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Regulatory Requirements for Participation in WHO Prequalification Programme for Parenteral Products

Aditi Muskan Jha*[,a], Maitrey Zaveri[a], Shirish Patel[b], Zuki Patel[a]

[a]*Department of Pharmaceutical Regulatory Affairs, K. B. Institute of Pharmaceutical Education and Research, A constituent college of Kadi Sarva Vishwavidyalaya, Gate No 1, Kadi Campus Rd, Sector 23, Gandhinagar, Gujarat 382016*

[b]*Otsuka Pharmaceuticals India Pvt. Ltd., 21st Floor, B-Block, Westgate Nr. YMCA Club, Sarkhej - Gandhinagar Hwy, Ahmedabad, Gujarat 380015*

Abstract

The Parenteral Product like IV injections, vaccines, etc which is very sensitive including their manufacturing process, storage all plays very important role. A small mistake can destroy the pharmaceutical product and also dangerous for the human kind. Also, in a COVID-Era, we know the importance of the parental product and their life cycle management.

So, this article focuses on the World Health Origination Pre-Qualification Programme which plays very important role in the parenteral product Safety, Quality And their efficacy.

The article contains WHO Prequalification Programme Framework in which all the parameters and its evaluation frameworks. The WHO PQ various stages and their market impact that it can help industry and they can show that their product have the Quality that's why they have WHO PQ Acceptance Letter. The article review that what is GMP requirements that WHO PQ wants. They also included the how to risk Management and quality Control is necessary. It is also very importance of Stability studies and requirements, for parenteral product this step is very necessary, as stability of parenteral product is very important. The WHO PQ also requires CTD or eCTD dossier which includes various Modules.

Conclusion: The WHO Prequalification Programme plays a crucial role in guaranteeing that injectable products meet global standards for quality, safety, and efficacy by conducting thorough GMP inspections and evaluating CTD dossiers, particularly Module 3 (Quality). For those working in Regulatory Affairs, obtaining WHO PQ approval enhances the product's credibility and facilitates participation in international tenders.

Keywords: WHO Prequalification; Parenteral products; GMP compliance; Stability Requirements; Zone IVb stability; CTD documentation

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*Corresponding author. E-mail address: aditimuskanjha@gmail.com (AM Jha)

1. Introduction

World Health Organisation Pre-Qualification Programme plays a very crucial role to ensure the Quality, Safety & Efficacy of the parenteral product. The WHO PQ especially focus on Good Manufacturing Practices and they conduct regular inspection whether they comply with guidelines and ICH guidelines. They also require CTD dossier of the Pharmaceutical Product in various 5 Modules are required which included: Module 1: Regional & Administrative Information, Module 2: Overall Summary, Module 3: Quality, Module 4: Non-Clinical Overview & Module 5: Clinical Overview

For Regulatory Affairs Professional, the dossier is their greatest responsibility which included compilation of all the required documents and ensures the product met with their guidelines. The WHO PQ acceptance letter also plays a major market impact as having this letter shows the company credibility and they can win any tenders and customer's trust. For Parenteral Product the Module 3 plays a major role as it is very important because it includes various information like stability studies, storage condition etc. (1)

2. WHO Prequalification Programme Framework

2.1 Programme Overview and Scope

The WHO PQ Programme plays a very crucial role in the quality, safety and efficacy the drug product. The Evolution framework of the WHO PQ mentioned in the

table below which plays very import role in the Lifecycle Management of the Drug Product. (2)

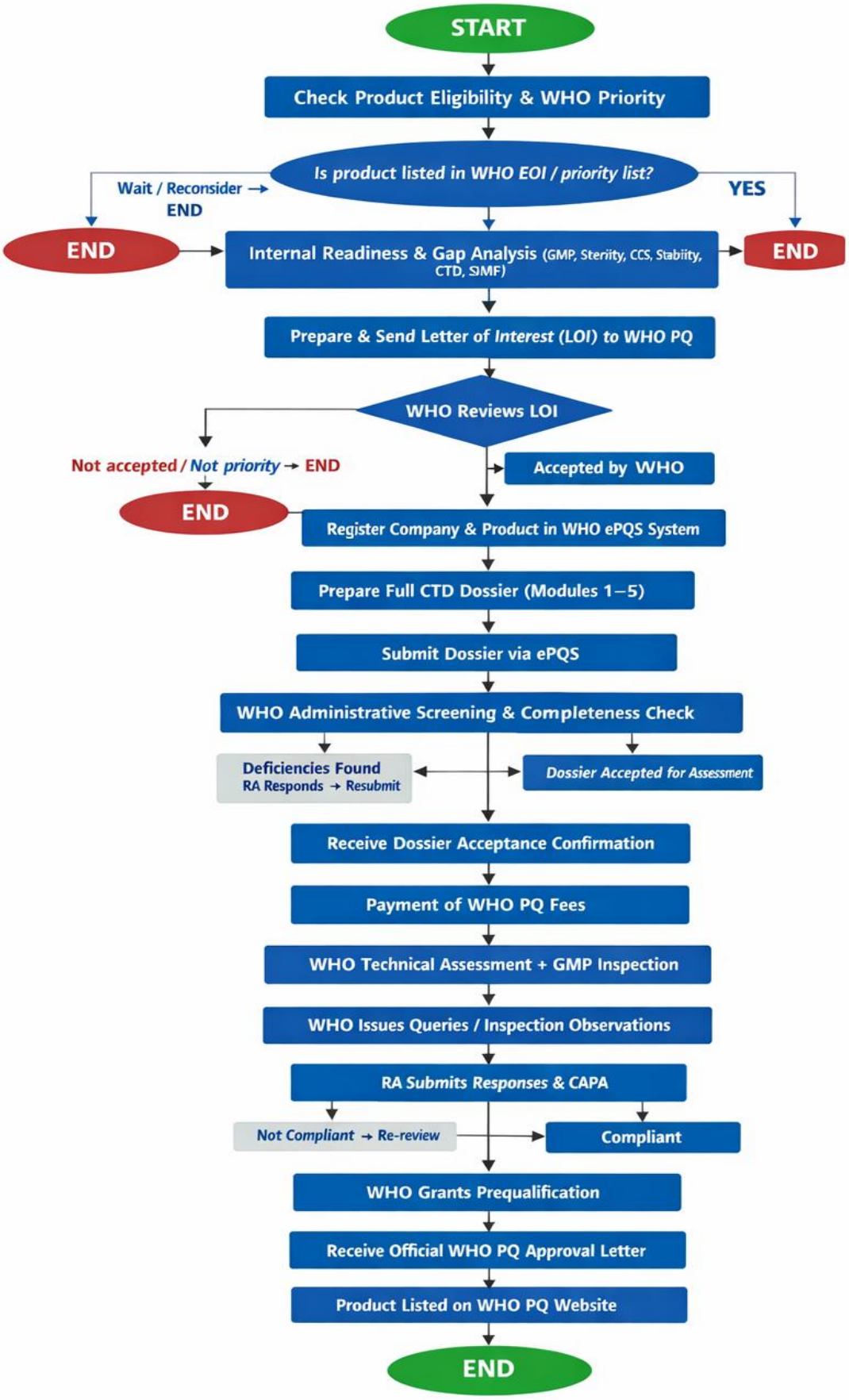

Figure 1. WHO Prequalification Process for Parenteral Products (1)

Table 1. Overview of the WHO Prequalification Programme and Its Evaluation Framework

Parameter	Explanation
What it's for	A global seal of approval that helps manufacturers especially from developing countries prove their medicines meet international standards.
How it started	Originally created just to ensure vaccines being bought internationally were safe and reliable.
How it grew (from 2001)	Expanded beyond vaccines to cover HIV/AIDS, malaria, and TB medicines, then later reproductive health products and other essential medicines.
Where it stands today (2024)	Now covers over 800 approved products from more than 150 manufacturers across 45 countries.
How products are evaluated	A two-part check: both the factory where the medicine is made and the medicine itself have to pass.
What they actually check	Three things: the quality of the medicine, its safety, and whether it actually works.
Why manufacturing matters	The factory must follow strict, validated quality systems to ensure every batch produced is consistent.
Extra rules for injectables	Medicines that go directly into the body face a higher bar — sterile manufacturing, contamination-free processing, and cleanliness controls are all closely reviewed.

2.2 Five-Stage Evaluation Process

The Five Stage Evaluation Process of WHO PQ Process workflow involves following steps:

a) Expression of Interest Submission

b) CTD Dossier Preparation

c) Technical Desk Review

d) GMP site inspection

e) Product Quality Lab Testing

The detailed about all images mentioned below:

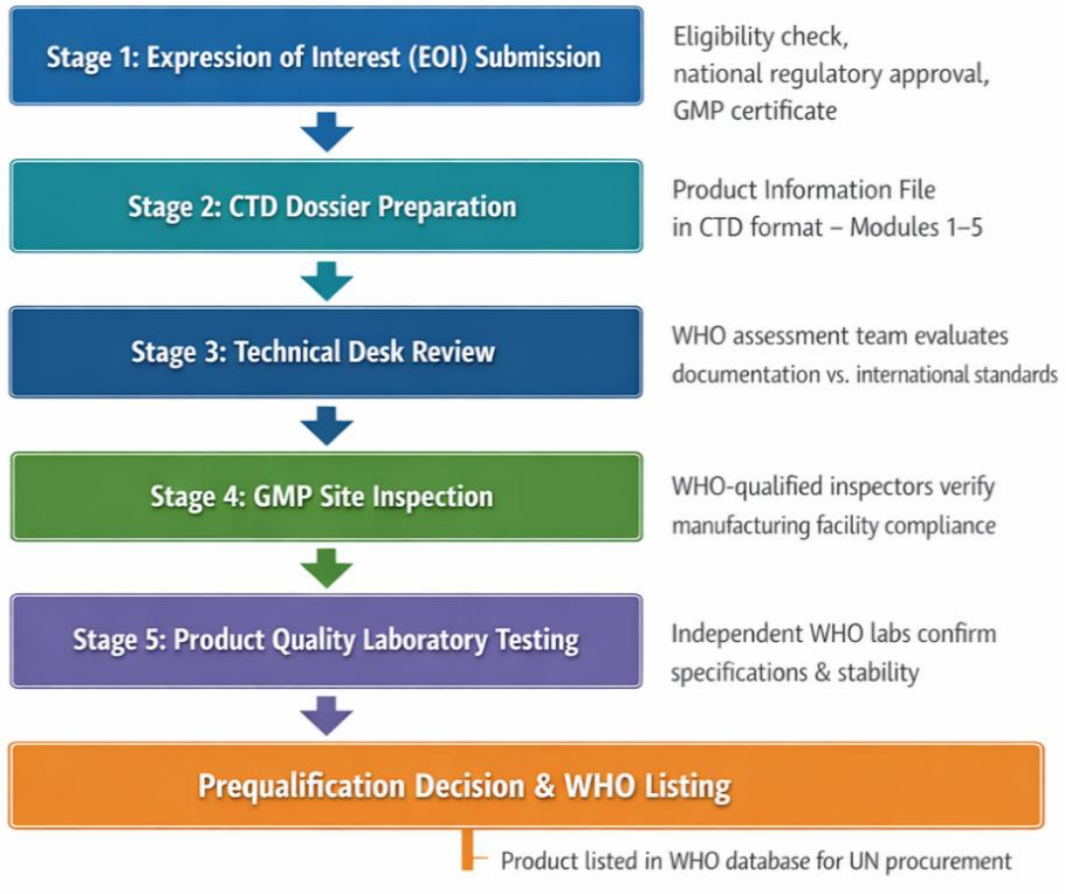

Figure 2. WHO Prequalification Process Workflow

2.3 Benefits and Market Impact

Manufacturers gain worldwide acknowledgment, entry into UN agency markets and global health organizations, and approval from national regulatory bodies via WHO Prequalification.

The Benefits of WHO PQ are

a) Market Access

b) Regulatory Recognition

c) QA Signal

d) Commercial Advantages

e) Regulatory improvements

They also put special focus on the Parenteral Product as they are prone to Quality issues and requires special care.

Table 2. Key Benefits of WHO Prequalification for Manufacturers

Benefit Area	Explanation	Who It Affects
Market Access	Opens the door for manufacturers to supply medicines to big UN agencies like GAVI, the Global Fund, and UNITAID.	Manufacturers, Procurers
Regulatory Recognition	Makes it easier and faster for companies to get approved in multiple countries at once, without going through each one separately.	Regulatory Authorities, Manufacturers
Quality Assurance Signal	Acts as an independent guarantee that a product is safe, effective, and up to standard building trust with patients and health systems.	Patients, Health Systems
Commercial Advantage	Boosts a company's chances of being picked as a preferred supplier for donor-funded health programmes.	Manufacturers, Donors
Regulatory Improvement	Regular check-ins and re-assessments push companies to keep raising the bar on their quality systems over time.	Manufacturers, WHO
Extra Rules for Injectables	Injectable products go through extra scrutiny — covering sterile manufacturing, contamination-free processing, and cleanliness controls.	Manufacturers, Donors

3. Good Manufacturing Practice Requirements

Every manufacturing plant must demonstrate adherence to WHO Good Manufacturing Practice standards as described in Technical Report Series 986. (3) These comprehensive guidelines establish requirements for facility infrastructure, equipment qualification protocols, process validation frameworks, personnel training systems, quality control laboratory capabilities, and documentation management systems.

Table 3. Key GMP Requirements for Sterile Parenteral Manufacturing (3)

GMP Category	Explanation	Regulatory Reference
Cleanroom Classification	The most critical areas must meet Grade A (ISO 5) — the cleanest level. The surrounding background area for sterile work must be Grade B (ISO 7).	WHO TRS 1033, Annex 1
HEPA Filtration	The cleanest zones must use top-grade HEPA H14 filters, with air fully recirculated — no outside air mixing in.	EU GMP Annex 1
Terminal Sterilization	Products can be sterilized using high-heat autoclave (121°C for at least 15 mins), dry heat (250°C), or radiation. The sterilization kill rate must be measured and validated.	WHO TRS 1033
Filter Validation	Filters used for sterilizing liquids must be 0.22 µm grade and proven to block bacteria effectively, tested to ASTM F838 standards.	ASTM F838 / PDA TR26
PUPSIT	Every filter must be integrity-tested right before use and after sterilization — using bubble point or diffusion tests. This is not optional.	EU Annex 1 (2022) / WHO
D-Value Determination	The sterilization process must be validated using biological indicators — tiny organisms used to confirm the process actually kills what it's supposed to.	PDA TR1 / ISO 11138
Media Fill Studies	A simulation test where growth media is run through the process instead of real product. Must pass at least 3 consecutive runs with zero contaminated units out of every 5,000.	WHO TRS 1033, Annex 1
Media Fill Studies (AQL)	Same zero-tolerance rule applies — not a single contaminated unit is acceptable out of 5,000 tested.	WHO TRS 1033, Annex 1

4. Risk Management and Quality Control

4.1 Quality Risk Management Framework

The WHO highlights the importance of implementing quality risk management principles throughout the entire product life cycle, adhering to the ICH Q9 guidelines. Risk management approaches assist in identifying potential quality risks, assessing their effects on product safety and effectiveness, and establishing the required control measures.

4.2 Quality Control Testing Requirements

To ensure the safety and effectiveness of parenteral products throughout their lifespan, quality control laboratories implement comprehensive testing programs that assess the products against established specifications. (4)

The mentioned below is requires parameter to pass the Quality Control Testing which includes various parameters like Sterility (very Important for Parenteral Product), Bacterial Endotoxin which included LAL test, Particulate Matter, Assay of the product or check the potency if the product by comparing them with the standard product, pH as the pH of the parenteral product is very necessary, container closure integrity to check whether container is reacting with the product or not & most importantly leakage of the container. After passing

test only then only the product can pass to the next stage. (5)

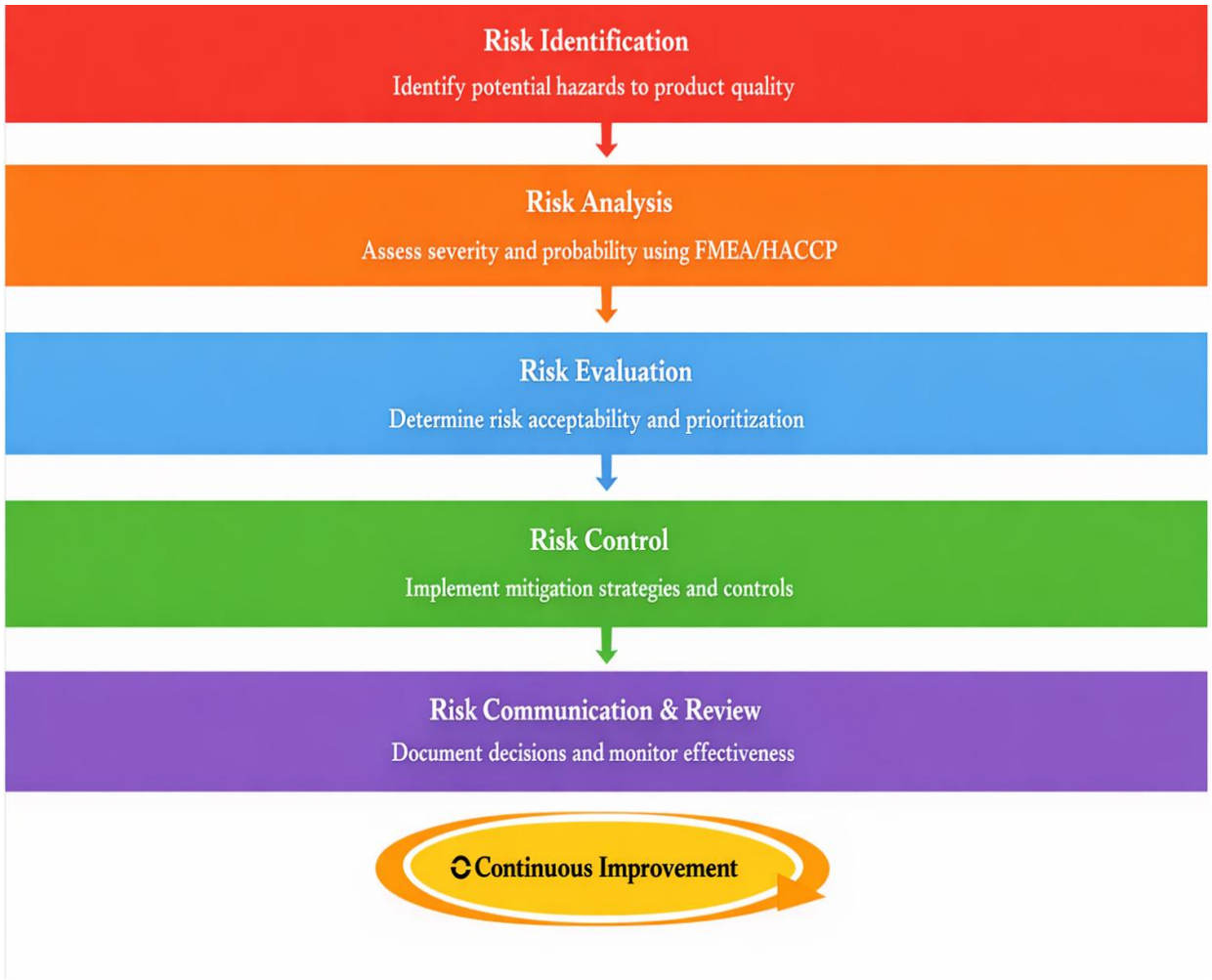

Figure 2. Quality Risk Management Cycle for Parenteral Products. (6)

Table 4. Essential Quality Control Testing for Parenteral Products

Test Parameter	How It's Tested	What's Acceptable
Sterility	The product is passed through a membrane filter or directly introduced into growth media to check if anything grows.	Absolutely zero microbial growth — none at all.
Bacterial Endotoxin	A LAL assay is used a sensitive test that detects harmful bacterial toxins in the product.	Must be 5 EU/mL or less.
Particulate Matter	Checked using light obscuration (a beam of light detects particles) or examined under a microscope.	Must meet USP <788> limits — tiny particles in injectable products are strictly controlled.
Assay / Potency	The strength of the active ingredient is measured using HPLC, UV light analysis, or a biological activity test.	Must fall between 95% and 105% of the stated strength — not too weak, not too strong.
Related Substances	HPLC is used with validated methods to detect any impurities or breakdown products in the medicine.	Must comply with ICH Q3B(R2) guidelines for acceptable impurity levels.
pH	Measured using a properly calibrated pH meter.	Depends on the specific product — each medicine has its own acceptable pH range.
Container Closure Integrity	The packaging seal is tested using vacuum decay, dye ingress, or helium leak methods to check for any gaps or failures.	Must meet WHO TRS 1033, Annex 1 standards — no leakage allowed.
Media Fill Studies	A simulation run where growth media replaces the actual product, repeated at least 3 times consecutively.	Zero contaminated units out of every 5,000 — no exceptions.
Container Closure Integrity (ISO)	Same sealing tests — vacuum decay, dye ingress, or helium leak.	Must comply with ISO 14644 requirements.

Container Closure Integrity (Leakage)	Same sealing tests applied again with a focus on physical leakage.	Absolutely no leakage permitted.

5. Stability Testing Requirements (7)

Stability studies are mandated by WHO for conditions classified as climatic Zone IVb (30°C/75% RH), which represent hot and humid tropical environments where many resource-limited countries are located. This is essential to confirm that pharmaceuticals maintain their quality throughout their entire shelf life in real storage conditions found in the intended markets.

The Stability testing is very important for parenteral product as parenteral product is very sensitive as their stability of parenteral product plays a major role. And mainly storage conditions of the parenteral product because wrong storage condition can destroy the product and may be dangerous for consumer health.

Table 5. Zone IVb Stability Testing Parameters for Parenteral Products. (7)

Study Type	Storage Conditions	Time Points	Key Tests
Long-term (Real-time)	Stored at 30°C with 75% humidity — mimics real-world tropical storage conditions.	Checked at 0, 3, 6, 9, 12, 18, 24, and 36 months.	Strength, degradants, pH, particles, sterility, endotoxin, and container seal integrity.
Accelerated	Stored at a hotter and more humid 40°C / 75% humidity to fast-track ageing of the product.	Checked at 0, 1, 2, 3, and 6 months.	Strength, degradants, pH, and how the product looks.
Intermediate	A middle-ground condition — 30°C but slightly lower humidity at 65%.	Checked at 0, 6, 9, and 12 months.	Strength, degradants, pH, and appearance.
Photostability	The product is exposed to light following ICH Q1B guidelines (Option 1 or 2).	Tested once at the end of light exposure.	Strength, colour change, and clarity of the product.
Freeze-Thaw	The product is repeatedly frozen to -20°C then thawed back to 25°C — done 5 full cycles.	Tested after each freeze-thaw cycle.	How it looks, particle levels, and strength.
In-Use Stability	Kept at 25°C after the vial or pack has been opened or reconstituted — simulates real patient use.	Monitored from 0 up to 24 hours, or as stated on the label.	Strength, degradants, sterility, and particle levels.

6. Technical Documentation Requirements

Regulatory submissions are prepared in the Common Technical Document (CTD) format, which is composed of five modules standardized among ICH member countries. (5)

Table 6. CTD Module Structure for WHO Prequalification Dossier (Parenteral Products)

CTD Module	What It Contains	Extra Requirements for Injectable Products
Module 1: Regional Administrative Information	The basics — cover letter, application form, product information, and labelling.	Must include WHO Expression of Interest (EOI) confirmation and national registration certificates from relevant countries.
Module 2: Overviews and Summaries	A high-level Quality Overall Summary (QOS) plus overviews of the non-clinical and clinical data.	Must clearly explain the sterile manufacturing strategy and justify why the chosen sterilization method was selected.
Module 3: Quality	The technical heart of the dossier — covers the drug substance, the finished drug product, and supporting appendices.	Must include sterilization validation, PUPSIT results, container seal integrity testing, extractables and leachable data, particle control, and endotoxin control.
Module 4: Nonclinical	Lab and animal study reports covering pharmacology, how the drug moves through the body, and toxicology.	Must include a toxicological assessment of any chemicals that may leach out of the packaging or container into the product.
Module 5: Clinical	All clinical study reports and supporting literature references from human trials.	Must include bioequivalence data and/or pharmacokinetic studies specifically for the injectable form of the product.

7. Conclusion

In today's era after suffering from pandemic like Covid or suffering from dangerous virus CORONA virus, we got the importance of parenteral products and their importance. So, to gain the trust of the consumers the WHO PQ acceptance is very important because the parenteral products quality is important.

For Regulatory Affairs department, it is necessary to ensure to comply with all the GMP, Technical and CTD dossier documents requirements as they are very crucial for the WHO PQ acceptance letter. The Regulatory affairs person also ensures that cross functional department like quality assurance department, quality control department, Research & Development etc.

In the future also, they are very important to participate in various competitions, tenders like UNICEF and consumer

trust. Having WHO PQ acceptance is a proves that the parenteral product is very safe for use including safety, Quality & Efficacy of the product.

After gaining the letter we also have to maintain the trust of the organisation as life cycle management. WHO PQ also ensure after giving the letter, the company is still maintaining their good manufacturing practices etc with various programmes like Post Market Surveillance.

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Conflict of Interest

The author declares that there is no conflict of interest regarding the publication of this article.

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