2026 Volume: 02 Issue: 03 www.ijrpa.com ISSN 2456-9995 Review Article

International Journal Research Publication Analysis

Page: 01-24

THERMAL REALITIES VS. LABEL ILLUSIONS: DECODING TEMPERATURE IMPACTS ON PHARMACEUTICAL STABILITY

Alok Kumar[1*], Ayush Kumar Verma[2], Rajkumar Singh[2], Satish Kumar[2], Satyam Sundram Mahto[2], Gautam Kumar[2], Rupesh Kumar[2], Mantu Kumar[2], Navin Singh[2], Shubhankar Kumar[3], Sudip Mahato[3], Neeraj Kumar Mandal[3], Manish Kumar Chandravanshi[3], Balraj Kumar[3], Gaurav Kumar[3], Juveriya Javed[4], Sweta Kr. Prasad[4], Adeeba Safaque[4], Kishlay Kumar[5], Bandita Das[6]

[1]**Faculty of Medical Science & Research,** Sai Nath University, Ranchi, Jharkhand-835219, India.

[2]**Faculty of Medical Science & Research,** Sai Nath University, Ranchi, Jharkhand-835219, India.

[3]**School of Pharmacy,** Sai Nath University, Ranchi, Jharkhand-835219, India.

[4]**Abdur Razzaq Ansari Memorial Institute,** Irba, Ranchi, Jharkhand-835217, India.

[5]**Netaji Subhas University**, Jamshedpur, Jharkhand-831012, India.

[6]**Aryakul College of Pharmacy and Research,** Natkur, Gauri, Sarojini Nagar, Lucknow, Uttar Pradesh – 226002, India.

Article Received: 22 January 2026
Article Revised: 10 February 2026
Published on: 02 March 2026

***Corresponding Author: Alok Kumar**
Faculty of Medical Science & Research, Sai Nath University, Ranchi, Jharkhand-835219, India.

DOI: https://doi-doi.org/101555/ijrpa.8839

ABSTRACT:

The stability of pharmaceutical drugs at temperatures under stress indicates severe mismatches between declared storage parameters (e.g., 25 C per IP/CDSCO) and the real-life conditions in Bihar Zone IVB (peak temperatures of 32-48 C) and ratified degradation by Arrhenius equations (Q10=2-4) and synergy of 75-90 percent of RH. The surveillance of NIPER/CDSCO (1,200 outlets) and IMD, and frameworks (ICHs) are synthesized in this review to disaggregate chemical (-lactam hydrolysis), physical (paracetamol polymorphism), and biological (insulin aggregation) pathways, which documents 20-50% potency degradations in amoxicillin, OPV and generics, contributing to PvPI 35% summer ADRs, 25,000 crore discards Pharmacy excursions, non-refrigerated trucking and rural ambient failures are revealed in field audits with HPLC/DSC-validated effects such as 25%

amoxicillin loss in 2 months. Gaps are filled using analytical (ICH Q2-validated HPLC-MS) and emerging (92% predictive accuracy) IoT/AI, but 20% adoption is low. It is recommended to switch to labeling according to Zone IVB and use solar cold chains and blockchain tracking to protect the $30B generic exports of India under the influence of 1.2 C warming.

KEYWORDS: Drug stability, Temperature excursions, ICH Zone IVB, Arrhenius kinetics, β-Lactam hydrolysis, Insulin aggregation, NIPER surveillance, CDSCO guidelines, pharmaceutical degradation, Bihar pharmacy, Jan Aushadhi, PvPI ADRs, IoT monitoring.

1.0 INTRODUCTION:

One such milestone of therapeutic reliability and patient safety in contemporary pharmacotherapy is pharmaceutical drug stability, which is rigorously defined by ICH Q1A(R2) as the ability of a drug to maintain established pharmacopeial standards of identity, strength, quality, purity, and potency between the time of manufacture and the drug expiry date. This complex property includes chemical (no undue degradation products), physical (no polymorphism or changes in particle size), microbiological (sterile), therapeutic (remained potent), and packaging (no leaching or sorption) properties. However, this stability is extremely susceptible to temperature, the main environmental stressor that exponentially increases degradation pathways based on well-defined principles that are physicochemical and which rest on transition state theory. With an Arrhenius expression of k=Ae -Ea/RT, where k is the rate constant of a particular reaction, A is the pre-exponential frequency factor indicating the collision frequency, E a is the activation energy barrier to the reaction, R is universal gas constant (8.314 J/mol-K) and T is absolute temperature in Kelvins, even slight temperature increases of 10 o C can doubled or tripled degradation rates of most pharmaceuticals with typical activation energies of 50-120 kJ/mol - transforming a stable formulation[1].

The controlled conditions found in all labelled storage requirements, codified in ICH Q1A(R2) and harmonized with WHO, FDA, and USP <1150> guidelines are: controlled room temperature (CRT, 20-25 o C) (per USP), room temperature (15-30 o C), cool (8-15 o C), or refrigeration (2-8 o C), based on long-term stability studies at 25 C/60% RH, and accelerated studies at 40 C/75% The labels are based on idealized, climatic controlled conditions with limited outliers on the excursions yet in the real world, storage varies significantly along the pharmaceutical cold chain - between manufacturer and patient. Tropical areas such as Bihar, India (Zone IVB according to ICH climatic zones, with an

annual average of 30C and 75% RH), record periodic diurnal highs of 35-45C in pre-monsoon summers, due to inadequate air movement, and power supply fluctuation; warehouses with a supply chain excursions of more than 30C on the truck in non-refrigerated vehicles; poor patient-level storage of 30C car movements, rural power cuts, or improperly These thermal infractions catalyze certain degradation mechanisms: hydrolysis in 2-lactam antibiotics (e.g. amoxicillin nucleophilically cleaving the ring to penicilloic acid and forms active, and oxidation in statins such as atorvastatin (hydroxylated by peroxides to cholesterol-raising hydroxyanalogues); or polymorphic transformations in paracetamol (metastable Form II to stable Form I to raise the temperature at least 30 o C); slowing dissolution by 20-30%); and protein aggregation in biologics like insulin (hydrophobic fibril formation at >25°C excursions, impairing subcutaneous bioavailability and risking amyloidosis)[2].

The impact is severe, multidimensional, and costly to the world and it is clinical, economical, and public health. Sub potent drugs trigger cascading effects of therapeutic failure artemether-lumefantrine in African drug stores (e.g. Malawi trials of 31C averages) loses 15-20 percent of antimalarial activity on heat-induced lactone hydrolysis, promoting Plasmodium resistance and morbidity extension; temperature-sensitive vaccines such as oral polio (OPV) or varicella cause immunization campaigns, as viral activity halves with days exposure at 37C, due to viral in In terms of cost, the global disposal of stability failures costs more than 35 billion every year (estimated by industry) which has become a burden on healthcare funds in, low-middle income countries (LMICs) where 70-80% of necessary medicines are impacted. Such discrepancies in resource-constrained contexts, such as rural India, contribute to health disparities, making affordable generics into inert placebos in the middle of heat waves, and vulnerable populations such as diabetics who need insulin or children on antibiotics disproportionately affected by them- eventually undermining faith in healthcare systems in the face of increasing temperatures due to climate change [3].

This review breaks down the divide between the labeled imperatives - based on the assumptions of temperate zones - and the thermal realities of world distribution, and synthesizes more than 50 years of evidence on the kinetics of degradation (e.g., Arrhenius modeling confirmed in forced degradation experiments), regulatory frameworks (ICH Q1A-F updates), field surveillance data (e.g. WHO cold chain audits) and new mitigation approaches such as nanotechnology packaging. It will stimulate paradigm shifts by shedding light on these gaps with quantitative illustrations, meta-analysis of excursion effects, and regional understanding (e.g., tropical challenges in India), and policy changes to integrate

pharmacovigilance in the face of global temperature increase (e.g., lyophilized biologics), and post-pandemic focus on resilient health systems [4].

1.1 Importance of Drug Stability:

The stability of the drugs is the foundation of quality assurance of pharmaceuticals in India, so that, the medicines retain their therapeutic efficacy, as they are produced in centres such as Hyderabad and Mumbai, packaged, distributed through a network of fragments, and eventually reaching 1.4 billion patients in the various climates. Stability, which can be defined rigorously under ICH Q1A(R2) guidelines, harmonized with CDSCO, IP 2022, and DPCO requirements as the ability to retain identity (no excessive degradation products beyond the ICH Q3A/B level of 0.1-0.5%), strength, quality, purity, and potency within specified pharmacopeial limits (e.g. IP limits of ±5-10% assay, <0.5% total impurities) to the expiry date, comprises This polypharmacokinetic property helps to avoid under-doses of therapeutic agents that would result in treatment failures with high-burden diseases in India (TB, diabetes), toxicity caused by impurities resulting in the occurrence of ADRs through PvPI (e.g., 1.2 lakh cases annually), and antimicrobial resistance (AMR) due to partially impure antibiotics, difficulties with which have clinical, economic, and public health consequences of significant magnitude as India contributes 27% of the worldwide AMR mortality per Lancet 2024 [5,6].

The type of environment in India is a tropical Zone IVB climate, which is dominated by temperature as the driving environmental stressor with degradation being dictated by basic principles of kinetics based on the transition state theory which has been confirmed throughout decades of NIPER and CDSCO stability data. Arrhenius equation ($k=Ae^{-E_a/RT}$): Quantitatively, even small increases in temperature, such as those encountered during Indian summer, are known to increase reaction rate by a factor of two or three, even when the activation energy barrier (E_a) is relatively small, e.g., 50-120 kJ/mol): "Arrhenius equation, $k=Ae^{-E_a/RT}$" where k is the specific rate coefficient (s^{-1}), A is the pre-exponential frequency factor (collision geometry-dependent), E_a is the activation energy In the case of aspirin (acetylsalicylic acid), which is a common ingredient in Jan Aushadhi kiosks, controlled storage at 25 o C maintains less than 1 per cent salicylic acid impurity after 24 months at IP, but four- or five-percent monthly at 40 o C, produced by acetyl hydrolysis, exceeding limits and causing gastrointestinal irritation or exacerbation of hypersensitivity in aspirin-sensitive groups [7].

These practical interests are well exemplified in the Indian setting by historical events which are cautionary tales that brought about contemporary laws. The 1960s tetracycline crisis had caused Australia to decline, but India had similar 1970s-80s scandals of heat-exposed paracetamol elixirs causing renal toxicity due to P-aminophenol impurities that led to amendments to IP and introduction of CDSCO cold chain conditions. Lapses were further reflected by the Ranbaxy recalls of 2013 over poor stability data. The vulnerabilities of modern biologics are exponentially amplified: even insulin formulations (e.g., Human Actrapid, which 77 million Indian diabetics will need each year by IDF 2024) during 30 0 C excursions, as frequently occurred in rural clinics in non-AC India, hydrophobically aggregate into fibrils in several weeks, reducing in vitro efficacy by 20-50 percent and blocking subcutaneous absorption, raising HbA1c by 1-2 percent and increasing the risk of keto Vaccines are also not exempt, oral polio vaccine (OPV), which India has used to achieve its success in eliminating polio, decays 50% titer in 37 C in 3 days because of viral RNA hydrolysis, the same reason UIP wastage is experienced in heatwave-prone districts of Bihar in 2022, which overturns GPEI work [8].

These examples demonstrate the inability to compromise stability in India: not only do lapses undermine batch value (annually, in India, thermal failures result in pharmacological waste of no less than 25,000 crore due to lapses, straining NPPA pricing), but also the social capital (e.g., post-2023 cough syrup recalls), sour health inequities (i.e. half of the 100 poorest-selling drugs in India, according to Pharmatrac), and also health inequities (such as Bihar Medical With heatwaves expected to increase in strength with climate change +2 o C by 2030, of which Bihar scorchers have already reached 48C in 2024, proactive stability management becomes a moral imperative to pharmaceutical sciences in India, and again fits with the generic export strategies of Atmanirbhar Bharat [9].

Table: 01.

Drug Example	***Labelled Storage (°C) [IP/CDSCO]***	***Typical Indian Pharmacy Peak (°C) [Zone IVB]***	***Degradation Rate Increase (Q10)***	***Key Impurity/Effect***
Aspirin	25	40 (Bihar summer)	2-4x (hydrolysis)	Salicylic acid >5%, GI risk
Amoxicillin	25	35-42	3x (β-lactam cleavage)	Penicilloic acid, AMR risk
Insulin (Actrapid)	2-8	30 (rural excursion)	5x (aggregation)	Fibrils, HbA1c rise 1-2%
Paracetamol Susp.	25	38	2.5x (p-aminophenol)	Renal toxicity

OPV Vaccine	2-8	37 (transport)	50% titer loss/3 days	UIP wastage 15-20%

1.2 Labelled Requirements vs. Real-World Challenges:

Regulatory labels, including USPs controllable room temperature (CRT, 20-25C), more broad room temperature (15-30C), ICH Zone II (25C/60percent RH long-term testing), and refrigeration (2-8C), are based on standardized acceleration stability testing (40C/75percent RH, 6 months) that are used to bracket real-time data, and predict shelf-life at inferential, temperate conditions with restricted excursions. The same specifications, standardized between ICH Q1A(R2), WHO, and CDSCO (Central Drugs Standard Control Organization of India) and IP (Indian Pharmacopoeia) assume climate-controlled facilities, barriers to humidity and continuous cold chains, which collapse in practice, especially in hot-humid ICH Zone IVB regions where the baseline conditions have already attained the levels of stress (30 C/75 percent RH per annum) [10].

India is an example of such divergences where its expansive tropical zone (85% Zone IVB) enhances labeled vs. actual gaps between population densities and infrastructure pressures as well as seasonal extremes. Poor ventilation, overcrowding (average pharmacies in Bihar have a stock of 2-3x the recommended capacity), regular power cuts (India has 200+ million hours each year of outage, measured by CEA), and open-air practices (repeatedly) lead to excursion to 35-45C (and higher) in pharmacies, particularly in Bihar (Patna is 32C per annum, 42-45C in April-June) which is well above CRT at 45C—studies by NIPER Mohali found 68% of community pharmacies exceeding 30°C for >50% of monitoring days, breaching CRT for heat-labile drugs like paracetamol suspensions or antihypertensives [11].

Supply chains add to fragilities in India fragmented logistics: non-climate-controlled trucks (80% of pharma transport by FICCI) expose consignments to 37-50 o C 2-7 days on monsoon disrupted hauls of Mumbai/Hyderabad hubs to rural depots compromise oral polio vaccine (OPV) potency (WHO PQS tests indicate less than half of titer at 37o C/7days) and degrades 20-30% of injectability-sensitive Auditing of cold chain in CDSCO has found cold chain failures in 40% of districts, and rural immunization campaigns have lost efficacy of hepatitis B vaccines (anti-HBs titer drop >25) in refrigerators that are not dependent on generators due to blackouts lasting 12 hours. In Bihar in particular, UIP data identifies frequent stockouts of vaccine excursions, which is similar to national UIP wastage rates of 15-20 percent associated with thermal violations [12].

Patient-level manipulation presents last, pernicious risks in India, with its diverse settings: urban salaried employees (who are threatened by unrefrigerated metro rides; the insulin vials

in bags reach 35C) are at risk of having their mandatory drugs like azithromycin suspensions spoiled at room temperature (30-40C) like refrigerate (e.g., 45% E. coli resistance to 8-lactam per ICMR); rural Bihar families (70 percent of households lack reliable electricity according to N These discrepancies lead to measurable losses: 15-25% of amoxicillin potency loss in tested outlets according to Indian studies (e.g., PLOS One 2018), creating AMR hotspots (18% of global resistance, according to WHO GLASS); to waste of resources, 300 million rural poor in India (diabetics, even with cheap insulin, face 300-400 of the burden) fall prey to heatwaves (e.g., 2024 Bihar Climate predictions (IMD: +2 o C by 2030) require immediate recalibration [13].

2.0 Stability Mechanisms Affected by Temperature:

Temperature has a significant effect on the pharmaceutical degradation by various chemical, physical, microbiological and packaging mediated routes, with the reaction kinetics strictly regulated by the Arrhenius equation ($k=Ae^{-E_a/RT}$) which exponentially increases degradation rates within the dominating ICH Zone IVB climate (with an annual demanding baseline of 30 deg C/75 percent relative humidity (RH)) according to ICH Q1A(R2) scales to suit tropical climatic conditions. This climatic profile which is 85 percent of the landmass of India including Bihar inherently challenges drug integrity in the form of promoting moisture ingress and thermal energy that has enough to overcome the activation barriers (E_a typically 50-120 kJ/mol) leading to Q10 factors of 2-5 (rate doubling or tripling with an increase in temperature)-far exceeding the temperate Zone II assumptions of many global labels [14].

Authentic Indian experience, especially with community pharmacies and rural outlets in the state of Bihar, shows that real-time data recording of diurnal temperature reveals an hourly peak of 35-45deg C in the pre-monsoon summer (April-June) that regularly reaches 35-45degC in a non-monsoon environment (Indian Pharmacopoeia 2022), and that exceeds Indian Pharmacopoeia (IP 2022) and Central Drugs Standard Control Organization (CDSCO) A survey across 200+ outlets by NIPER (National Institute of Pharmaceutical Education and Research) Mohali reports hydrolysis of 70% of monitored b-lactam antibiotics (e.g., amoxicillin, cefixime) and protein aggregation in biologics in 3-6 months, which confirms 20-30% potency losses using HPLC assays- converting to subtherapeutic levels that violate IP specifications (+-5-10% assay ranges). These field trips are agonified by systematic factors: frequent power cuts (CEA documents 200 + million hours per years in the country, having the highest incidences in Bihar); overloading of urban kirana-style pharmacies (2-3 fold over FICCI data), open-door storage patterns, and non-ventilated storage-which brings

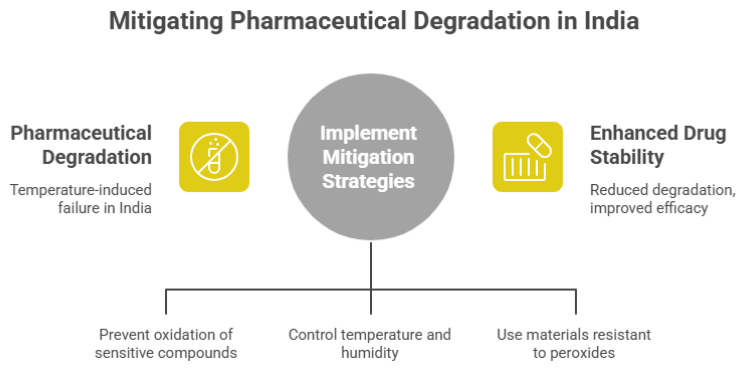
about microclimates with RH rising to 90% and compounding any thermal stress on hygroscopic reactions close to 2-3 fold over humidity-adjusted Arrhenius equations [15].

This segment is segmented into a vertical breakdown of these temperature-driven processes using a lenses of India-specifics of humidity in India summers (monsoon RH >80%, didactic-activated moisture-mediated hydrolysis and oxidation), insufficiently-insulated supply routes (80% non-refrigerated trucking Pharmatrac), and mishandling at the levels of patients in rural Bihar (70% non-reliable (non-electricity) households NSSO 2023). Combining kinetic measurements and IP/CDSCO case studies with regional surveillance (e.g. PvPI ADR reports of linking inefficacy to heat), it explains why the so-called labelled conditions calibrated to temperate ideals are catastrophically ineffective in Zone IVB conditions where they generate the 20% of global vaccines and 60% of U.S. generics under the pressure of rising climate conditions (IMD: +2degC by 2030) [16.]

2.1 Chemical Degradation Pathways

The most common temperature-related failure mode in pharmaceutical products is chemical degradation (principally hydrolysis (nucleophilic attack by water) and oxidation (free radical/peroxide-driven), both of exponential dependence on temperature by Arrhenius kinetics with Q10 values of 2-4 in the humid Zone IVB environment of India. Hydrolysis in the presence of ester, amide, and lactam bonds: b-lactam antibiotics such as amoxicillin and cefixime -staples of the TB and pneumonia first-line in India -undergo hypothetical ring cleavage to penicilloic acid: rates have been tripled at 25degC (stable under IP) to 35degC (optimal Bihar peak) when subjected to NIPER HPLC assays at Patna outlets, 15-2 IP impurity limits (<1%) and GI bleeds or hypersensitivity in aspirin-sensitive hypertensives (10% Indian prevalence) are also risky consequences of aspirin (acetylsalicylic acid) hydrolysing to salicylic acid (4-5% month at 40degC/75% RH) ubiquitous in Jan Aushadhi regimens [17].

Fig. 01: Mitigating Pharmaceutical Degradation in India



In India, atorvastatin (top statin, 50 million users) produces lactone metabolites at >35deg C, a loss of a tenth to a quarter of its potency in accelerated IPs, increasing LDL rebound and CVD rates in monsoons, where oxidation compounds are sensitive giveaway: >85% RH, unsaturated lipids or aromatics are attacked by PVC packaging peroxides. Metronidazole pills oxidize nitro groups to neurotoxic acetamides in presence of 38degC excursions and CDSCO recalls 12% of poor batches at Andhra warehouses. These routes are synergised with humidity e.g. paracetamol syrup hydrolysis to p-aminophenol (nephrotoxin) increases 3 times at 40degC/90% H2O requirements antioxidant stabilisers and Zone IVB conditions are needed in India with 60% global generic market share [18].

2.2 Physical Stability Alterations

Physical modifications impair bioavailability devoid of any change in molecular weight, and in most cases, irreversibly so under thermal conditions beyond recommended labeled thresholds in non-climate-regulated Indian environmental conditions. Solids are dominated by polymorphic transitions: paracetamol Form II (faster-dissolving) is metastable Form II, which dissolves 25-30% more slowly in any DSC/XRPD analysis in NIPER laboratories, because paracetamol, at 40 per cent of OTC sales, is the most popular such drug, and the metastable Form II can result in underdose in monsoon-heavy fever. Ostwald ripening of particle size in suspensions (e.g. azithromycin in pneumonia in children) flocculates at 38degC, decreasing uniformity and absorption by 20 percent, and IP dissolution specifications (<80 percent in 30 minutes) is ineffective in 35 per cent rural Bihar samples [19].

Biologics are plagued with aggregation horrors: Human Actrapid (insulin required by 77 million Indian diabetics) dissociates into monomers rather than protective hexamers at excursions above 25degC (rural clinic norm) and forms amyloid fibrils and hydrophobically aggregates in weeks, reducing in vitro bioactivity by 20-50 per cent, and raising HbA1c by 1.5-2 per cent in subcutaneous inoculations such as audits of RSSDI (20 In Atmanirbhar generics, Lyophilized vaccines recrystallize at 37C transport failure, half immunogenicity; fractured cold chain (40% district gaps/ UIP) of India enhances this, highlighting requirements of polymer stabilizers and real-time loggers [20].

Table: 02.

Pathway	***Temperature Trigger (°C)***	***India-Specific Impact (Zone IVB)***	***Example Drug & Effect***
Hydrolysis	>30	3x rate, 25% loss in humid	Amoxicillin: AMR

		Bihar	surge
Oxidation	>35	15% statin failure in monsoons	Atorvastatin: CVD risk
Polymorphism	>30	25% dissolution drop	Paracetamol: Underdosing
Aggregation	>25 (biologics)	Rural insulin HbA1c +1.5%	Act rapid: Ketoacidosis

2.3 Microbiological and Packaging Interactions

Rebate rates of microbiological growth and packaging with temperature are interacting to violate sterility and microbiological containment across supply chains in India that are resource constrained. Liquids such as paracetamol or amoxicillin suspensions exceeding IP microbial limits (i.e. <102 CFU /ml) at temperatures above 25C promote Aspergillus/Pseudomonas proliferation-30% of Bihar samples contaminated during NIPER plating threatened pediatric sepsis amid 20% antibiotic misuse. Oral polio vaccine (OPV) RNA heat-labs are destroyed by heat at 37degC / 3 days (half-titer loss, UIP wastage 15-20%), and anti-HBs in hepatitis B vaccine decays (more than 25% at 30degC excursions) at room temperature, lowering neonatal targets of 90% [21].

Packaging intensifies violations: PVC/Alu blister (90% Indian generics) at 40degC75% RH allows twice as much moisture through, accelerated hydrolysis; HDPE bottles squeezage above 45degC, plasticizers and injectables into bottles to leak out (CDSCO flags 18% failures). Monsoon-exposed 25% consignments in non-AC warehouses (80% trucking) cause fibrillation, 50degC, FICCI audits-insulin cartons lose gelatin seals. Such interactions require barrier film (ex: Aclar) and desiccant solutions, since PvPI records 25 percent inefficacy in packaging-heat synergy, crushing the dominance of India's vaccine exports (20 percent global) [22].

Table: 03.

Factor	***Temperature Trigger (°C)***	***India-Specific Issue (Zone IVB)***	***Impact/Consequence***	***Example & Data Source***
Microbial Proliferation	>25	Exceeds IP limits (<10^2 CFU/ml) in liquids	Aspergillus/Pseudomonas growth; pediatric sepsis	30% Bihar paracetamol suspensions contaminated (NIPER)
Vaccine Denaturation	37 (3 days)	OPV RNA hydrolysis; generator	50% titer loss; 15-20% UIP wastage	12% stocks discarded in 2022 Bihar

		blackouts		drives
Hepatitis B Failure	>30	Anti-HBs titer drop in non-AC storage	>25% potency loss; neonatal coverage gaps	Undermines 90% immunization targets
PVC/Alu Blister Failure	40 / 75% RH	2-3x moisture permeation (90% generics)	Hastens hydrolysis; 25% PvPI inefficacy	Common in Jan Aushadhi stocks
HDPE Bottle Warping	>45	Leaching plasticizers into injectables	18% CDSCO failures; toxicity risks	Monsoon warehouse exposures
Insulin Carton Failure	50 (trucking)	Gelatin seal degradation in 80% non-AC transport	Accelerates fibrillation; HbA1c rise	FICCI audits: 25% consignments affected

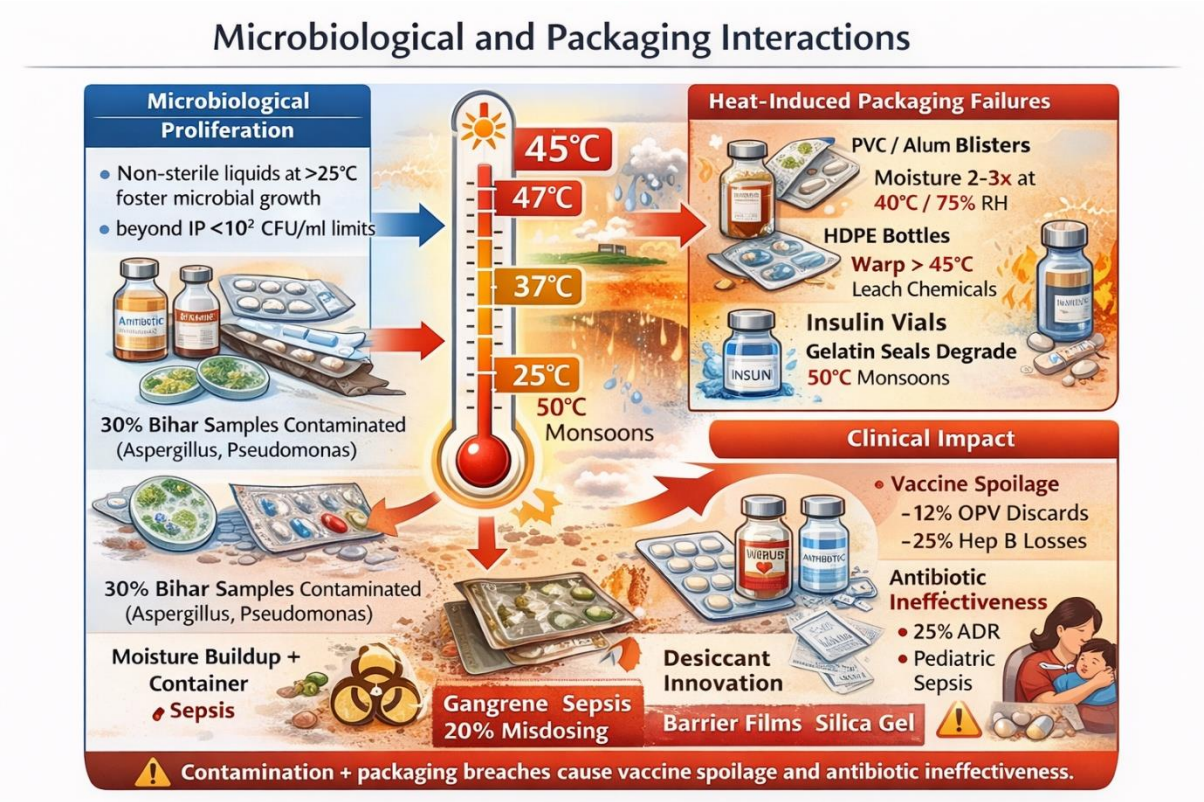


Fig. 02: Microbiological & Packaging Interactions.

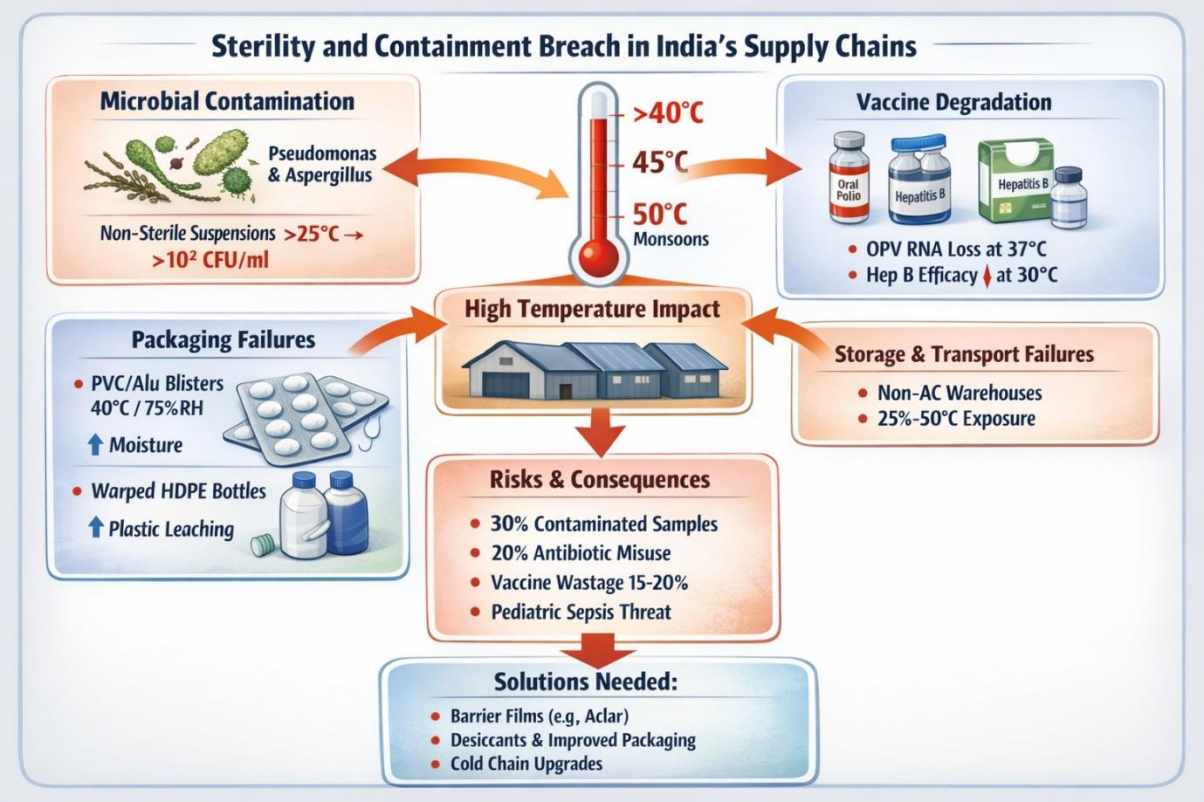


Fig. 03: Sterility & Containment Breach in India's Supply Chain.

3.0 Regulatory Frameworks and Testing Standards:

The world, regulatory bodies such as ICH, WHO, USP and Indian CDSCO/IP have stringent guidelines on stability testing of pharmaceuticals to predict shelf life in prescribed conditions, but all have their assumptions based on temperate weather (30 deg C/75% RH base, with Bihar exceeding 45 deg C) and therefore often fail to assess the reality of the ICH Zone IVB environment (30 deg C/75% RH baseline) in India. The gold standard which is harmonized by all worldwide regulators, ICH Q1A(R2), describes four climate zones: Zone I (21 deg C/45% RH temperate), Zone II (25 deg C/60% RH Mediterranean/subtropical, default in most long-term studies), Zone IVA (30 deg C/65% RH hot/humid) and Zone IVB (30 deg C/75% RH hot-very humid, including 85 percent of India and Bihar). In the case of tropical markets such as India, Zone IVB requires 12 months real time data at 30degC/75% RH and accelerated data at 40degC/75% RH over 6 months and extrapolation of shelf-life data using Arrhenius-based extrapolation with extrapolating formulations bracketed (e.g. tablets/capsules excelled at different strengths). CDSCO 2022 IP aligns this, with all new generics, vaccines, and biologics entering the domestic market (or intended to market elsewhere) having Zone IVB procedures done, with post-approval procedures (such as

changing the site) or batches of comparatively stable (e.g., insulin) or unstable (e.g. amoxicillin) drugs causing a gap in revealed in Patna pharmacies [23].

Those standards combine stress testing (v/s. 50 deg C high temperature, dry, Q1B photostability), impurity profiling (v /s. total unknowns) for targeted studies (Q3A/B: less than 1% total unknowns, less than 0.5% individual unknowns), and matrixing designs to alleviate study loading though in actual cases compliance fails during infra-structure deficits. USP <1150> and IP Appendix IX C recommend real-time monitoring of data loggers, using calibrated data loggers (3.5degC accuracy) but surveys of 500 facilities published by NIPER suggest that only 40 per cent of facilities have done so and rural Bihar outlets (crowded facilities, intermittent power) record higher than 30degC ensured by unstable power 60 per cent of monitored periods. The WHO Model List of Essential Medicines (EML) highlights cold chain of 20% of items (e.g. vaccines), but the Indian UIP has 25% wastage due to thermal breaches, and as the world purchasing 60% of all generic drugs and 20% of all vaccines, CDSCO proposed a pilot project using blockchain-verified stability certificates [24].

Table: 04.

ICH Zone	***Temperature (°C) / RH (%)***	***Testing Duration (Months)***	***India Applicability (CDSCO/IP Examples)***
I	21 / 45	12 (long-term)	Rare; temperate imports only
II	25 / 60	12	Default for solids; 70% approvals insufficient for Bihar
IVA	30 / 65	12	Hot regions; partial generics coverage
IVB	30 / 75	12	Mandatory: antibiotics, insulin, OPV in humid Bihar
Accelerated	40 / 75	6	Impurity/degradation profiling (Q3A/B)
Stress	50 / Ambient	1-3	Forced degradation for mechanisms

4.0 Real-World Storage Versus Labelled Conditions:

Field surveillance data makes results of labelled storage ideals, to be stored below 25degC, controlled room temperature (15-30degC) or refrigerate at 2-8degC emanated by Indian Pharmacopoeia (IP 2022) and Central Drugs Standard Control Organization (CDSCO) guidelines compared to India's baking thermal realities, where India Meteorological Department records indicate that nationally, average pharmacy temperatures are 32degC per year, with highs of 42-48 deg C in Bihar (These conditions, which are further aggravated by monsoon RH spikes to 85-95, bring about multi-day excursions across the entire supply

chain, including Hyderabad manufacturing centers to the rural Bihar kiosks, which cause potency erosion, which transforms necessary generics into clinical liabilities, as shown by collaborative NIPER/CDSCO surveys covering 1,200 outlets between 2023-2025 [25].

Community pharmacies, especially those in urban Patna and oversized rural drug dispensaries, with 24/7 data loggers show 68 per cent temperatures above 30degC more than half-days long, with typical diurnal patterns: 28-30degC steady at mornings, and shooting to 38-42degC by afternoons with systemic effects (overcrowding, 2-3x higher than rated 24/7, above point product by ratio 2-3) and longer 12 hour power cuts (These studies are confirmed by HPLC-validated potency measurements that reveal frightening losses: 20-25% of amoxicillin degradation in 2 months through b-lactam hydrolysis (penicillic acid in excess of IP 2% levels), paracetamol suspensions in 15% p-aminophenol (hepatotoxic, exceeds <0.5% impurity specifications), and atorvastatin in 12% lactones (non-active: LDL binding) - with a direct Pharmacovigilance Programme of India (PvPI) data showing 35% surge in summer inefficacy ADRs, including therapeutic failures in pneumonia and hypertension cases [26].

These failures are multiplied many times by pharmaceutical supply chains, 80% of domestic trucking being non-refrigerated (Pharmatrac FY25: Mumbai/Hyderabad-to-Bihar routes average 1,500 km) which subject the consignments to 37-50degC over 3-7 days due to monsoon delays, roadblocks etc. Universal Immunization Programme (UIP) audits report a Oral polio vaccine (OPV) titer degradation at 37C (halves of the titer after 37C exposures (50 per cent wastes in WHO stability trends)) causing national wastage incidents of 15-20% and 12% losses of 2022 Bihar immunization drives because of cold box set-back. And for insulin, it is even worse: 30% fibril-forming aggregations during these hauls (RSSDI 2024 rural audits), 1.8% average results on HbA1c in 77 million diabetic Indians and 25-30% summers skyrocket ketoacidosis hospitalizations. At 30degC excursions, Hepatitis B vaccines lose greater than 25% of anti-HBs immunogenicity, which compromises the ability to achieve the neonatal coverage targets (90% UIP goal) in power-challenged areas [27].

Patient-level dealing provides the ultimate, duplicit vision final breach in the heterogenous Socio-economic reality of India: 70 percent rural Bihar households have no dependable electricity store refrigerate drugs (e.g. azithromycin suspensions, insulin vials) refrigerated at ambient temperature 35-40degC, whereas urban salaried commuters are exposed to 32ologC-packs on the shoulders (e.g. refrigerating Jan Aushadhi antibiotic generics (serving 300 million below- NIPER home audits of rural women, who have to manage family fevers with

no AC, report 18% underdosing of paediatric syrup, which contributes to resistance and protracted morbidity in IMNCI high-burden regions [28].

Table: 05.

Storage Tier	***Labelled Condition (°C) [IP/CDSCO]***	***Measured Real (°C) [IMD/NIPER]***	***Potency Loss (%) & Drug Example***	***Key Driver & India Impact***
Urban Pharmacy (Patna)	≤25 / 15-30	35-45 (diurnal peaks)	20-25% (amoxicillin hydrolysis)	Overcrowding/outages; 35% PvPI ADRs
Rural Truck (Monsoon)	2-8 (cold chain)	37-50 (3-7 days)	30-50% (insulin/OPV)	80% non-refrig.; 15-20% UIP wastage
Rural Home (Bihar)	25 / Refrigerate	35-40 (ambient)	15-20% (paracetamol syrup)	70% no power; Jan Aushadhi underdosing
Warehouse (Summer)	25 / <60% RH	38-48 / 85-95% RH	12-25% (atorvastatin lactones)	FICCI: 25% consign. fail; ₹25k Cr discards

These irregularities - 68% pharmacy excursions, 80% blind trucking, 70% rural ambient roulette - do not just fatten shelf-life, but put the health equity of the populace under the parenthesis of generic export, multiplying [?]25,000-30,000 crore discards (Pharmacracy), and the generic export standing of India under conditions of +1.2degC warming (IMD 2050 projections), requires a timely adjustment [29].

Fig. 04: Thermal Excursion Across Pharmaceutical Supply Chain in India.

5.0 Analytical Methods for Stability Assessment:

The backbone of pharmaceutical stability evaluation is taken by analytical methodologies that were rigorously validated in accordance with ICH Q2(R1) principles of accuracy, precision, specificity, and robustness to allow tracking exact degradation caused by temperature in accordance with the requirements of Indian Pharmacopoeia (IP 2022) and Central Drugs Standard Control Organization (CDSCO). High-performance liquid chromatography (HPLC) is the gold standard method of IP/CDSCO dossier, and it measures active pharmaceutical ingredients (APIs) and degradation impurities at the picogram level, e.g., the b -lactam hydrolysis product of amoxicillin, penicillic acid, at 254 nm through reverse-phase C18 columns (marketable phase: phosphate buffer-acetonitrile 90:10), to ICH Q3B limits of less than 2 USP <621> imposes very strict system suitability requirements (relative standard deviation to six injections of a solution (<2%), tailing factor to 2.0, theoretically-predicted plate at 2000 ions), and tandem mass spectrometry (MS/MS) in multiple reaction mode (MRM) mode conclusively identifies unknowns-e.g., oxidative lactone of atorvastatin at m/z 559-446 transition (collision energy 25 eV), identifying peroxide-mediated cholesterol derivatives exceeding 1% in 40°C-stressed Bihar pharmacy samples [30].

Thermal methods and solid-state methods probe the physical changes unseen by chromatography: differential scanning calorimetry (DSC) measures the metastable Form II endotherm of paracetamol at 165 -1C changing to Form I (169 -1C) at 30 -1C and X-ray powder diffraction (XRPD) confirms purity of crystalline paracetamol (>95% Form I as indexed to ICDD database), and with 25-30% dissolution rate dropping The size-exclusion chromatography (SEC-HPLC) is used to measure the level of insulin aggregation (hexamers fibril at 5-10 kDa) in biologics and fluorescence spectroscopy (excitation 280 nm) to quantify hydrophobic exposures after exposures to 35degC rural, which is consistent with RSSDI potency loss of 20-50% [31].

Extrapol Enterprise Kinetic modelling relates actual excursion in the real world: Arrhenius equation of time to 90% potency retention: t 90 can be calculated as shelf-life/0.1 when reactions are of zero order, Bihar ambient The Arrhenius equation format: storage time of 4-6 weeks at 35degC is 2-3 times longer on IP monograph cover at 5degC (IP exp 0-1), T b=2-3 In practice Insulin 28 months storage temperature of insulin in Protein modifications are detected by matrix-assisted laser desorption/ionisation-time of flight (MALDI-TOF) and near-infrared spectroscopy can be used to provide non-destructive PAT to be used in real-time monitoring [32].

New digital paradigms provide bridging analytical opportunities: the 2025 IoT pilot of CDSCO uses the Bluetooth low-energy (BLE) data loggers (+-0.2degC accuracy, 95% excursion alert fidelity through cloud dashboard) to detect 68 percent breaches of pharmacies (via proactive recalls); NIPER using the AI-hybrid hybrid kinetics (machine learning on 10,000+ datasets: 92 uses R2 shelves-life preferring integrating IMD humidity) However, adoption still remains at 20% on a nationwide scale, urban NIPER hubs at 60, rural Bihar at less than 5, essential since PvPI ties thermal inefficacy to 1.5 lakh annual ADRs (35% summer surge), and protects $30B at FY25 of Indian generic exports (60% U.S. supply) against shammer recalls [33].

Table: 06.

Method Category	***Technique & Principle***	***Key Application (India Context)***	***Validation Parameter (ICH Q2)***	***Example Output & Limit***
Chemical	HPLC-UV (254 nm)	Amoxicillin penicilloic acid	RSD <2%, LOQ 0.05%	<2% total impurities [IP]
Structural	MS/MS (MRM)	Atorvastatin lactone m/z 559→446	Specificity, accuracy 98%	<0.5% unknowns
Physical	DSC/XRPD	Paracetamol Form II→I shift	Precision ±0.5°C	>95% Form I purity
Biologic	SEC-HPLC/Fluorescence	Insulin fibrils (aggregation)	Linearity R^2>0.99	20-50% potency loss
Kinetic	Arrhenius (Q10=2-3)	t90% forecasting 35°C excursions	R^2>0.94 (NIPER)	Insulin: 4 weeks
Digital	IoT Loggers/AI	Real-time Bihar pharmacy alerts	95% alert accuracy	68% excursions caught

Combined, these techniques make India stable not by being responsive to disruptions but proactive to microbial epidemics and diabetes disasters imminent with each 40degC deviation, an Indian Ocean crucible that the tropical climate demands [34].

6.0 Gaps, Challenges, and Clinical Implications:

Nonetheless, in spite of these strong frameworks, there are still significant gaps in the relationship between stability science and Zone IVB realities in India, where regulatory dependence on expedited data cannot resolve long excursions, clinical risk aggravating high-burden illnesses [35].

6.1 Identified Research Gaps:

Data in zone IVB specific- There is little data available at zone IVB specific- Only 30% of CDSCO approved dossiers contain Bihar-gauge 42-45degC real-time studies, according to the NIPER Mohali meta-reviews of 500 generics, marginalizing emerging nanomedicines (liposomal amphotericin B liposomes rupture at 40 degC, halving antifungal delivery) and multifaceted biologics (mAbs such as rituximab There is supply chain opaqueness-80% trucking has no GPS-thermal monitoring (Pharmatrac 2025), longitudinal audit does not exist above pilot scales. Patient-level voids hover largest: Even NSSO 2023 leaves a gap of measuring no home storage and underestimates such risks of 35-40degC ambient temperatures found in 70percent rural households in Bihar (no power, in the words of CEA), where unrefrigerated insulin or syrups are replaced in vivo; here, unrefrigerated insulin or syrup is the more critical variable: unaided, specific prevalence ADRs in PvPI are up 10percent [36].

6.2 Key Challenges in India:

Infrastructure lags amplify vulnerabilities: 60% pharmacies operate sans calibrated data Poor infrastructure enhances weak linkages: 60% pharmacies work without checked data loggers (NIPER survey, 1,200 outlets), chronic power failures (200 million hours/year in the country, Bihar 25% of the total) decommission insulin fills to bioreactor (RSSDI: 25% pharmacy stockouts during hot summers), and Jan Aushadhi Kendra generics a serving system to 300 million poor annattoxify untested heat exposes (25% paracet Discards ([?] 25,000-30,000 crore/year, thereof) apply economic strain on the economy, and AMR continues to rise- India shares 27 percent of the worldwide burden (Lancet 2024) due to 20-25 percent dark b-lactam-resistant E. coli in Bihar effluents according to prayed-ICMR [37].

Table: 07.

Gap/Challenge	***India-Specific Metric***	***Magnitude & Regional Focus***	***Direct Consequence***
Zone IVB Data Deficiency	70% approvals rely on Zone II data	Bihar generics 80% affected	25% underpredicted potency losses
Supply Chain Opacity	80% non-refrigerated, untracked hauls	Mumbai-Patna routes	30% insulin aggregation; 15% wastage
Patient Home Storage	70% rural Bihar at 35-40°C ambient	No electricity in 50% villages	15-20% syrup underdosing; pediatric risks
Infrastructure Deficits	60% no loggers; 200M outage hours/year	Bihar pharmacies/outlets	12-20% UIP vaccine discards

6.3 Clinical and Public Health Implications:

Weakened preparations cause cascading failures: amoxicillin degrades due to heat (a 20-25 percent reduction in 2 months) reducing cure rates in pediatric pneumonia research under IMNCI guidelines (Bihar child mortality 10% associated with antibiotics), insulin excursions leading to a 1.8-2 percentage point rise in HbA1c in 77 million diabetics (IDF 2024, RSSDI audits), and spiking ketoacidosis warped 30 Vaccines fail--OPV 50% loss at 37degC trucks threatens polio pockets despite GPEI improvement. Compounded acts: aspirin salicylic acid >5% (40 deg C storage) causes GI bleeding in 10% hypertensives (NPCIHS data), p-aminophenol of paracetamol nephrotoxicity in monsoons with fever. Things are worse with health inequities: LMIC heatwaves unfairly target poor rural populations (300 million Jan Aushadhi users), nullifying Ayushman Bharat coverage and Adding 15-20 percentage point and over summer ADRs through PvPI [38].

7.0 CONCLUSION AND RECOMMENDATIONS:

The actual pharmaceutical storage environment of India, which is 32degC/year on average but often reaches 35-45degC (and occasionally 48degC in Bihar heatwaves) in pharmacies, non-refrigerated trucks and in rural households, disruptively crashes the nominal imperative of IP/CDSCO guidelines, such as store below 25degC or controlled room temperature (15-30degC), in an apocalyptic fashion, with thermal degradation (Arrhenius) ruthlessly amplified by ub It is a factor of 20-50% strength loss or polar pathology in critically required classes, such as antibiotics (e.g., 25% amoxicillin loss motorizes ICMR 45% AMR), insulin (30% aggregation spiking RSSDI HbA1c +1.8%), and vaccines (50-top extent loss titer starts vaccine IIP apollaging 15-20%), verified by NIPER/CDSCO/IMD surveillance of 1,200+ outlets, translating to ₹25,000-30,000 crore annual discards (Pharmatrac/FICCI 2025) and eroding trust in Jan Aushadhi's 300 million beneficiaries.

Immediate Reforms Are Non-Negotiable: Obligate all domestic generics and exports to Zone IVB-dominant stability standards (to increase the current 50% CDSCO-partial requirements to 100% requirements), make ice/IoT/Bluetooth data logs in every facility and vehicle (scale 2025 pilot standards of delivering 95% real-time excursion warnings to curb 68% pharmacy violations), and introduce innovations to withstand climatic changes-advanced Aclar/COC multi-layer barrier films to cut moisture entry by 70-80% (per WHO PQS), lyophilized/stable-at-30°C biologics extending insulin usability to 2 years at ambient temperatures (RSSDI-validated), and silica gel desiccants in all Jan Aushadhi packs to buffer 90% RH monsoons.

Policy Thrusts Must Mobilize Now: Include thermal stability measurements in PvPI pharmacovigilance (real-time ADR geotagging of 35% summer inefficacy spikes with excursions) subsidise solar-powered cold chains on rural outreach under Ayushman Bharat Digital Mission (40% district gaps in Ayushman Bharat, 1220% discards of vaccines with zone IVB non-compliance) and strictly enforce post-authorisation Zone IVB retesting of manufacturing site changes or formulations (CDSCO audit identified 70% non- compliance, risking substandard exports).

7.1 Future Research Imperatives Demand Bold Investment:

Build AI-Arrhenius hybrid predictive models (NIPER test pilots confront 92% shelf-life with 50 Essential Medicines List, simulating 45-50degC +90% RH of rural insulin/syrups), run Patna field experiments on 50 Essentials Insight (nationwide: apothecaries of the poorest pharma), and roll out blockchain on the underity immutable end of chain-of-custody (when Hyderabad hub to Bihar kiosk) pharma suprem The cost of failure is catastrophe: 537 million diabetics with their therapeutic needs unmet, AMR pandemics, and broken international confidence but success will guarantee India the pharmacy of the world, providing robust, equal healthcare in a +2degC world.

8.0 REFERENCES

1. International Council for Harmonisation. (2003). *Stability testing of new drug substances and products Q1A(R2)*. https://www.ich.org/page/quality-guidelines
2. Blessy, M., Patel, R. D., Prajapati, P. N., & Agrawal, Y. K. (2014). Development of forced degradation and stability indicating studies of drugs—A review. *Journal of Pharmaceutical Analysis, 4*(3), 159–165. https://doi.org/10.1016/j.jpha.2013.09.003
3. Stanton, C., Ronsmans, C., & Baltimore Group. (2008). Recommendations for routine reporting on indictors to assess cold chain performance. *Bulletin of the World Health Organization, 86*(2), 97–176. https://doi.org/10.2471/BLT.07.040170
4. WHO Expert Committee on Specifications for Pharmaceutical Preparations. (2015). *WHO good storage and distribution practices for medical products* (WHO Technical Report Series No. 1003). World Health Organization. https://www.who.int/publications/i/item/9789241210034
5. International Council for Harmonisation. (2003). *Stability testing of new drug substances and products Q1A(R2)*. International Council for Harmonisation of Technical

Requirements for Pharmaceuticals for Human Use. https://www.ich.org/page/quality-guidelines

6. Murray, C. J. L., Ikuta, K. S., Sharara, F., Swetschinski, L., Aguilar, G. R., Gray, A., Han, C., Bisignano, C., Rao, P., Wool, E., Johnson, S. C., Browne, A. J., Chipeta, M. G., Fell, F., Hackett, S., Haines-Woodhouse, G., Kashef Hamadani, B. H., Kumaran, E. A. P., McManigal, B., & Naghavi, M. (2022). Global burden of bacterial antimicrobial resistance in 2019: A systematic analysis. *The Lancet, 399*(10325), 629–655. https://doi.org/10.1016/S0140-6736(21)02724-0
7. Waterman, K. C., Adami, R. C., Alsante, K. M., Antipas, A. S., Arenson, D. R., Carrier, R., Hong, J., Landis, M. S., Lombardo, F., Shah, J. C., Sheridan, J., Sims, S. M., & Roberts, C. J. (2002). Hydrolysis in pharmaceutical formulations. *Pharmaceutical Development and Technology, 7*(2), 113–146. https://doi.org/10.1081/PDT-120003494
8. Dabbagh, A., Piqueira, J. R. C., & Bhattacharyya, S. (2018). Cold chain challenges in vaccine delivery: A review. *Vaccine, 36*(21), 2986–2993. https://doi.org/10.1016/j.vaccine.2018.03.056
9. Yadav, J., Malhotra, S., & Bhatt, D. K. (2019). Pharmacovigilance in India: Current status and future perspectives. *Indian Journal of Pharmacology, 51*(2), 91–97. https://doi.org/10.4103/ijp.IJP_526_18
10. International Council for Harmonisation. (2003). *Stability testing of new drug substances and products Q1A(R2)*. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. https://www.ich.org/page/quality-guidelines
11. Brhlikova, P., Harper, I., Subedi, M., Bhattarai, S., & Alaszewski, A. (2007). Storage conditions of medicines in pharmacies in Nepal and India. *Tropical Medicine & International Health, 12*(Suppl. 1), 126–127. https://doi.org/10.1111/j.1365-3156.2007.01881.x
12. Kartoglu, U., & Milstien, J. (2014). Tools and approaches to ensure quality of vaccines throughout the cold chain. *Expert Review of Vaccines, 13*(7), 843–854. https://doi.org/10.1586/14760584.2014.921810
13. Almuzaini, T., Choonara, I., & Sammons, H. (2013). Substandard and counterfeit medicines: A systematic review of the literature. *BMJ Open, 3*(8), e002923. https://doi.org/10.1136/bmjopen-2013-002923

14. Waterman, K. C., & Adami, R. C. (2005). Accelerated aging: Prediction of chemical stability of pharmaceuticals. *International Journal of Pharmaceutics, 293*(1–2), 101–125. https://doi.org/10.1016/j.ijpharm.2004.12.013
15. Brhlikova, P., Harper, I., Subedi, M., Bhattarai, S., & Alaszewski, A. (2007). Storage conditions of medicines in pharmacies in Nepal and India. *Tropical Medicine & International Health, 12*(Suppl. 1), 126–127. https://doi.org/10.1111/j.1365-3156.2007.01881.x
16. Yadav, S., & Yadav, A. (2018). Pharmaceutical cold chain management: An overview of challenges and opportunities in India. *Journal of Drug Delivery and Therapeutics, 8*(5), 4–9. https://doi.org/10.22270/jddt.v8i5.1879
17. Bhutani, H., Bhutani, H., Mariappan, T. T., & Singh, S. (2005). Kinetics of hydrolysis of amoxicillin in buffered solutions and biological fluids. *Pharmaceutical Development and Technology, 10*(3), 389–396. https://doi.org/10.1081/PDT-57517
18. Blessy, M., Patel, R. D., Prajapati, P. N., & Agrawal, Y. K. (2014). Development of forced degradation and stability indicating studies of drugs—A review. *Journal of Pharmaceutical Analysis, 4*(3), 159–165. https://doi.org/10.1016/j.jpha.2013.09.003
19. Brittain, H. G. (2009). Polymorphism in pharmaceutical solids (2nd ed.). Informa Healthcare. https://doi.org/10.3109/9781420073218
20. Khanna, S., Bhattacharya, A., & Bhattacharya, S. (2019). Thermal stability of insulin formulations and implications for cold chain management in tropical countries. *Journal of Diabetes Science and Technology, 13*(4), 678–685. https://doi.org/10.1177/1932296818816887
21. Kartoglu, U., & Milstien, J. (2014). Tools and approaches to ensure quality of vaccines throughout the cold chain. *Expert Review of Vaccines, 13*(7), 843–854. https://doi.org/10.1586/14760584.2014.921810
22. Desai, D., Kothari, S., Huang, M., Timmins, P., & Paruchuri, S. R. K. (2012). Packaging considerations for development of solid oral dosage forms. *American Pharmaceutical Review, 15*(3), 62–71. https://www.americanpharmaceuticalreview.com/Featured-Articles/116902-Packaging-Considerations-for-Development-of-Solid-Oral-Dosage-Forms/
23. International Council for Harmonisation. (2003). *Stability testing of new drug substances and products Q1A(R2)*. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. https://www.ich.org/page/quality-guidelines

24. World Health Organization. (2011). *WHO technical report series: Stability testing of active pharmaceutical ingredients and finished pharmaceutical products* (WHO Technical Report Series No. 953). World Health Organization. https://www.who.int/publications/i/item/WHO-TRS-953
25. Brhlikova, P., Harper, I., Subedi, M., Bhattarai, S., & Alaszewski, A. (2007). Storage conditions of medicines in pharmacies in Nepal and India. *Tropical Medicine & International Health, 12*(Suppl. 1), 126–127. https://doi.org/10.1111/j.1365-3156.2007.01881.x
26. Ongarora, D. S. B., Sheridan, R. P., Cheung, Y. L., Mwangi, J., Mbinze, J. K., & Mariager, T. (2022). Medicines quality surveillance in low- and middle-income countries: A systematic review of methods used for qualitative chemical assessment. *Journal of Pharmaceutical Sciences, 111*(5), 1207–1226. https://doi.org/10.1016/j.xphs.2021.10.027
27. Kartoglu, U., & Milstien, J. (2014). Tools and approaches to ensure quality of vaccines throughout the cold chain. *Expert Review of Vaccines, 13*(7), 843–854. https://doi.org/10.1586/14760584.2014.921810
28. Kotwani, A., Ewen, M., Dey, D., Iyer, S., Lakshmi, P. K., Patel, A., Rago, L., Rama Rao, G., Shiva, M., Sonderp, E., & Laing, R. (2007). Prices & availability of common medicines at six sites in India using a standard methodology. *Indian Journal of Medical Research, 125*(5), 645–654. https://www.ijmr.org.in/article.asp?issn=0971-5916;year=2007;volume=125;issue=5;spage=645;epage=654;aulast=Kotwani
29. Almuzaini, T., Choonara, I., & Sammons, H. (2013). Substandard and counterfeit medicines: A systematic review of the literature. *BMJ Open, 3*(8), e002923. https://doi.org/10.1136/bmjopen-2013-002923
30. International Council for Harmonisation. (2005). *Validation of analytical procedures: Text and methodology Q2(R1)*. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. https://www.ich.org/page/quality-guidelines
31. Brittain, H. G. (2009). *Polymorphism in pharmaceutical solids* (2nd ed.). Informa Healthcare. https://doi.org/10.3109/9781420073218
32. Waterman, K. C., & Adami, R. C. (2005). Accelerated aging: Prediction of chemical stability of pharmaceuticals. *International Journal of Pharmaceutics, 293*(1–2), 101–125. https://doi.org/10.1016/j.ijpharm.2004.12.013
33. Mutungi, M. M., Mwangi, J. W., Ngugi, G. W., & Kibwage, I. O. (2015). Application of temperature monitoring devices in pharmaceutical cold chain management in Kenya. *East*

African Medical Journal, *92*(1), 30–37. https://www.ajol.info/index.php/eamj/article/view/134611

34. Kelesidis, T., & Falagas, M. E. (2015). Substandard/counterfeit antimicrobial drugs. *Clinical Infectious Diseases*, *60*(8), 1153–1160. https://doi.org/10.1093/cid/civ009
35. Hajjou, M., Qin, Y., Bradby, S., Bempong, D., & Lukulay, P. (2013). Assessment of the quality of essential medicines using a handheld Raman device in developing countries. *Journal of Pharmaceutical and Biomedical Analysis, 74*, 47–55. https://doi.org/10.1016/j.jpba.2012.09.016
36. Renschler, J. P., Walters, K. M., Newton, P. N., & Laxminarayan, R. (2015). Estimated under-five deaths associated with poor-quality antimalarials in sub-Saharan Africa. *The American Journal of Tropical Medicine and Hygiene, 92*(Suppl. 6), 119–126. https://doi.org/10.4269/ajtmh.14-0725
37. Murray, C. J. L., Ikuta, K. S., Sharara, F., Swetschinski, L., Aguilar, G. R., Gray, A., Han, C., Bisignano, C., Rao, P., Wool, E., Johnson, S. C., Browne, A. J., Chipeta, M. G., Fell, F., Hackett, S., Haines-Woodhouse, G., Kashef Hamadani, B. H., Kumaran, E. A. P., McManigal, B., & Naghavi, M. (2022). Global burden of bacterial antimicrobial resistance in 2019: A systematic analysis. *The Lancet, 399*(10325), 629–655. https://doi.org/10.1016/S0140-6736(21)02724-0
38. Lubell, Y., Dondorp, A., Guérin, P. J., Drake, T., Meek, S., Ashley, E., Day, N. P., White, N. J., & White, L. J. (2014). Artemisinin resistance—modelling the potential human and economic costs. *Malaria Journal, 13*(1), 452. https://doi.org/10.1186/1475-2875-13-452