Global Strategy for the nuBeam BNCT Platform:

A Structured Regulatory Plan for U.S. PMA Submission and Parallel Canadian and Mexican Market Entry

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Executive Summary of Strategy

The nuBeam BNCT System is an advanced device-led combination product intended to deliver Boron Neutron Capture Therapy using a compact accelerator, beam shaping assembly, real-time dosimetry, and a dedicated treatment planning software suite. The global regulatory approach is anchored in the United States, where the system is classified as a Class III medical device requiring a Premarket Approval application. The U.S. pathway establishes the foundational engineering, software, nonclinical, human factors, and clinical evidence packages that will be leveraged for parallel submissions in Canada and Mexico.

In the United States, the strategy centers on a modular PMA supported by extensive nonclinical testing, IEC 60601 compliance, ISO 14971 risk management, IEC 62304 Class C software documentation, and a prospective IDE clinical study designed to evaluate safety and clinical performance across relevant cancer cohorts. Human factors validation and drug–device coordination requirements form core components of the PMA. The IDE pivotal trial also provides the primary evidence for international submissions.

Canada serves as the first parallel market. Under the Medical Devices Regulations, nuBeam is classified as a Class IV medical device requiring a Medical Device License supported by MDSAP certification, bilingual labeling, and, if required, a Canadian Investigational Testing Authorization. Health Canada generally accepts foreign clinical and engineering data, enabling direct reliance on U.S. PMA evidence with minimal supplemental testing. The Canadian submission timeline is significantly shorter, positioned for approval shortly after core PMA modules reach maturity.

Mexico functions as the second parallel market and utilizes the U.S. evidence package with added requirements under COFEPRIS, including full Spanish documentation, compliance with NOM radiation protection and GMP standards, and authorization for both the investigational drug and device prior to initiating local clinical activities. While Mexico accepts foreign data, limited local bridging or justification may be required to support long-term safety monitoring commitments.

The integrated strategy reduces redundant testing, harmonizes engineering and quality system activities, and aligns clinical evidence generation across jurisdictions. The sequence begins with U.S. design controls, nonclinical programs, software verification, and HF validation, progresses through IDE clinical execution, and then advances to country-specific submissions. This coordinated approach ensures efficient use of resources, predictable regulatory interactions, and a clear pathway toward multi-market approval and commercialization.

Detailed Regulatory Strategy

1. Introduction and Global Strategy Overview

The nuBeam BNCT System represents a modern accelerator-based platform for Boron Neutron Capture Therapy. It integrates neutron generation, beam shaping, dosimetry, patient positioning systems, and treatment planning software to deliver highly localized radiation therapy to tumors that have absorbed a boron-10 pharmaceutical agent. Because device performance and drug pharmacokinetics must be coordinated, the system is regulated as a device-led combination product in the United States.

This regulatory strategy uses the United States PMA pathway as the primary global approval route. Canada and Mexico progress as parallel markets that rely on U.S. nonclinical, software, and clinical evidence, supplemented by jurisdiction-specific requirements. This approach avoids redundancy, reduces time to approval, and ensures alignment across North American markets.

2. Device Description and Mechanism of Action

The nuBeam Suite includes an accelerator-based neutron generator, a beam shaping assembly, real-time neutron and gamma detectors, a treatment planning system, a treatment delivery console with interlocks, and patient immobilization components. Patients are administered a boron-10 agent that accumulates in tumors. When irradiated with epithermal neutrons, boron-10 undergoes a nuclear reaction that releases high-LET particles, selectively destroying tumor cells.

The system relies on consistent performance from several coordinated elements. These include:

- Proper timing between boron drug infusion and beam activation
- Treatment plan accuracy and dose calculation integrity
- Real-time dosimetry monitoring
- Mechanical and software safety interlocks
- Correct patient positioning and workflow sequencing

These interactions require extensive design controls, usability engineering, and risk mitigation.

3. Primary Market Strategy

United States PMA- the Anchor Pathway

3.1 Regulatory Classification and Pathway

In the United States, nuBeam is classified as a Class III medical device requiring a Premarket Approval application. There is no predicate for BNCT systems. The system requires an

Investigational Device Exemption for clinical investigation. FDA regulates the system as a device-led combination product.

- Lead Center: CDRH
- Consulting Center: CDER

3.2 Core U.S. Regulatory Requirements

Evidence needed for PMA includes:

3.2.1 Design and Development Controls

- ISO 13485-compliant quality system
- Design verification and validation traceability
- Compliance with radiation safety regulations

3.2.2 Safety and Performance Testing

- IEC 60601 series for electrical safety and EMC
- Mechanical and environmental evaluation
- Neutron dosimetry, beam profiling, and leakage assessments
- Verification of hardware and software interlocks

3.2.3 Software Documentation

- IEC 62304 Class C lifecycle documentation
- System architecture and hazard analysis
- Verification and validation testing
- Cybersecurity controls

3.2.4 Risk Management

- ISO 14971 risk analysis
- Radiation exposure hazards
- Software failure modes
- Drug timing and workflow risks
- Use-related risks

3.2.5 Human Factors

Summative validation demonstrating safe execution of all critical clinical tasks including:

- Patient identification
- Plan verification
- Drug timing confirmation
- Positioning and alignment
- Beam enable sequence
- Emergency stop actions

3.3 Clinical Strategy for IDE and PMA

The pivotal study supporting the PMA will be a prospective multicenter trial enrolling approximately sixty to one hundred twenty patients.

Primary objectives:

- Safety
- Local tumor control and objective response

Secondary objectives:

- Progression-free survival
- Overall survival
- Quality of life assessments
- Long-term toxicity outcomes

Drug-device timing will be built into eligibility, treatment preparation, and workflow protocols. IDE evidence will serve as the basis for U.S. approval and will be leveraged for Canadian and Mexican submissions.

3.4 PMA Modular Submission

The modular PMA will include:

- Nonclinical testing
- Software documentation
- Manufacturing information
- Clinical evidence
- Labeling
- Administrative content

Anticipated review timeline is twelve to eighteen months after final module submission.

4. Parallel Market Strategy

Canada Class IV MDL

4.1 Regulatory Classification

Health Canada regulates nuBeam as a Class IV device under the Medical Devices Regulations. A Medical Device License is required. Manufacturers must be certified under the Medical Device Single Audit Program. Drug components used in BNCT are reviewed separately under a Clinical Trial Application.

4.2 Technical Evidence Requirements

Canada accepts foreign engineering and clinical data that comply with international standards. U.S. PMA evidence is expected to satisfy most requirements.

Canada-specific additions

- Bilingual labeling in English and French
- UDI compliance under Canada's device identification framework
- MDSAP certification
- Submission of recognized test reports

4.3 Clinical Evidence Strategy

Canada allows reliance on foreign clinical studies. The IDE pivotal study is the primary evidence source. If required, a Canadian Investigational Testing Authorization may be pursued to generate supplemental data. Due to the novel nature of BNCT, Health Canada may request justification regarding patient population comparability or treatment conditions.

4.4 MDL Submission and Review

The MDL application includes device description, intended purpose, effectiveness and safety evidence, a risk management summary, software and human factors documentation, bilingual labeling, and quality system certification. Typical review timelines are approximately seventy five to ninety days following acceptance.

5. Parallel Market Strategy

Mexico COFEPRIS Class III Registration

5.1 Regulatory Classification

Mexico classifies nuBeam as a Class III high-risk medical device. A Registro Sanitario is required, and a Mexican legal representative must act as the registration holder. BNCT requires separate authorization for the investigational drug and device prior to clinical study activities.

5.2 Technical and Documentation Requirements

Mexico accepts IEC and ISO test data but requires compliance with additional NOM standards.

Key NOMs applicable

- NOM-137: Radiation therapy safety
- NOM-008: Radiation protection for radiotherapy facilities
- NOM-241: Good manufacturing practices
- NOM-220: Pharmacovigilance obligations

All submission materials must be in Spanish.

5.3 Clinical Evidence Strategy

COFEPRIS accepts foreign clinical data, including U.S. IDE results, as the primary evidence base. Supplemental bridging cases or justification may be required. Ethical oversight is

provided by CONBIOETICA and local institutional committees. Long-term safety monitoring is expected for high-risk radiological treatments.

5.4 Registration File and Review

The Registro Sanitario file includes technical documentation, nonclinical testing, software evidence, human factors data, risk management information, radiation safety analyses, labeling, and importer or registration holder documentation. Review periods generally range from six to twelve months.

6. Harmonized Global Testing and Documentation Strategy

A harmonized testing framework ensures consistency and reduces duplicated regulatory submissions. The U.S. PMA testing suite serves as the foundation for Canadian and Mexican submissions.

6.1 Testing reused across all jurisdictions

- IEC 60601 electrical and EMC tests
- Environmental and mechanical tests
- Neutron dosimetry and beam characterization
- Radiation leakage and shielding assessments
- IEC 62304 Class C software evidence
- ISO 14971 risk management file
- IEC 62366 human factors validation
- Cybersecurity assessments

6.2 Region-specific additions

- Bilingual labeling for Canada
- Spanish documentation for Mexico
- MDSAP audits for Canada
- NOM compliance for Mexico
- Local authorizations where required

7. Labeling and Device Identification Strategy

United States

Labeling Architecture

All labeling elements must be developed under design controls and stored in the DMR. Labeling includes:

- Package labels
- Device labels
- IFU / Operator Manual
- Service & Installation Manuals

- Radiation safety signage
- Electronic documents (eIFU, if permitted)
- UDI data submissions

UDI Requirements

- Comply with **21 CFR Part 830**.
- Include:
    - DI (Device Identifier)
    - PI (lot/serial number, expiration, manufacturing date)
- Submit to **GUDID**

IFU & Manuals

Must include:

- Indications, contraindications, warnings, and precautions
- Drug–device timing instructions (BNCT-specific)
- Radiation hazard warnings per **21 CFR 1020**
- Emergency procedures
- Installation requirements for neutron-generating systems

Symbols

- ISO 15223-1 permitted, but require U.S. explanation if not universally recognized.

Service Manual

Mandatory for:

- Accelerator maintenance
- Neutron source replacement
- Calibration and dosimetry procedures
- Electrical and radiation shielding checks

Canada

- Bilingual labeling in English and French

UDI Requirements

- Required under Canada's device identification regulations.
- Must include UDI on:
    - Label
    - Packaging
    - All marketing materials

Translations

- All labeling must be bilingual: English + French.
- MAH must approve translation accuracy.

IFU Requirements

Must include:

- Radiation therapy risk information
- Canadian emergency contact information
- French technical terminology aligned with bilingual clinical standards

Symbols

- ISO 15223-1 symbols accepted without text.
- Canadian-specific caution symbols used for radiation where applicable.

Importer Labeling

- Importer name + address may be required if distributing through multiple Canadian establishments.

Mexico

- Full Spanish labelling

UDI Requirements

- Mexico is implementing UDI in phases—include UDI voluntarily to harmonize future compliance.

Translations

- All labeling must be in Spanish.
- No English allowed unless bilingual format is approved.

NOM Requirements

Device must include:

- **NOM-137** radiation warning labels
- **NOM-008** facility safety instructions
- **NOM-241** GMP labeling elements
- **Country of origin**
- Full importer/MAH contact details

IFU Requirements

Detailed Spanish operator manual including:

- BNCT workflow

- Dosimetry and calibration
- Safety interlocks
- Troubleshooting
- Drug–device coordination steps

Symbols

- ISO 15223-1 symbols allowed but must be supported by Spanish text.
- Radiation warning triangle per Mexican standards required.

Importer Labeling

- Importer/MAH must appear on primary label.
- Registration number (Registro Sanitario) must be printed clearly.

Service Manual

Must be provided in **Spanish** and include:

- Preventive maintenance schedules
- Dosimetry calibration
- Parts replacement intervals
- Instruction for COFEPRIS inspections

8. Post-Market Surveillance Strategy

United States

- Medical Device Reporting under 21 CFR 803
- PMA post-approval studies
- Annual reporting obligations

Canada

- Mandatory problem reporting
- Recall and corrective action procedures
- MDSAP surveillance audits

Mexico

- Technovigilance obligations under national guidelines
- Registration holder responsibilities
- COFEPRIS inspections and periodic reporting

9. Integrated Regulatory Milestone Overview

The United States PMA serves as the foundation for North American market entry. Evidence generated for the PMA supports the Canadian Class IV MDL and the Mexican Class III

registration with minimal duplication. This harmonized strategy ensures consistent technical documentation, efficient regulatory pathways, and coordinated timelines across markets.

10. Market Authorization Holder (MAH) Requirements and Responsibilities

1. United States – MAH Requirements

In the U.S., the Legal Manufacturer (listed on the device label) automatically serves as the effective MAH.
There is no separate MAH designation, but the legal manufacturer must comply with the following:

Responsibilities

- **Regulatory Ownership**
    - Holds the PMA and signs all FDA submission forms.
    - Maintains Design History File (DHF), Device Master Record (DMR), and Device History Records (DHR).
- **Quality System Compliance**
    - Maintain full compliance with 21 CFR 820 QMSR (aligned with ISO 13485).
    - Oversee supplier controls, production, and process validation.
- **Labeling & UDI Control**
    - Maintain labeling review/approval under design controls.
    - Ensure UDI assignment and GUDID submission.
- **Post-Market Surveillance**
    - MDR reporting under 21 CFR 803.
    - PMA Post-Approval Studies (if required).
    - Annual PMA Reports under 21 CFR 814.84.
- **Inspections**
    - Subject to unannounced FDA and ISO-based inspections.

2 Canada – MAH Requirements (Medical Device Establishment License + MDSAP)

In Canada, the MAH is the License Holder of the Class IV Medical Device License (MDL). Foreign manufacturers must also have:

- MDSAP Certification

- Canadian Importer/Distributor Licenses

Responsibilities

- **Regulatory Ownership**
    - Maintain the MDL and submit amendments.
    - Provide bilingual labeling (English & French).
    - Notify Health Canada of significant changes.
- **Quality & Establishment Licensing**
    - Maintain MDSAP certification annually.
    - Ensure importers/distributors hold valid establishment licenses.
- **Post-Market Surveillance**
    - Mandatory reporting of incidents under SOR/98-282.
    - Recall procedures and corrective actions.
    - Annual MDSAP surveillance audits.
- **Labeling Oversight**
    - Approve French translations.
    - Verify UDI compliance under the Canadian Device Identification regulations.

Mexico – MAH Requirements (Registro Sanitario Holder)

Mexico requires a local legal entity to hold the Registro Sanitario.
This MAH can be:

- A Mexican subsidiary, or
- A third-party registration holder (Importador/Distribuidor Autorizado)

Responsibilities

- **Regulatory Ownership**
    - Responsible for the COFEPRIS registration.
    - Submits renewals every 5 years.
    - Requests variation updates when changes affect safety/performance.
- **Post-Market Surveillance (Technovigilancia)**
    - Comply with NOM-220-SSA1-2016.
    - Report adverse events within required timelines.
    - Maintain safety reporting system and periodic summary reports.

- **Labeling & Translation**
    - Ensure full Spanish labeling.
    - Apply NOM-required radiation warnings and manufacturer/importer information.
    - Maintain control of IFUs and technical manuals in Spanish
- **Import & Commercialization Responsibilities**
    - Obtain import permits (when needed).
    - Ensure customs documentation and invoices match the registered device.
    - Maintain distribution records for traceability.

11. Regulatory Plan for the MAH (PMS, Labeling Control, Renewals, Reporting)

The Market Authorization Holder plays a central role in ensuring ongoing compliance with regulatory, quality, and post-market requirements in each country. The plan below outlines how the MAH will manage post-market surveillance, labeling control, renewals, and reporting activities in the United States, Canada, and Mexico.

11.1 United States – MAH Regulatory Plan

Post-Market Surveillance (PMS)

In the U.S., the MAH must comply with FDA's post-market reporting and monitoring obligations. This includes:

- Submitting **Medical Device Reports (MDRs)** within **30 days** of identifying an adverse event.
- Escalated reporting within **5 days** for events that require immediate attention.
- Overseeing any **PMA Post-Approval Studies**, when required, to continue evaluating device performance and safety.

Labeling Control

Labeling in the U.S. must be maintained under design control procedures. The MAH is responsible for:

- Ensuring all labeling and IFUs remain accurate, controlled, and up to date.
- Managing updates through a formal **change control process**.
- Updating UDI information in **GUDID** whenever changes affect device identification.

Renewals & Ongoing Reporting

- Submitting the **Annual PMA Report**, summarizing safety updates, manufacturing changes, and ongoing clinical findings.
- While PMA approvals do not require annual renewal, **PMA supplements** must be filed for any significant:
    - Manufacturing modifications
    - Design revisions
    - Labeling updates

11.2 Canada – MAH Regulatory Plan

Post-Market Surveillance (PMS)

In Canada, the MAH must follow the Medical Devices Regulations (SOR/98-282) for post-market monitoring. This includes:

- Reporting **serious risks within 10 days**.
- Reporting less critical device issues within **30 days**.
- Maintaining a comprehensive **complaint file** that documents investigation and corrective actions.

Labeling Control

The MAH must ensure all labeling meets Canadian requirements:

- Providing labeling and IFUs in **both English and French**.
- Ensuring updated instructions and safety information are distributed to all Canadian importers and distributors.
- Reviewing UDI compliance annually, as Canada expands its device identification requirements.

Renewals & Ongoing Reporting

- Completing **annual MDSAP surveillance audits**, required to maintain the Class IV Medical Device License (MDL).
- Notifying Health Canada of any changes impacting:
  - Labeling content
  - Quality system status
  - Safety or performance concerns
- While the MDL itself does not require annual renewal, any significant change to the device or labeling must be submitted as an **amendment**.

11.3 Mexico – MAH Regulatory Plan

Post-Market Surveillance (Technovigilancia)

In Mexico, the MAH must comply with **NOM-220-SSA1-2016**, which establishes strict vigilance and reporting timelines:

- Reporting **serious adverse events within 48 hours**.
- Reporting expected but non-serious events within **10 business days**.

- Maintaining a **national technovigilance database** and trend analysis system for safety monitoring.

Labeling Control

Because Mexico requires full Spanish labeling, the MAH must:

- Review and approve all Spanish translations to ensure accuracy and regulatory compliance.
- Maintain strict control of all user-facing documents, including:
    - Instructions for Use (IFU)
    - Service and maintenance manuals
    - Clinical operator guides
- Ensure the Registro Sanitario number appears clearly on every label and package.

Renewals & Ongoing Reporting

- Renew the **Registro Sanitario every 5 years** to maintain market approval.
- Submit variation notifications for any significant:
    - Safety updates
    - Labeling modifications
    - Manufacturing site or process changes
- Support COFEPRIS during routine audits or site inspections, ensuring full transparency and readiness.

Regulatory Deliverables Comparison for the nuBeam Suite BNCT System in the United States, Canada, and Mexico

Category	USA (FDA)	Canada (Health Canada)	Mexico (COFEPRIS)
Regulatory Authority	FDA – CDRH (lead), CDER (consult)	Health Canada – MDD	COFEPRIS – Medical Devices Division
Classification	Class III (21 CFR 860)	Class IV (highest risk)	Class III (Alta Tecnología)
Regulatory Pathway	PMA (21 CFR 814)	Class IV MDL (Medical Device License)	Registro Sanitario (High-risk device)
Combination Product Status	Device-led combination product (21 CFR 3 & 4)	Treated as device; drug assessed separately	Device-led combination product; drug-link evaluated
Clinical Study Requirement	IDE required; pivotal PMA clinical trial	Accepts foreign PMA/IDE data; bridging may be required	Accepts foreign data; may need local clinical study/bridging
Preclinical / Bench Testing	Full IEC 60601, EMC, dosimetry, mechanical, cybersecurity, HF	Full IEC 60601, EMC, dosimetry, mechanical, cybersecurity, HF	IEC/ISO required; may require NOM compliance (NOM-241, NOM-137, NOM-013-NUCL)
Software Requirements	IEC 62304 Class C full documentation	IEC 62304 Class C	IEC 62304 Class C + Spanish documentation
Risk Management	ISO 14971 full risk file	ISO 14971 required	ISO 14971 required
Human Factors (HF/UE)	Full HF validation required (IEC 62366)	HF evidence recommended	HF validation required (Spanish interface)
Manufacturing Requirements	QSR (21 CFR 820) OR QMSR (ISO 13485:2016)	MDSAP mandatory	ISO 13485 + NOM-241 GMP compliance

Manufacturing Audit	FDA inspection	MDSAP covers audit obligation	COFEPRIS audit or MDSAP acceptance
Labeling Requirements	English, UDI (21 CFR 830), all manuals	English + French, UDI rollout by 2025	Spanish IFU, NOM symbols, MAH info, country of origin
Translation Requirements	English only	Mandatory French + English	Spanish required for all documentation/labeling
UDI Status	Mandatory for Class III (GUDID)	UDI mandatory (phase-in)	Not mandatory, but GTIN/UDI often used
Country of Origin Labeling	Required	Required	Mandatory ("Hecho en EE.UU.")
Drug–Device Interaction Requirements	Strong coordination (BNCT agent timing)	Must include interaction description	Required, with COFEPRIS evaluation
Post-Market Surveillance (PMS)	MDR (21 CFR 803), PMA Post-Approval Study, Annual Reports	Mandatory Incident Reporting, Recalls (HC guidelines)	Technovigilancia reporting, annual renewal, FSCA
Recalls & Corrections	21 CFR 806	Mandatory recall SOP	Mandatory recall/FSCA via MAH
Local MAH Requirement	Not required (manufacturer in USA)	Not required if manufacturer is certificate holder	Mandatory Mexican MAH / legal representative
MAH Responsibilities	PMS, MDR, recalls, QSR compliance	Reporting, vigilance, MDEL control	Registration, vigilance, recalls, import permits
Documentation Submission Format	PMA Modular Submission (FDA eCopy)	STED-like Medical Device License Dossier	COFEPRIS dossier (Spanish + notarized docs)
Typical Approval Timeline	12–18 months	~75–90 days (if complete & MDSAP compliant)	6–12 months (may vary based on testing & reviews)
Facility Requirements	Radiation room cert + NCRP/IAEA compliance	Radiation facility provincial compliance	NOM-013-NUCL radiation licensing + shielding documentation
Testing Laboratories	FDA-recognized labs	ISO 17025 / MDSAP-recognized labs	Labs recognized by COFEPRIS (or accepted foreign labs)

Acceptance of Foreign Evidence	FDA demands full PMA data	Accepts EU/FDA data strongly	Accepts FDA/EU data with Spanish translation
IFU, Manuals, Service Documents	English	English + French	Spanish (all documents)
Clinical Data Submission	Full PMA Module 5	Foreign clinical data + justification	Foreign or local data + Spanish translation
Drug Component Regulation	CDER consult; drug cross-labeling	Drug regulated separately	Drug import + compatibility documentation
Expected Dossier Size	Very large (15–25+ GB modular PMA)	Medium (STED/IMDRF structure)	Medium-to-large, with notarized translations

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