Biodosimetry – challenges to product development and regulatory approval

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The Biomedical Advanced Research and Development Authority (BARDA) is committed to developing and gaining regulatory approval of rapid and accurate biodosimetry diagnostic tests to aid in patient management after a possible acute exposure to ionizing radiation. To date, BARDA has provided significant financial and technical support for the advanced development of 1) Point-of-Care Triage Screening Tests to rapidly discriminate between individuals needing immediate medical evaluations from those who could be sent home and followed up later, and 2) High-Throughput Laboratory Screening Tests that accurately quantify a patient's absorbed dose. Both technologies have relied on host-response biomarkers as surrogate detectors of absorbed energy. Development and regulatory approval of biodosimetry-based diagnostics has proven challenging; more than a decade of research efforts has identified several limitations in this approach to biodosimetry and gaps in regulatory guidance, particularly for immunoassays and molecular tests.

Use of biomarkers as a replacement for physical measurement of radiation is significantly affected by inter-individual response variability, lack of specificity, and dose response. Because human studies are not ethical nor feasible, studies in animal models are required to demonstrate accuracy and performance; bridging studies are necessary to confirm the validity of selected models oftentimes using radiotherapy (RT) patients as an intermediate step between the intended use population and animals. However, RT patients are rarely representative of the intended use population and provide only a limited source of dose levels and radiation regimen. So far, animal models have not shown adequate similarities to humans in terms of biomarker's homology, kinetics, and fold-change.

A shift in the radiation biodosimetry paradigm away from physical dose assessment and toward biomarkers of effect is timely. Agnostic diagnostics leveraging biomarkers for type and severity of damage and for prognosis would fit in the current approach of medical management and would facilitate biodosimetry product sustainability in the marketplace. Further understanding of natural history of radiation damage and identification of biomarkers of effect is necessary to link pathophysiological changes to animal models or to other human conditions for medical management.