Technology Readiness Levels (TRL)
of Medical Countermeasures for Chemical Threats

Select the TRL that most closely describes the level of development of the medical countermeasure or program.

TRL 1 Target Identification Stage

Basic research on cellular and molecular processes to identify targets for medical countermeasure[1] development for identified threats (agents and/or syndromes).

TRL 2 Validated Screening Tool Stage

A predictive target has been identified and incorporated into a reliable *in vitro* assay that can be used to screen chemical/biological libraries; *OR* a predictive *in vivo* assay model has been optimized and characterized for reliability.

TRL 3 "Hit" Identification

Compounds/biologicals that are "active" in the screens have been identified in the chemical/biological libraries.

3A *In vitro* activity appropriate to the mechanism of CBRN agent, or

3B Preliminary *in vivo* data indicating the potential for activity (non-GLP adequate).

TRL 3.5 Hit to "Lead"

Active hits have been verified in terms of structure, target interaction, and counterscreening.

3.5A Affinity, potency, and selectivity have been established.

3.5B Medicinal chemistry and structure-activity analysis, or other approaches, have been used to optimize the desired activity and bioavailability and to reduce toxicity and side effects resulting in a few lead candidates.

TRL 4 Preliminary Leads stage / Proof of Concept Stage

4A Development of small animal models appropriate for testing prospective interventions for the desired indications (via natural history studies, pathophysiology investigations, etc.)

4B Demonstration of *in vivo* activity (acute or long-term) in small animal models according to the product's intended use.

TRL 5 Optimized Leads Stage / Pre-Clinical Stage

5A Demonstration of acceptable Absorption, Distribution, Metabolism and Elimination. This would include initial determination of PK/PD properties and toxicity in rodents.

5B Further optimization of the chemistry of the therapeutic for bioavailability, potency selectivity. To include PK/PD in 2-3 species.

TRL 6 Candidate Drug

A single therapeutic candidate has been fully characterized for manufacturability, pharmacology, and a formulation established for safety testing and stability. Any regulatory issues have been defined.

6A Toxicity, toxicokinetics, and immunogenicity (for biologics) **(GLP)**.

6B Chemical, manufacturing and control. **(GMP)** - Drug pilot lots prepared for scale-up.

6C Development of animal models for definitive efficacy and dose-ranging studies.

6D Proof of concept efficacy studies in small animal models.

6E Dose ranging studies in small animal models.

TRL 7 IND Ready

A full package is prepared for submission to the FDA (if a significant risk device study), for submission to an IRB (if a non-significant risk device study), or for submission to an IRB (if waived according to FDA exemptions from IDE requirements 812.2(c)(3)).

AT THIS POINT, THE FDA OFFICE OF COMPLIANCE CAN BE CONTACTED REGARDING PRODUCTION PROBLEMS.

TRL 8 Phase 1

Initial studies in humans to determine the safety and pharmacokinetics (dose finding) of the clinical test formulation.

- **8A** Continued development of animal models, protocols and assays to support licensure in consultation with FDA.
- **8B** Continuation of process development for cGMP manufacturing at a scale compatible with USG requirements.
- **8C** Initiation of accelerated stability studies of the cGMP product in a formulation and container compatible with USG requirements.
- **8D** Clinical studies that establish safety assessment.

AT THIS POINT, THE FDA OFFICE OF COMPLIANCE SHOULD BE CONTACTED REGARDING PRE-APPROVAL INSPECTIONS.

TRL 9 Phase 2

Human safety studies and surrogate markers for efficacy (this may require the use of consistency lot material).

- **9A** Emergency Use Authorization (EUA) - enabling efficacy studies in an animal model(s) accepted by FDA (if necessary).
- **9B** Continuation of process development for cGMP manufacturing at a scale compatible with USG requirements.
- **9C** Continuation of stability studies of the cGMP product in a formulation and container compatible with USG requirements.
- **9D** Clinical studies for preliminary assessment of suitable human efficacy endpoints and expansion of human safety database as appropriate.

TRL 10 Phase 3 (if required) and Definitive Animal Efficacy (if required)

- **10A** Definitive efficacy studies in animal model(s) to support licensure/approval (GLP).
- **10B** Manufacturing of consistency lots at a scale compatible with USG requirements.
- **10C** Continuation of stability studies of the cGMP product in a formulation and container compatible with USG requirements.
- **10D** Demonstrate efficacy in animal models for Special Populations.
- **10E** Clinical studies that establish human efficacy and human risk/benefit assessment to the extent feasible and appropriate.

TRL 11 Licensure, Approval, Clearance

TRL 12 Post-licensure and post-approval activities

TRL 13 Expanded efficacy (if appropriate)

Fielded therapeutics may in some cases be available for other uses to meet new threats. FDA guidance is needed.

[1] Medical countermeasures include diagnostics, prophylactics, and therapeutics.

[2] In "Accelerated Approval" and "Animal Rule" drug and biologics approvals, there remains a regulatory commitment for the application holder to complete confirmatory efficacy studies. There also may be Phase 4 commitments and other regulatory requirements to conduct additional safety, efficacy, drug interaction studies, including studies in special populations.