Biomedical Product Maturity Guidelines

Congressionally Directed Medical Research Programs

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Overview

Product Maturity in DoW Medicine

Within the U.S. Department of War medical acquisition and research enterprise, biomedical product maturity refers to the developmental progress of a medical solution as it transitions from a conceptual scientific theory into a validated, safe, and effective capability fielded to the Warfighter.

Because medical development involves unique regulatory hurdles (such as FDA approval), clinical trials, and strict safety standards, measuring product maturity ensures that the military does not field unproven or unsafe solutions, or waste valuable defense resources on non-viable technologies.

Why the DoW Measures Product Maturity

The DoW utilizes standardized maturity scales—primarily Technology Readiness Levels and Knowledge Readiness Levels—to systematically evaluate medical solutions for three critical reasons:

Strategic Objective	Why the DoW Measures It	Impact on the Warfighter
Risk Mitigation & Decision-Making	Medical research is inherently high-risk. Measuring maturity levels provides objective, standardized milestones to determine whether a project should receive continued funding or be phased out before entering costly clinical trials.	Prevents "milestone creep" and ensures only scientifically sound concepts move forward.
Regulatory & Milestone Alignment	DoW medical products must align with FDA clearance pathways (such as IND, IDE, 510(k), or PMA). Measuring maturity ensures that scientific milestones sync perfectly with federal regulatory gates.	Accelerates the transition from laboratory bench to battlefield medicine by avoiding regulatory bottlenecks.
Transition and Fielding Readiness	The DoW needs to know exactly when a product is ready to transition from Science and Technology funding to Advanced Development and ultimate deployment in operational environments.	Ensures that deployed medical personnel receive fully cleared, stable, and highly effective tools and protocols.

TRLs and KRLs fall into a standard 1-to-9 scale tailored to the unique regulatory, clinical, and scientific milestones of medical product development. This includes the development of physical products (such as drugs, biologics, vaccines, and medical devices) as well as the knowledge gained from testing clinical guidelines, clinical tools, or health care policies.

This guide explains, compares, and contrasts these maturity levels.

Technology Readiness Levels

The TRL conceptual framework was originally established to track the engineering maturity of hardware and software systems. The DoW, U.S. Department of Veterans Affairs, and other federal and non-federal entities have since adapted and tailored the TRL framework to align with standard scientific milestones and FDA regulatory phases.

This tailored framework tracks a biomedical solution from its initial basic idea and scientific discovery, through proof-of-concept and animal testing, to clinical trials, and ultimately to regulatory approval and full operational deployment. This typical product development pipeline is illustrated in **Figure 1**.

Figure 1. Product Pipeline From Basic Idea to Product Implementation

Biomedical TRL Overview

The progression of a biomedical product (such as a drug, biologic, or device) can be divided into nine distinct maturity levels. The following table provides a fundamental overview of these phases.

Readiness Level	Phase Name	Description & Milestones Met
TRL 1	Basic Research	Initiate scientific literature reviews and market surveys. Observe basic principles and maintain scientific awareness.
TRL 2	Concept Formulation	Generate hypotheses. Develop research ideas and experimental protocols to address a defined medical problem.
TRL 3	Initial Proof-of-Concept	Test hypothesis and demonstrate initial proof-of-concept (PoC) in a limited number of laboratory (*in vitro*) or preliminary animal models.
TRL 4	Laboratory Validation	Complete initial absorption, distribution, metabolism, and excretion studies, and rigorously demonstrate safety in defined laboratory environments or animal models.
TRL 5	Preclinical to Clinical Transition	Complete successful GLP studies to support regulatory review (e.g., IDE or IND application) and secure approval to begin preliminary human studies.
TRL 6	Early Clinical Trials	Demonstrate initial clinical safety and support the progression to broader safety and effectiveness trials (e.g., phase 1 clinical trials or early device safety testing).

Readiness Level	Phase Name	Description & Milestones Met
TRL 7	Advanced Clinical Trials	Secure agreement on advanced clinical endpoints and test plans (e.g., phase 2 or phase 3 trials). For devices, evaluate prototypes in operational or simulated environments.
TRL 8	Regulatory Approval	Meet all design specifications and obtain formal regulatory approval or clearance (e.g., FDA Premarket Approval or 510(k) clearance).
TRL 9	Full Operational Use	Field or market the product, conduct required postmarketing surveillance, and utilize the product in its intended operational environment or mission.

Knowledge Readiness Levels

While TRLs measure the maturity of tangible *materiel solutions (such as drugs and devices)*, the KRL scale evaluates the maturity of "knowledge products," such as treatment models, clinical guidelines, and service delivery strategies. The KRL framework measures the validity, replicability, and real-world generalizability of *health science research* to ensure that new research can be safely and effectively transitioned into clinical practice.

Developed in collaboration with the Defense Health Agency Research & Development-Medical Research and Development Command and the RAND Corporation, the KRL framework is highly relevant to healthcare organizations in making investment decisions in medical research.

The nine levels of KRL are grouped into three distinct stages of scientific maturity:

1. Foundational Research (Levels 1–3): Discovery of basic mechanisms and theoretical concepts.
2. Application (Levels 4–6): Evaluation of applied knowledge under highly controlled, ideal research environments.
3. Real-World Context (Levels 7–9): Validation of external efficacy in actual clinical or operational settings.

The KRL 9-Point Scale for Medical Research

The table below classifies the KRL scale into three stages and nine levels, providing a standardized framework to grade the maturity of biomedical knowledge products.

Maturity Stage	Level	Definition	Research Context & Focus
Foundational Research ***(Basic mechanisms, theoretical concepts)***	KRL 1	Basic Principles Observed	Conduct literature reviews, establish basic scientific observations, and initiate conceptualization of theoretical mechanisms.
	KRL 2	Concept Formulation	Develop specific hypotheses and research protocols to address a health problem.
	KRL 3	Proof-of-Concept	Conduct initial testing and demonstrate feasibility *in vitro* or in preliminary, exploratory models.
Application ***(Testing efficacy under ideal, controlled conditions)***	KRL 4	Efficacy in Controlled Environment	Test the knowledge product on target subjects under strict, highly managed research parameters to establish internal validity.
	KRL 5	Replicated Efficacy	Replicate the efficacy of the knowledge product across multiple highly controlled trial sites.
	KRL 6	Defined Application	Establish safe and effective limits, and prepare the product for testing in "noisy" real-world settings.
Real-World Context ***(Testing effectiveness and generalizability)***	KRL 7	Effectiveness in Relevant Environment	Evaluate the knowledge product in a representative real-world context (e.g., standard clinical practice) to assess how it performs outside the lab.
	KRL 8	Replicated Effectiveness	Confirm effectiveness and feasibility across diverse, representative real-world environments with varied patient populations.
	KRL 9	System Integration & Policy Adoption	Integrate the knowledge product into standard operating procedures, clinical practice guidelines, or official policies, to demonstrate routine utility.

Key Differences: TRL vs. KRL

Integrating both metrics provides a holistic view of medical readiness, which is vital when transitioning solutions from Science and Technology phases to Advanced Development.

Metric	Primary Focus	Success Criterion	Typical Output
TRL	Physical materiel, software, and hardware	Engineering performance and physical system integration	A medical device, drug, biologic, diagnostic kit, or other tangible medical product
KRL	Scientific evidence, treatment methods, and clinical guides	Scientific validity, replicability, and real-world clinical effectiveness	Clinical guidelines, preventive health programs, or triage protocols

Practical Examples

TRL Case Study 1: Hyperspectral Thermal Imaging Device for Burn Staging

TRL	Project Status & Milestones	What the Research Team Has Accomplished
TRL 1 *Basic Research*	Scientific principles observed	Reviewed academic literature on how different wavelengths of light absorb into necrotic (dead) versus viable skin tissue. No device exists yet; the team is just studying the physics of light absorption in skin.
TRL 2 *Concept Formulation*	Practical applications identified	Drafted a conceptual design for a handheld camera that uses specific light wavelengths to detect blood flow changes in burned tissue. Wrote mathematical algorithms to theoretically calculate burn depth.
TRL 3 *Initial Proof-of-Concept*	Analytical and experimental proof-of-concept	Built a crude, non-integrated benchtop sensor in the lab. Tested the sensor on synthetic tissue models to prove the light wavelengths can actually differentiate between simulated "burned" and "unburned" layers.
TRL 4 *Laboratory Validation*	Component integration in a lab environment	Integrated the sensor, camera, and algorithm into a working laboratory prototype. Tested the device on animal models (e.g., porcine skin) under controlled lab conditions to successfully map and stage actual burn wounds.
TRL 5 *Preclinical to Clinical Transition*	Component integration in a relevant environment	Refined the prototype to resemble a medical device. Submitted an IDE to the FDA and obtained IRB approval to begin limited testing on human patients in a controlled hospital clinic.
TRL 6 *Early Clinical Trials*	Prototype tested in a high-fidelity clinical environment	Conducted a phase 1, early feasibility clinical study. Used the HTI device on a small cohort of human burn patients at a major military medical center (e.g., Brooke Army Medical Center) to prove the device is safe to use and that the imaging matches clinical observations.
TRL 7 *Advanced Clinical Trials*	System prototype demonstrated in an operational environment	Built a ruggedized, battery-powered prototype. Conducted a larger, multi-site clinical trial to validate the device's accuracy in staging burns across diverse patient populations. Evaluated the device in simulated operational environments (e.g., military field training exercises) to evaluate durability and battery life.

TRL	Project Status & Milestones	What the Research Team Has Accomplished
TRL 8 *Regulatory Approval*	System completed and qualified through test and demonstration	Finalized and locked down the manufacturing process. Submitted a 510(k) premarket notification to the FDA and received clearance, officially establishing the device as safe and effective for marketing and clinical use.
TRL 9 *Full Operational Use*	Actual system proven through successful mission operations	Mass-produced, procured, and officially fielded the HTI device to forward surgical teams and combat medics. Utilized the device in real-world military operations to guide life-saving triage decisions for burned Warfighters, monitoring long-term safety via postmarketing surveillance.

TRL Case Study 2: "HemoStop," a Systemic Drug for Hemorrhage Control

TRL	Project Status & Milestones	What the Research Team Has Accomplished
TRL 1 *Basic Research*	Scientific principles observed	Studied the basic cellular mechanisms of blood coagulation and identified a specific synthetic peptide sequence that theoretically accelerates clot formation at active injury sites without causing systemic blood clots (thrombosis).
TRL 2 *Concept Formulation*	Practical applications identified	Formulated the chemical structure of "HemoStop". Outlined a theoretical drug delivery method (e.g., an intravenous injection) and designed laboratory-scale chemical synthesis protocols to produce small test batches of the drug.
TRL 3 *Initial Proof-of-Concept*	In vitro testing, feasibility studies, non-GLP animal studies, animal model refinement	Synthesized the drug compound in micro-quantities. Tested HemoStop in test tubes (*in vitro*) using human blood samples to prove it successfully accelerates clotting speed and stabilizes clot strength compared to a control. Tested the drug in living organisms (*in vivo*). Administered HemoStop to small animal models (e.g., rats or rabbits) with controlled internal hemorrhages, proving the drug targets the bleed, stops hemorrhage and does not cause immediate toxic side effects.

TRL	Project Status & Milestones	What the Research Team Has Accomplished
TRL 4 *Laboratory Validation*	In vivo testing in validated animal models	Completed absorption, distribution, metabolism, and excretion studies. Rigorously demonstrated pharmacokinetics, toxicity, safety and efficacy studies in a validated swine model of traumatic hemorrhage. Initiated discussions with the FDA.
TRL 5 *Preclinical Transition*	IND-enabling safety studies	Produced the drug in larger, highly standardized batches using GMP. Conducted rigorous toxicology and pharmacological studies in larger animal models within a GLP environment to determine safe dosage ranges. Completed additional pivotal animal studies. Submitted an IND application to the FDA.
TRL 6 *Early Clinical Trials*	Phase 1 Clinical Trials	Transitioned the drug into phase 1 human trials following FDA approval of the IND. Administered HemoStop to a small group (typically 20 to 80) of healthy human volunteers to evaluate its safety, tolerability, and how the human body metabolizes the drug (pharmacokinetics).
TRL 7 *Advanced Clinical Trials*	Phase 2 & Phase 3 Clinical Trials	Progressed the drug into phase 2 and phase 3 trials. Administered HemoStop to hundreds of actual trauma patients in emergency departments to evaluate its effectiveness in stopping severe internal bleeding, comparing survival rates against standard trauma care. Scaled up manufacturing to meet clinical-grade standards.
TRL 8 *Regulatory Approval*	FDA Approval (NDA or BLA)	Compiled all clinical trial data and submitted an NDA to the FDA. Received formal FDA approval for marketing and clinical use following a rigorous review of HemoStop's safety, efficacy, and manufacturing facilities.
TRL 9 *Full Operational Use*	Fielding and Postmarketing Surveillance	Packaged the drug in pre-filled, ruggedized autoinjectors and distributed to combat medics and forward surgical teams following DoW procurement. Medics utilized HemoStop to treat hemorrhaging Warfighters in real-world combat operations, while the manufacturer conducted mandatory FDA phase 4 postmarketing safety monitoring.

KRL Case Study 1: Comparison of Below-Knee Amputation Techniques

Maturity Stage	KRL	What the Research & Surgical Team Has Accomplished
Foundational Research ***(Basic concepts and observations)***	KRL 1 *Basic Principles Observed*	Reviewed biomechanical literature on limb-socket interface forces. Hypothesized that securing muscle directly to bone (Technique B) theoretically reduces skin breakdown and improves prosthetic control compared to the traditional flap (Technique A).
	KRL 2 *Concept Formulation*	Designed a formal protocol for a retrospective, observational study. Defined how to identify historical military amputee patients who received Technique A versus Technique B, and established measurable outcome metrics (e.g., pain scores, ambulation speed, and skin breakdown rates).
	KRL 3 *Proof-of-Concept*	Conducted a pilot review of a small patient database (e.g., 15 patients per technique). Demonstrated via initial data that patients receiving Technique B experienced fewer minor skin sores, establishing a "proof-of-concept" that justifies launching a larger, multicenter observational study.
Application ***(Testing efficacy under ideal, controlled conditions)***	KRL 4 *Efficacy in Controlled Environment*	Executed a large-scale observational study across major military treatment facilities (such as Walter Reed and San Antonio Military Medical Center). Analyzed the records of 200 matched patients, proving that under tightly controlled patient variables, Technique B showed statistically superior prosthetic adaptation outcomes.
	KRL 5 *Replicated Efficacy*	Expanded the study to include civilian trauma registries to ensure the findings were not isolated to a few highly skilled military surgeons. Successfully replicated the superior outcomes of Technique B (lower re-amputation rates and higher mobility scores) across diverse surgical teams and civilian trauma centers.

Maturity Stage	KRL	What the Research & Surgical Team Has Accomplished
	KRL 6 *Defined Application*	Analyzed the limits of the data. Defined exactly *which* blast-injury patients benefit most from Technique B, and identified contraindications (e.g., patients with severe local tissue infection where anchoring muscle to bone was too risky). Formulated the optimal surgical algorithm based on these defined limits.
Real-World Context ***(Evaluating effectiveness and integration)***	KRL 7 *Effectiveness in Relevant Environment*	Distributed the proposed surgical guidelines favoring Technique B as a "provisional recommendation" to active-duty orthopedic surgeons deployed at forward-operating combat hospitals. Initiated utilization of the technique in real-world combat environments to asses feasible under wartime constraints.
	KRL 8 *Replicated Effectiveness*	Collected feedback from deployed surgeons. Confirmed that despite austere field conditions, limited sterile equipment, and high-stress environments, Technique B remains highly effective and does not increase infection rates. Proved the technique is robust in the field.
	KRL 9 *System Integration & Policy*	Published the findings in premier journals (e.g., *Journal of Orthopaedic Trauma*). The DoW's Joint Trauma System officially updated its CPG, mandating Technique B as the primary surgical method for military combat amputations and securing the integration of the technique into residency training programs and board certification standards.

KRL Case Study 2: Prolonged Field Care Clinical Practice Guideline for Burn Wound Management

Maturity Stage	KRL	What the Research & Clinical Team Has Accomplished
Foundational Research ***(Basic concepts and observations)***	KRL 1 *Basic Principles Observed*	Conducted a comprehensive literature review of civilian and military database registries. Gathered historical data on burn wound infection rates, fluid resuscitation failures, and complications during delayed evacuations in combat zones.
	KRL 2 *Concept Formulation*	Drafted a theoretical concept for a new clinical protocol. Identified key components that a medic would need to

Maturity Stage	KRL	What the Research & Clinical Team Has Accomplished
		manage, such as simplified fluid calculation formulas, topical antimicrobial alternatives for austere environments, and pain management strategies.
	KRL 3 *Proof-of-Concept*	Reviewed the draft concepts with expert clinicians and military burn specialists. Mapped out a preliminary, step-by-step decision tree (algorithm) to ensure the proposed medical interventions are biologically sound and feasible for a medic's skill level.
Application ***(Testing efficacy under ideal, controlled conditions)***	KRL 4 *Efficacy in Controlled Environment*	Formatted the CPG is formatted into a draft manual. Tested the efficacy of the guidelines in a highly controlled environment, such as a medical simulation lab. Evaluated active-duty medics as they utilized the guidelines to treat high-fidelity patient simulators (burn manikins) to confirm they could successfully execute the steps.
	KRL 5 *Replicated Efficacy*	Replicated the simulation testing across multiple military training sites (e.g., Army, Navy, and Air Force medic training centers) Ensured that different medics, regardless of their specific branch training, could understand and successfully execute the protocol without errors.
	KRL 6 *Defined Application*	Defined the strict boundaries of the CPG. Outlined exactly when the guideline should be used (e.g., evacuation delayed >12 hours, burn size >20% Total Body Surface Area) and when it is contraindicated, preparing the knowledge product for real-world testing.
Real-World Context ***(Evaluating effectiveness and integration)***	KRL 7 *Effectiveness in Relevant Environment*	Distributed the CPG to a select group of operational units deployed in austere environments (e.g., Special Forces ODA teams) as an evaluative protocol. Utilized the guidelines during real-world training exercises and limited operational missions to test if the CPG was practical under combat stressors.
	KRL 8 *Replicated Effectiveness*	Analyzed feedback and clinical data from multiple deployed units. Refined the guidelines to fix real-world issues (e.g.,

Maturity Stage	KRL	What the Research & Clinical Team Has Accomplished
		simplifying the fluid chart because medics found it hard to read under red-light tactical conditions). Proved the effectiveness of the protocol is proven across diverse operational theaters.
	KRL 9 *System Integration & Policy*	Secured official adoption of the CPG by the JTS. Published it as an official DoW CPG, integrated it into the standard training curriculum for all military medics, and uploaded to the official JTS registry. Established the CPG as the mandated standard of care for prolonged burn management across the entire DoW.

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