td>
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<tr>
<td>Assay development</td>
<td>Design development &amp; small scale production</td>
<td>Manufacturing validation and scale up</td>
<td>Stockpile Production</td>
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<tr>
<td>Proof of concept studies</td>
<td>Hardware &amp; software qualification</td>
<td>FDA Review</td>
<td>Post marketing commitments</td>
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<tr>
<td></td>
<td>Clinical &amp; analytical assay qualification</td>
<td>Clinical &amp; analytical assay validation</td>
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<tr>
<td><strong>Research &amp; Discovery</strong></td>
<td>Pre-clinical studies</td>
<td>Clinical Trials – Animal or human efficacy studies</td>
<td>FDA Approval</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Sustain</td>
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<tr>
<td><strong>Advanced Development</strong></td>
<td>IND/510(k)/PMA Submission</td>
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<tr>
<td><strong>Procurement</strong></td>
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For more information go to [www.medicalcountermeasures.gov](http://www.medicalcountermeasures.gov)
Radiological Incidents

“A rare [incident] with a major impact is hard to prepare for”*

Radiological Dispersal Device (RDD)
Explosive
Non-explosive

Improvised Nuclear Device (IND)

Radiological Exposure Device (RED)

*COL Viktor Meineke, Ph.D., Director of the Bundeswehr Institute of Radiobiology, Munich
“Estimates of a victim’s whole body radiation dose using:
• Clinical biodosimetry: (blood count analysis, cytogenetics and possibly newer methods in development)
• Physical (geographic) dosimetry: retrospective reconstruction of an individual’s dose by linking his/her location during the incident to maps generated by computer models and real-time environmental radiation measurements”
Planning for a 10 Kiloton (KT) IND

The RTR system for a nuclear detonation response; theoretical zones in a 10 KT nuclear explosion at surface level
Radiation Exposure vs. Contamination

Contamination
External or Internal

Bioassay:
Internal Radionuclide Contamination

Am-241  Cs-137  I-131  Po-210  Sr-90
Co-60  Cm-242/244  Ir-192  Pu-239  U-235/238/239

Exposure
Primarily $\gamma$-Ray

Biodosimetry
Biodosimetry—Assessing Exposure

Physical Dosimetry
- At time of incident
- Measures photons of energy
- Dose to the physical device

Biodosimetry
- Subsequent to incident
- Measures biological effect (host response)
- Dose-dependent
- Dose or injury to person (whole body) or organ and tissue (partial body)
- Potentially more relevant to biological injury for triage and treatment decisions
Current Biodosimetry Capability

- Victim’s location relative to incident
- Signs and symptoms (↑ false positive rate)
- Blood cell counts (lymphocyte depletion kinetics)
- Laboratory-based cytogenetics (dicentric chromosome assay)

Government Initiatives:

- HHS NIH/NIAID supports early R&D through the CMCR program, grants, and cooperative agreements
- HHS BARDA awards advanced R&D and procurement contracts for product development and acquisition

Product Development Pipeline

Early potential candidates ➔ R&D ➔ V&V, Pre-Clinical ➔ Clinical ➔ FDA Licensed/Approved Product(s)
Spectrum of Radiation Effects

Figure 2. The Radiation Health Effects Spectrum

<table>
<thead>
<tr>
<th>OUTCOME</th>
<th>Survival Probable</th>
<th>Risk of Death Increases</th>
<th>Death Certain</th>
</tr>
</thead>
<tbody>
<tr>
<td>EARLY SIGNS</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
</tr>
<tr>
<td>DOSE (GRAYs)</td>
<td>0.5 – 1</td>
<td>1 – 2</td>
<td>2 – 3.5</td>
</tr>
<tr>
<td>HEALTH EFFECTS</td>
<td>Decrease in Blood cell Counts</td>
<td>Moderate to Severe Bone Marrow Damage</td>
<td>Severe Bone Marrow Damage, Slight GI Injury</td>
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<tr>
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<td>3.5 – 5.5</td>
<td>5.5 – 7.5</td>
<td>Severe GI and Bone Marrow Damage, Hypotension</td>
</tr>
<tr>
<td></td>
<td>7.5 – 10</td>
<td>10 – 20</td>
<td>Severe GI Damage, Pneumonitis and Cognitive Dysfunction</td>
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<tr>
<td></td>
<td>20 – 30</td>
<td></td>
<td>Cerebrovascular Collapse, Fever &amp; Shock</td>
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Early Signs of Bone Marrow Damage

Pancytopenia, Moderate GI Damage

Severe GI and Bone Marrow Damage, Hypotension

Severe GI Damage, Pneumonitis and Cognitive Dysfunction

Cerebrovascular Collapse, Fever & Shock
Biososimetry Concepts of Operation

Scenario: 10KT detonation in Metropolitan Center

Days 1-3: 1 Million People to Screen

Point of Care (POC) Device
- All potential victims (Low False Negative)

High-Throughput Diagnostic
- Reduced numbers

Assays for Clinical Management
- Patient follow-up (Low False Positive)

Initial Sorting (POC)

High Throughput Dosimetry Systems

> 2 Gy determination

Therapeutic administrations, monitoring, additional assays, i.e. DCA

Refinement and additional screening

OK to evacuate
Potential Biomarkers of Radiation Exposure

Molecular Biomarkers
• Modification of cell cycle control mechanisms
• Alterations to signaling pathways
• Alterations in gene expression
• Alterations in protein expression
• Changing redox status
• Induction of apoptosis
• Modulation in inflammatory molecules
• Electroparamagnetic resonance & optically-stimulated luminescence measured in teeth

Physical Biomarkers

Localized DNA double strand breaks induced by ionizing radiation detected by FITC–γH2AX antibody
What Makes a Good Molecular Radiation-Responsive Biomarker?

- **Specific**
  - Radiological, chemical, and biological

- **Sensitive**
  - Not variable
  - Low baseline

- **Predictive**
  - Long half-life
  - Dose-responsive

- **Robust**
  - Rapid, simple, accurate, and inexpensive detection

- **Noninvasive**
  - Blood (fingerstick)
  - Hair follicles
  - Breath
  - Urine
  - Tooth enamel
• **Point of Care (POC) Diagnostic**
  - Qualitative Assessment (Dose < 2Gy >)
    - Moderate false positive rate tolerable
  - Portable – easily deployed & supported
  - Usable in austere facilities
  - Usable by minimally trained personnel
  - Ease of patient tracking (low tech)

• **High Throughput (HT) Diagnostic**
  - Quantitative dose assessment up to 10Gy
  - Fixed laboratory installations
  - Requires highly trained operators
  - Low error rate (high sensitivity, specificity)
Challenges in Developing Effective Biodosimetry Tools

Target Product Profiles (TPPs)

• Different situations; different dosimetric endpoints
• Ultra-high throughput
• Sample processing and collection / minimally invasive
• Patient tracking
• Sensitivity within required dose range
• Specificity
• Signal stability
• Processing time
• FDA approval pathway for biomarker, bioassay, tool, and/or device
HHS Biodosimetry Programs

• NIH / NIAID* – basic research, concept refinement
  – Centers for Medical Countermeasures against Radiation (CMCR)

• BARDA – advanced research and development, procurement
  – Ongoing biodosimetry development contracts:
    • High-throughput diagnostic systems
    • Point of care diagnostic tools and assays

• CDC – procurement, sustainment

• Solicitations (www.fedbizopps.gov):
  – BAA-BARDA-CBRN-11-100-SOL-00009: “Advanced R&D of CBRN Medical Countermeasures” (vaccines, therapeutics, diagnostics) and innovative approaches
  – Currently accepting White Papers for advanced R&D

*NIAID = National Institute for Allergy and Infectious Diseases

For more information go to www.medicalcountermeasures.gov
Acknowledgements

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