FDA Acceptance of Outside the United States (OUS) Clinical Data

A High-Level Guide for Medical Device Manufacturers

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1. Executive Summary

FDA accepts clinical data from investigations conducted outside the United States (OUS) to support medical device applications and submissions, provided specific conditions are met. This guide outlines the key requirements, acceptance scenarios, and documentation needed to successfully leverage OUS clinical data.

The regulatory framework applies to IDEs, 510(k)s, De Novo requests, PMAs, HDEs, and PDP applications. Manufacturers may rely solely on OUS data if they meet the requirements outlined herein. However, beyond GCP compliance, sponsors must also demonstrate that OUS data are applicable to the US population and US medical practice and are factors that often present the greatest complexity in regulatory discussions.

2. Core Acceptance Criteria

FDA will accept OUS clinical data when all of the following conditions are satisfied:

1. **Good Clinical Practice (GCP) Compliance:** The investigation was conducted in accordance with GCP standards.
2. **Supporting Information Provided:** Required documentation demonstrating GCP conformance is submitted.
3. **Data Validation Capability:** FDA can validate the data through onsite inspection if necessary.
4. **US Applicability:** The sponsor demonstrates that the OUS data are applicable to the US population and US medical practice (see Section 4 for detailed guidance on this critical factor).

Note: Per FDASIA Section 569B, FDA accepts OUS clinical data if the sponsor demonstrates that the data are adequate under applicable standards to support clearance or approval. If FDA finds data inadequate, it must provide written notice with its rationale. "Adequate" means the data is scientifically valid and applicable to the US population. Acceptance is not automatic; it is contingent on the data's 'adequacy' to answer US safety and effectiveness questions.

3. Good Clinical Practice (GCP) Requirements

3.1 Definition of GCP

Per 21 CFR 812.28(a)(1), GCP is defined as a standard for the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical investigations that provides assurance that:

- Data and results are credible and accurate
- Rights, safety, and well-being of subjects are protected

3.2 Mandatory GCP Elements

Requirement	Description
IEC Review & Approval	Independent Ethics Committee must review and approve (or provide favorable opinion) before initiating investigation
Continuing IEC Review	Ongoing review of the investigation by the IEC throughout its duration
Informed Consent	Documented, freely given informed consent from subjects (or legally authorized representative) before participation

3.3 Recognized GCP Standards

FDA does not mandate a specific GCP standard. Sponsors may choose any standard meeting the regulatory definition, including:

- **ICH E6(R3):** Good Clinical Practice: Consolidated Guideline
- **ISO 14155:2020:** Clinical Investigation of Medical Devices for Human Subjects - Good Clinical Practice (current version; FDA recognized)

Note: ISO 14155:2020 replaced the 2011 edition. An amendment (A11:2024) and a new edition is in development. Sponsors should verify they are referencing the current recognized version. GCP compliance is not a checkbox, it is a data integrity audit

4. US Population and Medical Practice Applicability

GCP compliance alone does not guarantee FDA acceptance of OUS data. Per 21 CFR 814.15 and FDASIA Section 569B, sponsors must demonstrate that OUS clinical data are adequate under applicable FDA standards to support clearance or approval. This requires addressing the

applicability of data to the US population and US medical practice, which is often the most complex aspect of OUS data submissions.

4.1 Key Factors FDA Evaluates

FDA reviewers carefully evaluate three primary areas when assessing OUS clinical data:

Factor	Description and Considerations
Differences in Clinical Conditions	Standards of care may differ significantly between OUS regions and the US. These differences affect the benefit-risk analysis relative to standard US practice. Sponsors must explain how clinical practice in OUS study regions compares to US practice and whether differences impact study conclusions.
Differences in Study Population	Patient demographics (race, ethnicity, age, gender/sex), disease prevalence, comorbidity rates, and lifestyle factors (obesity, smoking) can vary substantially. If the device has disparate safety or efficacy effects across demographic groups, these differences may affect data applicability. Sponsors must demonstrate how the study population represents the intended US patient population.
Differences in Regulatory Requirements	OUS studies may be designed to satisfy foreign regulatory requirements (e.g., safety and performance) rather than FDA requirements (safety and effectiveness). This can affect endpoint selection, comparator choice, and study design. The study outcome must demonstrate that probable benefits outweigh probable risks under FDA's standards.

4.2 Specific Considerations by Factor

Clinical Conditions / Standard of Care

- What is the current standard of care for the target condition in the US vs. the OUS study region(s)?
- Are there differences in diagnostic criteria, treatment algorithms, or clinical guidelines?
- Do differences in healthcare infrastructure affect patient management or follow-up?
- Would the comparator arm (if used) represent an appropriate US standard of care?

Study Population Demographics

- How does the study population's racial and ethnic composition compare to the intended US population?
- Are there known differences in device performance, safety, or effectiveness across demographic groups?
- Do disease prevalence, severity, or comorbidity patterns differ between populations?
- Are lifestyle factors (BMI distribution, smoking rates) materially different?

- Does the study include adequate representation of subgroups relevant to the US population?

Regulatory and Study Design Alignment

- Were the study endpoints selected to demonstrate safety and effectiveness (FDA standard) or safety and performance (EU/other standard)?
- Is the study design (RCT, single-arm, etc.) appropriate for the FDA submission pathway?
- Does the study have adequate statistical power for FDA's evidentiary requirements?
- Are the follow-up duration and outcome measures consistent with FDA expectations?

4.3 Recommendations for Addressing Applicability

5. **Engage FDA Early:** Use the Pre-Submission (Q-Sub) process to discuss OUS data strategy before initiating or relying on OUS studies. FDA strongly encourages this for sponsors planning to use OUS data.
6. **Provide Detailed Justification:** Include a comprehensive discussion in submissions explaining why OUS data are applicable to the US population, addressing each factor above.
7. **Document Standard of Care Comparison:** Provide published literature, clinical guidelines, or expert opinion comparing OUS and US clinical practice for the relevant indication.
8. **Include Demographic Analysis:** Present study demographics with comparison to US census data or relevant US patient registries. Discuss any limitations.
9. **Address Known Variability:** If device performance may vary by patient characteristics, provide subgroup analyses or scientific rationale for why differences are not expected.
10. **Consider Supplemental US Data:** For high-risk devices or situations where applicability is uncertain, consider whether supplemental US clinical data (confirmatory study, registry data) may strengthen the submission.
11. **Poolability:** If combining OUS and US data, the sponsor must demonstrate that the study conduct and patient outcomes were sufficiently similar across regions to justify statistical pooling

5. Acceptance Scenarios

5.1 Scenario Matrix

Scenario	Condition	FDA Action
Full GCP Compliance	Investigation conducted per ICH E6, ISO 14155:2020, or equivalent GCP standard	Data accepted with appropriate supporting documentation
GCP Deviation with Explanation	Investigation did not fully conform to GCP, but sponsor provides explanation and mitigation steps	Case-by-case review; data may be accepted if credibility and subject protection demonstrated
Waiver Granted	Sponsor demonstrates compliance is impossible or unnecessary (e.g., foreign privacy laws prohibit disclosure)	Data accepted if waiver approved and alternative validation agreed upon
IVD Leftover Specimens	In vitro diagnostic investigation using leftover, de-identified biospecimens per FDA guidance	Enforcement discretion for informed consent; local laws must not conflict

6. Supporting Information Requirements

The extent of supporting information required under 21 CFR 812.28 varies based on the investigation's risk classification. Understanding these classifications is essential for determining documentation requirements.

6.1 Understanding Risk Classifications

The IDE regulations (21 CFR Part 812) describe three categories of device investigations: **Significant Risk (SR)**, **Non-Significant Risk (NSR)**, and **Exempt**. For detailed guidance on making these determinations, refer to FDA's guidance document: *"Significant Risk and Nonsignificant Risk Medical Device Studies"* (Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors).

Significant Risk (SR) Device

Per 21 CFR 812.3(m), a significant risk device is an investigational device that:

- Is intended as an implant and presents a potential for serious risk to health, safety, or welfare of a subject
- Is purported or represented to be for use in supporting or sustaining human life and presents a potential for serious risk
- Is for use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health, and presents a potential for serious risk
- Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject

Examples: Cardiac pacemakers, orthopedic implants, hydrocephalus shunts, extended-wear contact lenses.

Non-Significant Risk (NSR) Device

An NSR device investigation is one that does not meet the definition of a significant risk device. NSR investigations are considered to have an approved IDE when the IRB concurs with the NSR determination and approves the study. NSR studies must still comply with abbreviated IDE requirements under 21 CFR 812.2(b), including labeling, IRB approval, informed consent, monitoring, records, and reports.

Examples: Daily-wear contact lenses, ultrasonic dental scalers, certain external monitoring devices.

Exempt Investigations

Per 21 CFR 812.2(c), certain device investigations are exempt from most IDE requirements. Common exemption categories include:

- Legally marketed devices used in accordance with their labeling (cleared/approved devices within labeled indications)
- Certain diagnostic devices that are noninvasive, do not introduce energy, and meet other specified criteria
- Consumer preference testing or modification testing that does not assess safety/effectiveness
- Custom devices (limited to no more than 5 units per year) not being used to determine safety/effectiveness for commercial distribution

Note: Even exempt investigations may still require IRB approval and informed consent under 21 CFR Parts 50 and 56.

6.2 Making Risk Determinations for OUS Investigations

For investigations conducted in the US, the sponsor makes the initial SR/NSR determination, which is then reviewed by the IRB. FDA is the final arbiter if there is disagreement.

For OUS investigations, FDA does not expect foreign IECs to make this determination (SR vs NSR), as they may not be familiar with FDA's terminology. The FDA also will not require an IDE, regardless of risk. Instead, the sponsor or applicant makes the initial determination and should maintain documentation of the rationale. FDA may request this rationale under 21 CFR 812.28(a)(2). If FDA disagrees with a sponsor's NSR determination, FDA may request the additional supporting information required for SR investigations.

Sponsors may also request a Study Risk Determination from FDA through the Q-Submission Program prior to or during study conduct to obtain FDA's position on the risk classification.

6.3 Documentation Requirements by Risk Classification

Significant Risk	Non-Significant Risk	Exempt
All 812.28(b) elements required in submission	Subset of elements required; some upon FDA request only	Most elements upon FDA request only

6.4 Required Elements Detail (21 CFR 812.28(b))

Element	SR	NSR	Exempt
Names/addresses of investigators and facilities	**Required**	**Required**	On request
Investigator qualifications	**Required**	On request	On request
Description of research facilities	**Required**	On request	On request
Detailed protocol summary and results	**Required**	**Required**	On request
Device information and comparison	**Required**	**Required**	On request
Valid scientific evidence discussion	**Required**	On request	On request
IEC name, address, and compliance statement	**Required**	**Required**	On request
IEC approval summary	**Required**	**Required**	On request
Informed consent process description	**Required**	**Required**	On request
Subject incentives description	**Required**	On request	On request
Sponsor monitoring description	**Required**	**Required**	On request
Investigator GCP training description	**Required**	On request	On request

SR = Significant Risk; NSR = Non-Significant Risk

7. Waiver Process

Per 21 CFR 812.28(c), sponsors may request waivers from GCP requirements or supporting information requirements when compliance is impossible, unnecessary, or can be satisfied through alternative means.

7.1 Waiver Request Content

A waiver request must include at least one of the following:

- Explanation why compliance is unnecessary or cannot be achieved
- Description of alternative submission or course of action satisfying the requirement's purpose
- Other justifying information

7.2 Common Waiver Scenarios

- **Privacy Law Conflicts:** When foreign laws prohibit disclosure of case records or institutional records to FDA
- **Third-Party Data:** When the sponsor was not the original investigation sponsor and lacks complete GCP conformity documentation
- **IEC Documentation:** When IEC member qualifications cannot be obtained due to privacy laws

7.3 Submission Process

Waiver requests may be submitted via Pre-Submission, within the original application/submission, or as a supplement or amendment. The cover letter must clearly identify the waiver request under 21 CFR 812.28(c) and reference affected investigations.

8. Record Retention

Per 21 CFR 812.28(d), sponsors must retain records required under 812.28 for:

- **Marketing Applications:** At least 2 years after FDA decision on the application
- **IDE Support:** At least 2 years after termination or completion of the IDE

9. Key Recommendations

12. **Plan Early:** Incorporate GCP requirements and US applicability considerations into study planning from the outset
13. **Document Thoroughly:** Maintain comprehensive records that demonstrate GCP conformance
14. **Engage FDA Early:** Use Pre-Submission meetings to discuss OUS data strategy, applicability concerns, and any potential issues
15. **Address Applicability Comprehensively:** Prepare detailed rationale for how OUS data apply to US population and US medical practice
16. **Clearly Identify Location:** Use cover letters and cross-references to clearly identify where 812.28 requirements are addressed
17. **Proactive Waiver Requests:** If compliance barriers are anticipated, request waivers before submission

