THE NEUCO CUTTER PTCA CATHETER INTERNATIONAL REGULATORY STRATEGY

BY: GERALD T. RIGDON

24 TARGET COUNTRIES

1. Argentina
2. Australia
3. Canada
4. Brazil
5. Chile (unregulated)
6. China
7. Columbia
8. Cuba
9. Egypt
10. Hong Kong (volunteer)
11. India
12. Malaysia (volunteer)
13. Mexico
14. New Zealand (unregulated)
15. Philippines – SE Asia
16. Puerto Rico
17. Saudi Arabia
18. South Korea
19. Singapore – SE Asia
20. Taiwan
21. Thailand – SE Asia
22. Venezuela
23. Vietnam – SE Asia
24. Trinidad (unregulated)

IMPORTANT TERM

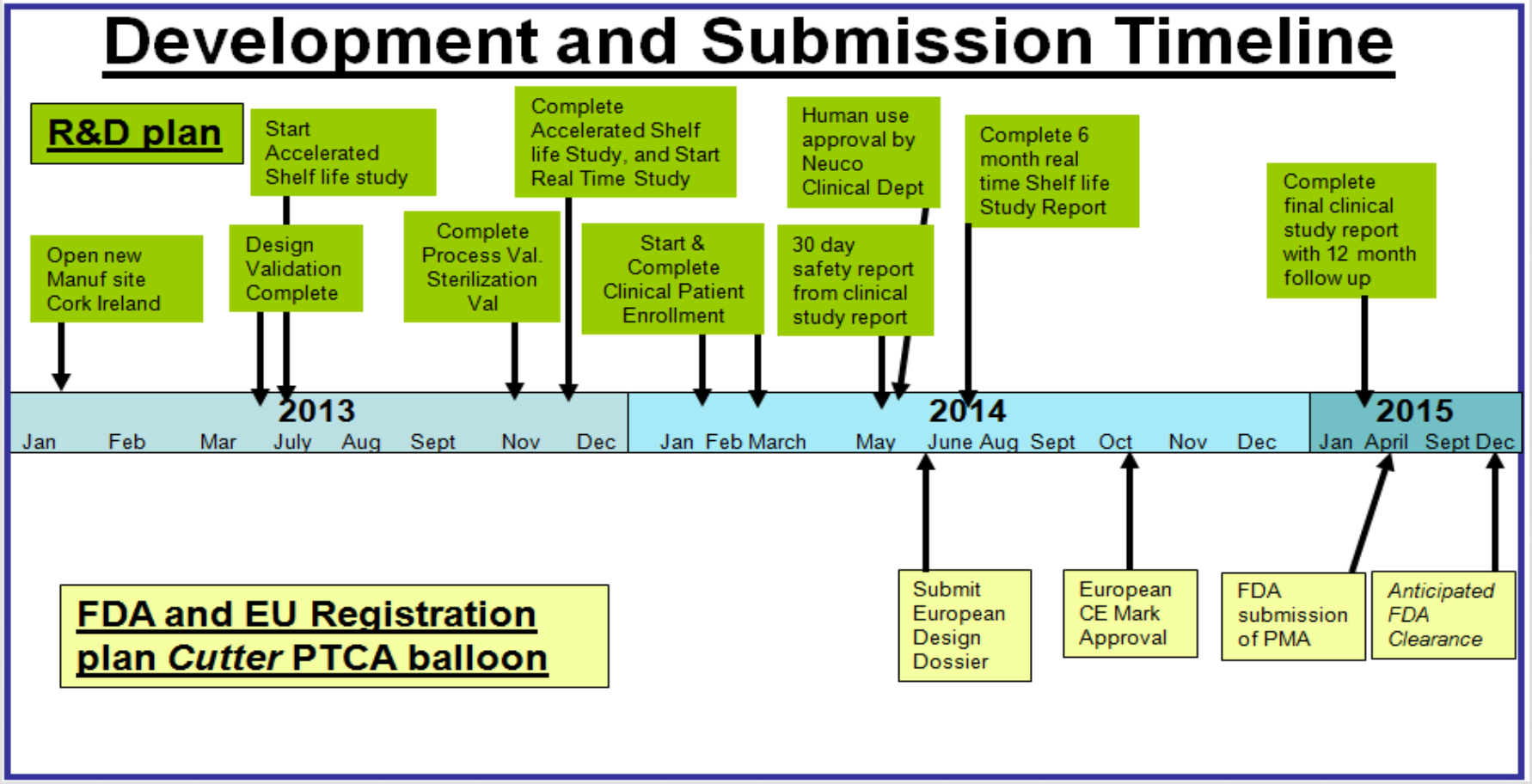
- **Certificate of Free Sale (CFS)**

This certificate is issued upon the CE approval of a medical device. If a product is manufactured outside the United States, this document must be provided to the countries requiring Country of Origin (CoO) approval.

KEY OBJECTIVES

- Review U.S. / European approval strategy
  - Other approvals dependent on this timeline
- Review the approval strategy for each of the 24 countries
- Identify risks/alerts and discuss mitigations
- Review the alignment/disconnects between regulatory strategy with sales and marketing forecasts

U.S. / EUROPE APPROVAL STRATEGY



UPFRONT
RISK CONCERNS – PRIOR APPROVAL

Prior Product (Baverick) Not Approved

- Canada
- China
- Cuba
- Egypt
- Hong Kong
- Malaysia
- Trinidad
- Venezuela
- Vietnam

Strategy/Mitigations:

- Leverage submission / approval learning from other countries
- Detailed understanding and regulatory requirements for above listed countries
- Leverage European CE Mark

UPFRONT
RISK CONCERNS – COO

Country of Origin Requirements (must have approval in country where manufactured prior to submission)

-Argentina
-Brazil
-China
-Columbia
-Cuba
-Egypt
-India
-Philippines
-Saudi Arabia
-Taiwan
-Thailand
-Venezuela

Strategy/Mitigations:

- Cutter is manufactured in Cork, Ireland
- EU (not U.S.) approval is sufficient
- Submit to Europe before FDA
- Use Intercontinental Standard Dossier

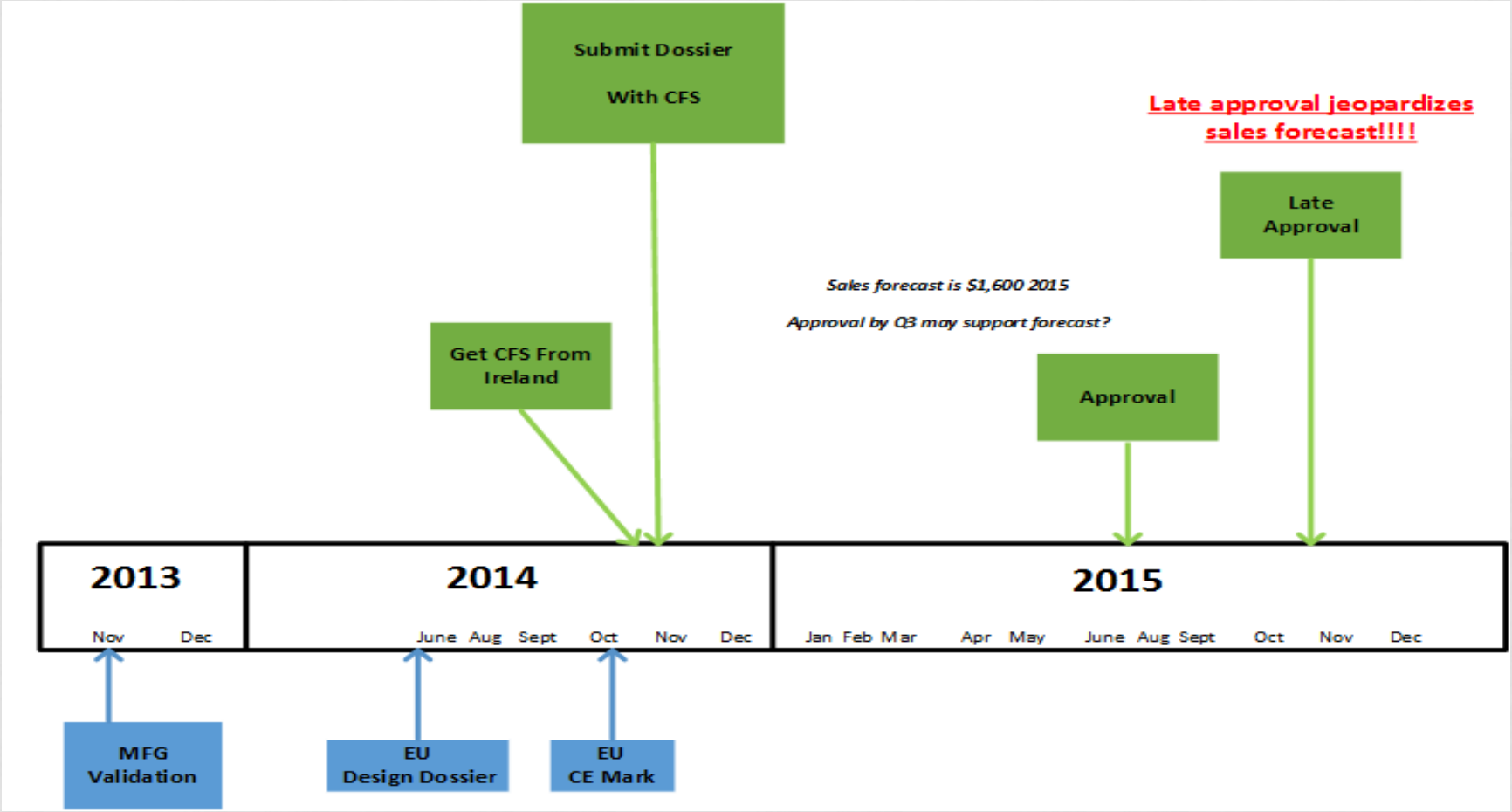
KEY STRATEGY

- Standard Technical File
- Parallel Submissions after CE Mark
  - 75% of countries
  - Exceptions
    - Unregulated
    - Volunteer Registrations
    - U.S. commonwealth
    - Using other GHTF countries for fast approval
    - More than 1 prior GHTF approval required

ARGENTINA

- Catheter Device Classification
  - GHTF Classification - D
  - GHTF Final Rule – 7
  - EU Class III
- Appoint Local Responsible Person
  - Use same one as Baverick approval
    - Authorization letter
- Submit Registration to Administration, National, Medicamentos, Alementos, and Technologia (ANMAT)
    - CFS required – must have CE mark prior to submission
    - 8 months review time….may take up to 12 months
    - Spanish labeling required
    - Local licenses
      - GMP
      - Import (registration held by distributor who must be used for import)
    - Fee - US$ 300

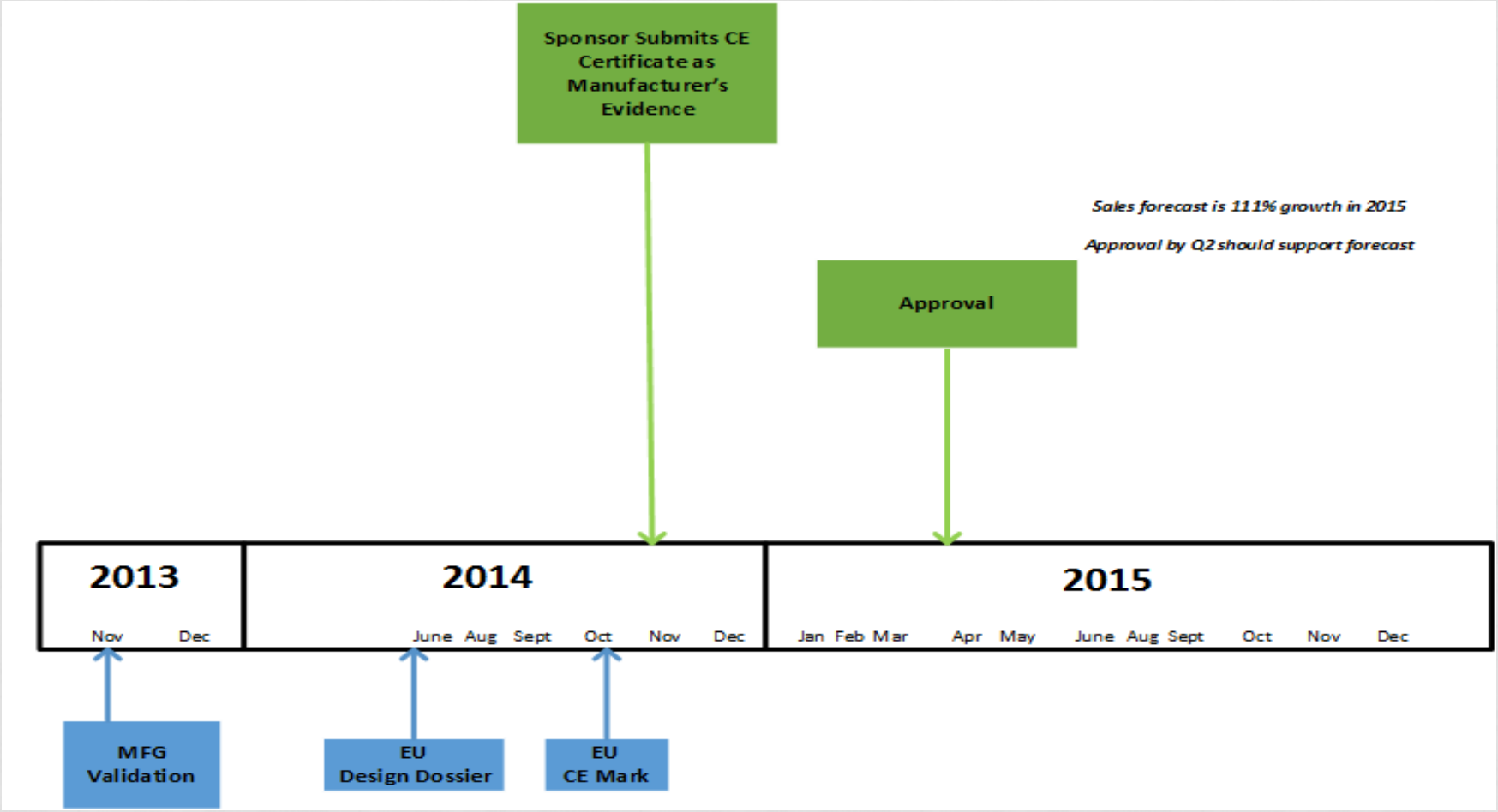
ARGENTINA TIMELINE



AUSTRALIA

- Catheter is Class III device
- Leverage European CE Mark for Therapeutic Goods Administration (TGA) Regulations
- Must have Australian sponsor
  - Use same sponsor as Baverick approval
- CE Mark Pathway
  - Sponsor submits CE Mark as Manufacturer's Evidence
    - 5 months review time
    - Application fee - AUD$ 800
    - Evaluation fee - AUD$ 16,400

AUSTRALIA SUBMISSION TIMELINE



CANADA

Catheter is a Class IV device

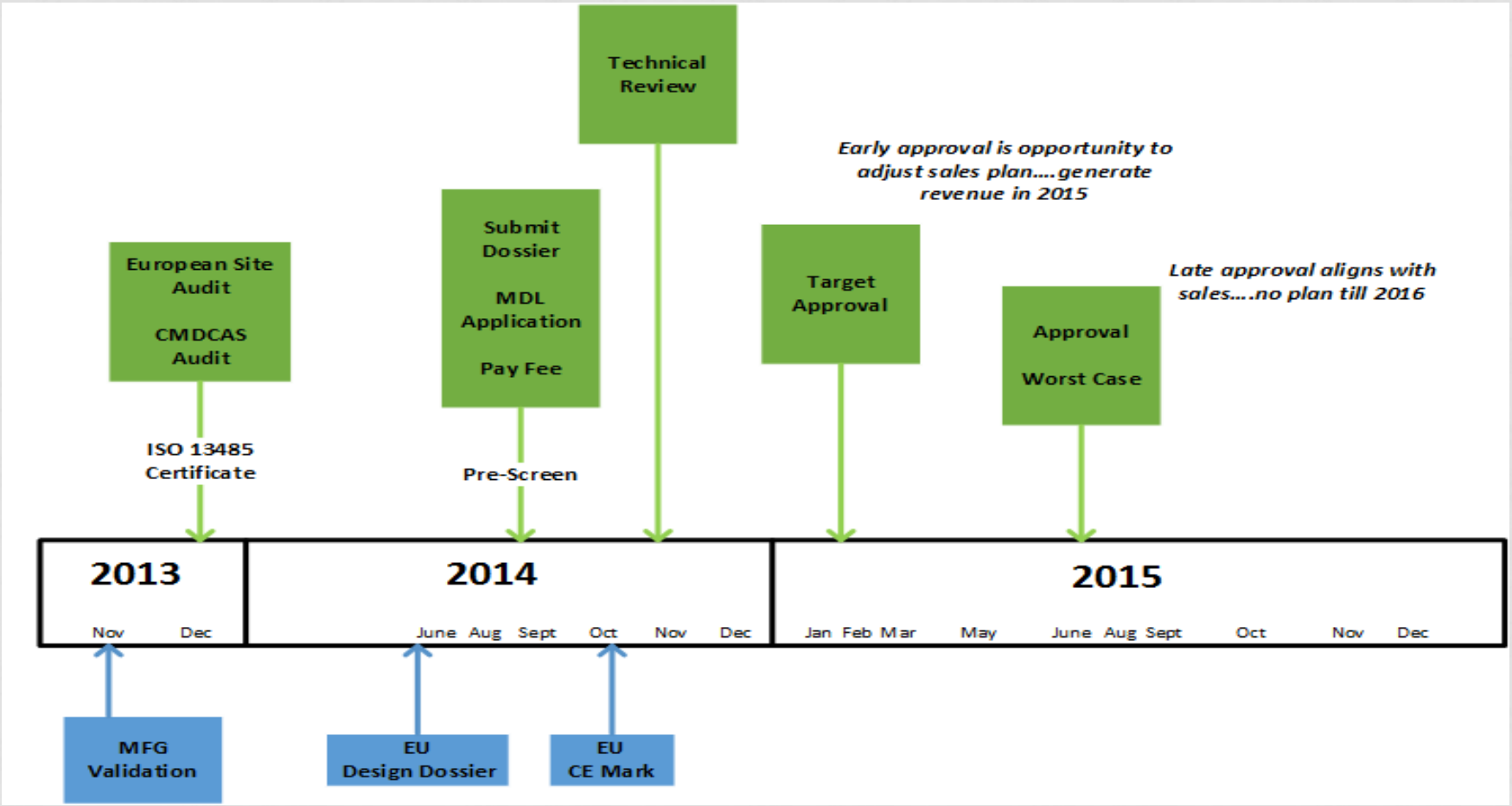
Requirements for Therapeutic Products Directorate (TPD) registration:

Step 1: Submit the registration file for pre-screening (60 days)

- ISO 13485 certificate
- Medical Device License (MDL) application
- Declaration of Conformity and pre-market review documentation
- New application fee – Can$ 11,750

Step 2: Submission for technical review (90 days)

CANADA SUBMISSION TIMELINE



BRAZIL

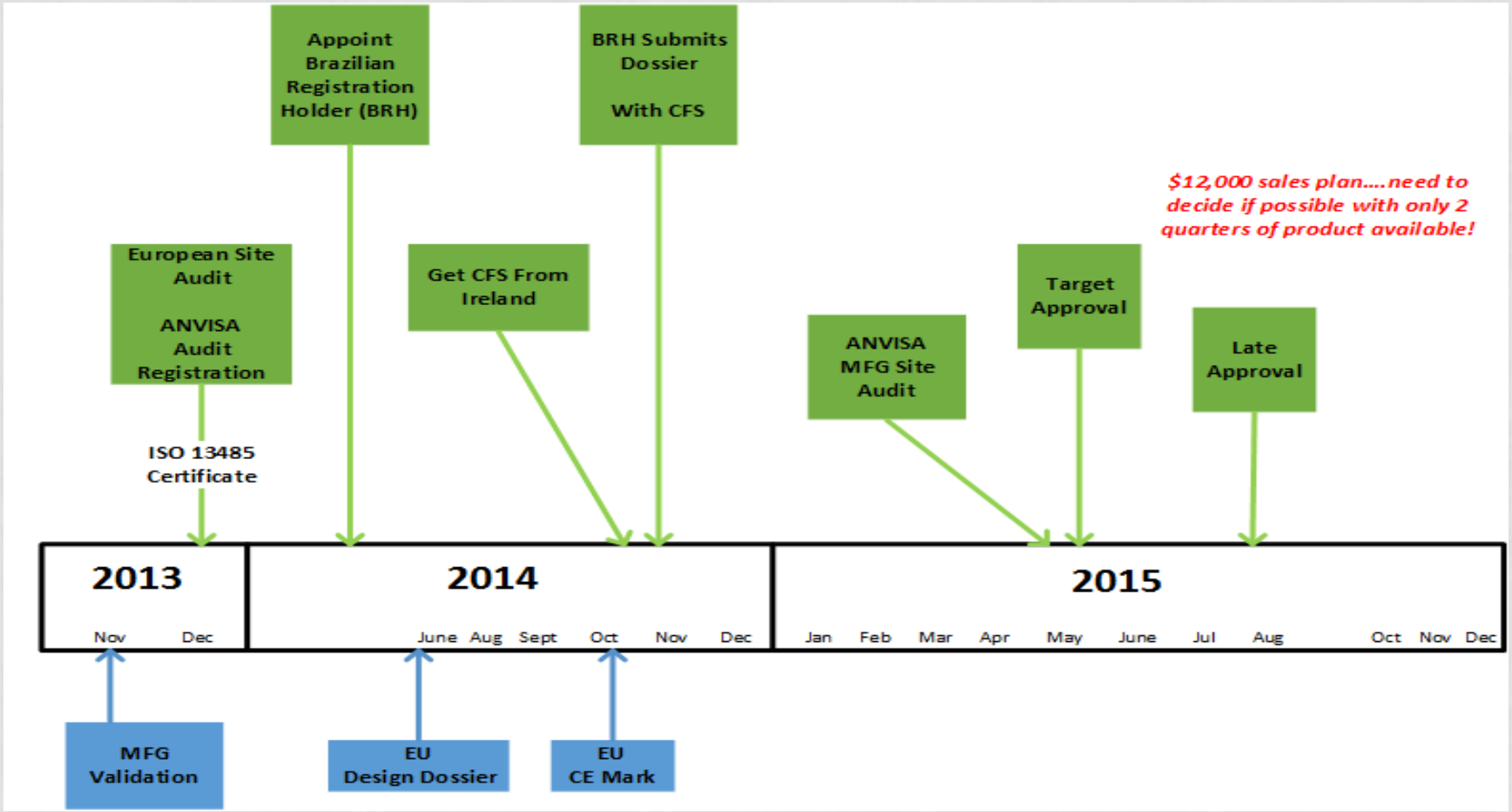
- Catheter is Class III device
- Appoint Brazil Registration Holder (BRH)
  - Use same BRH as Baverick approval
  - R$ 1K (US$ 500)

- Health Surveillance Regulatory Authority (ANVISA) Manufacturing Site Quality Audit
  - Fee - R$ 15K (US$ 7.5K)
  - Alert: 18 month lead time

- Alert: Product Changes (Limit unnecessary manufacturing changes)
  - ANVISA approval required/approval times are the same as new product submissions

- ANVISA Submission in Person
  - 6-9 months review time
  - Alert: Review is Closed Door
  - Technical Dossier, IFU, Product Labeling in Portuguese
    - CFS required – must have CE mark prior to submission
    - Fee - R$ 8K (US$ 4K)

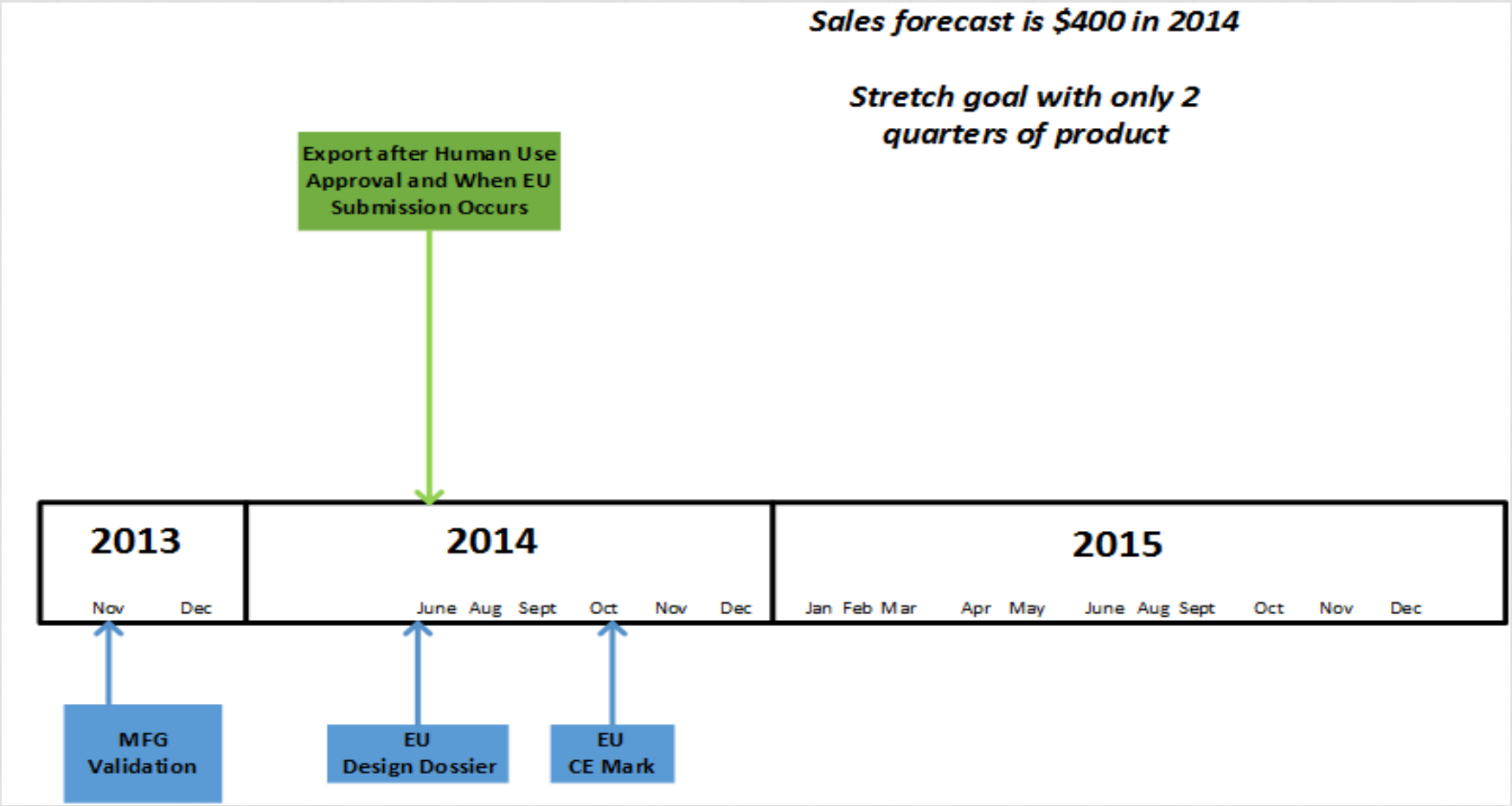
BRAZIL SUBMISSION TIMELINE



CHILE

- Unregulated
- Sell through distributor after Neuco's internal safety requirements are met

CHILE TIMELINE



CHINA

- Catheter is Class III device

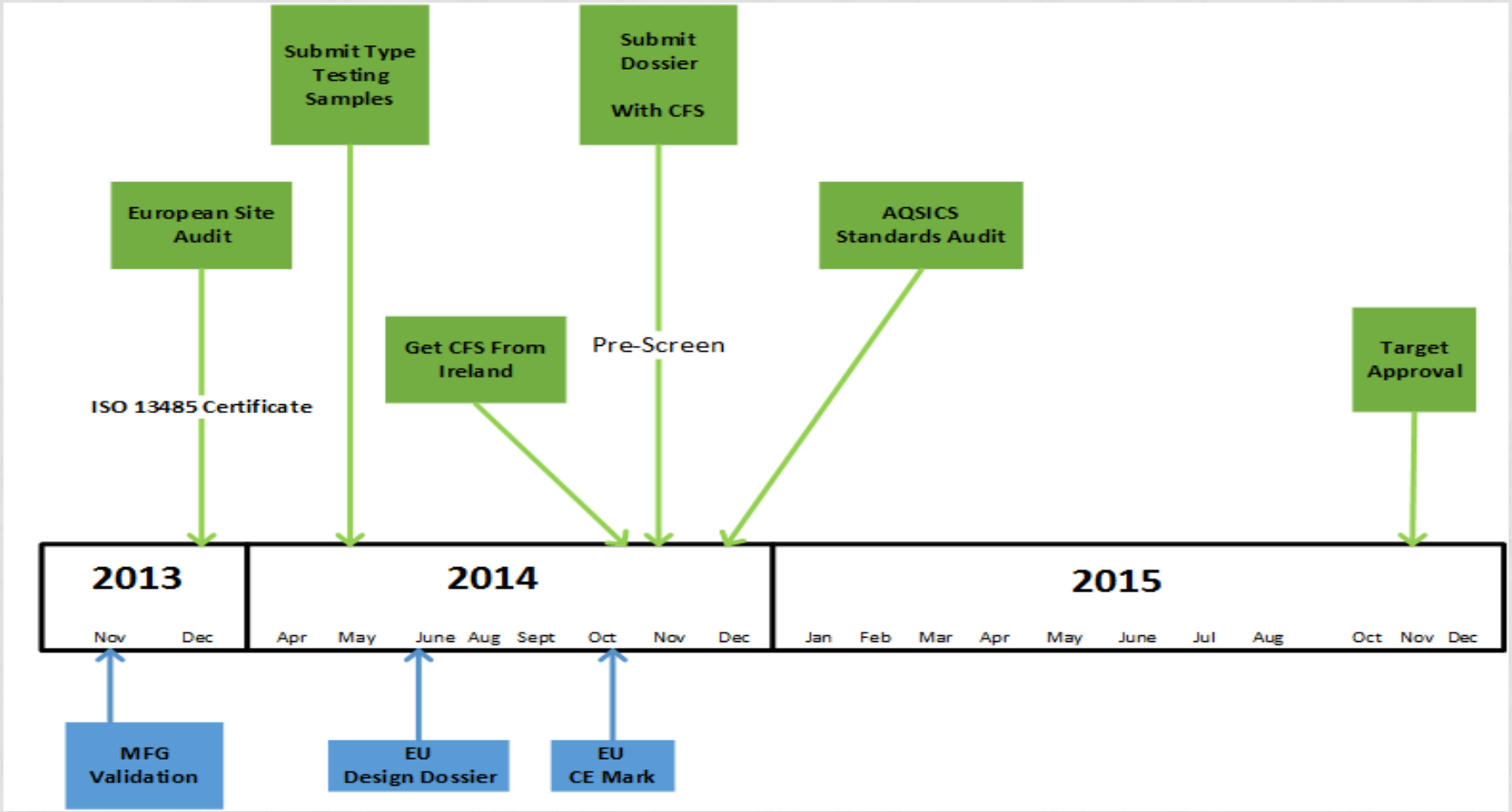
- Complete Type Testing (3-6 months)
  - Fee - US$ 5,000
  - Alerts:
    - Must get samples made and shipped to china for type testing
    - Work with lab to make sure device passes the China Standards tests
    - Avoiding questions during the review associated with the type testing

- Submit Registration to State Food and Drugs Administration (SFDA)
  - CFS required – must have CE mark prior to submission
  - Alert: Handling requests for propriety information
  - Alert: Make sure we can answer all questions in 60 days
  - No Fee

- Obtain Quality Manufacturing Certification to AQSICS Standard

- SFDA Review
  - Administrative (2 months)
  - Technical (10 months)

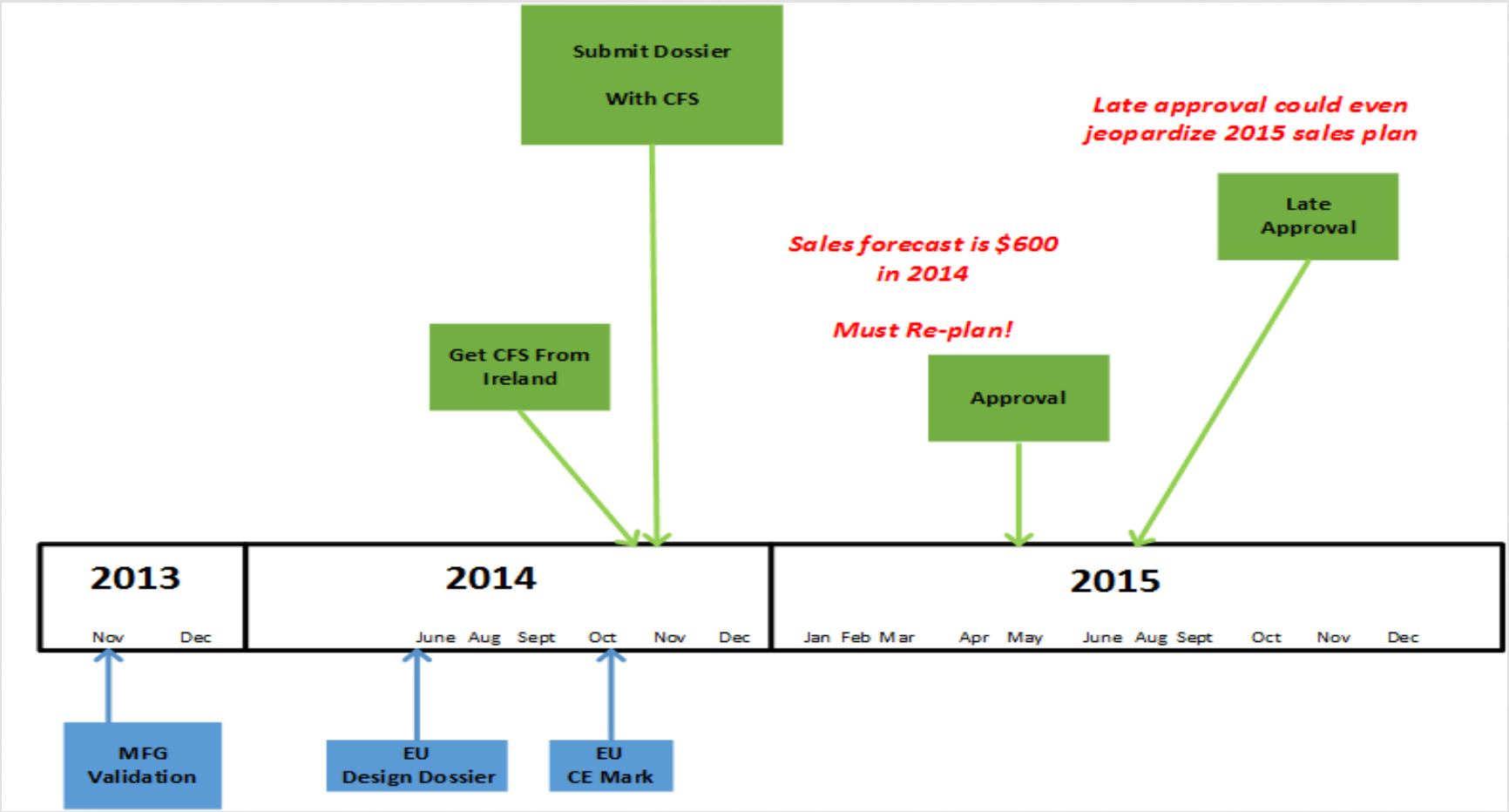
CHINA SUBMISSION TIMELINE



COLUMBIA

- Catheter Device Classification
  - GHTF Classification - D
  - GHTF Final Rule – 7
  - EU Class III
- Appoint Local Responsible Person
  - Use same one as Baverick approval
- Submit Registration to INVISA
    - CFS required – must have CE mark prior to submission
    - 6 months review time
    - Spanish labeling and distributor contact information required
    - Alert: BIS (Bureau of Industry and Security) License
      - Required to export into Columbia
    - Fee - US$ 300

COLUMBIA TIMELINE

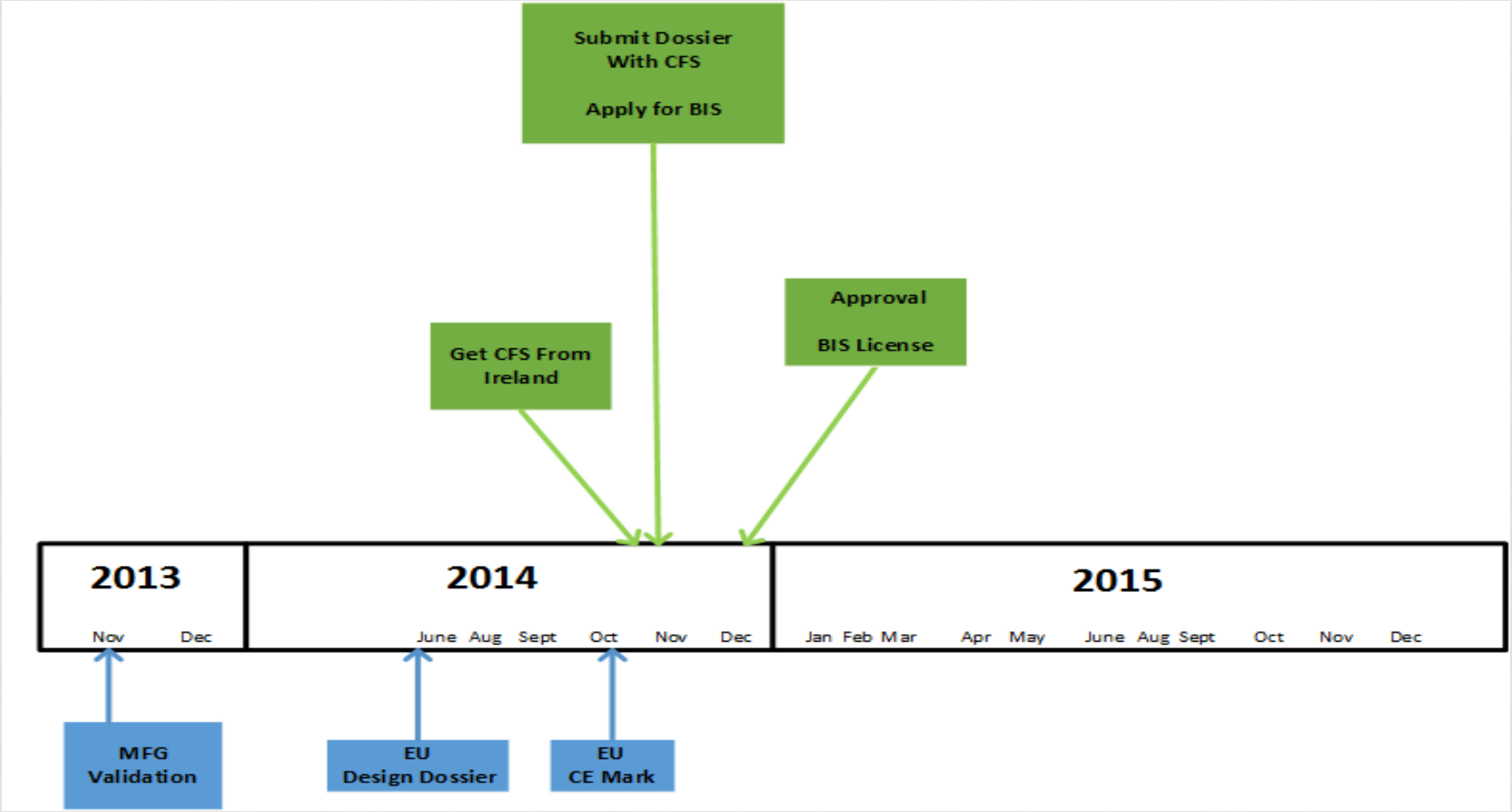


CUBA

- Catheter Device Classification
  - GHTF Classification - D
  - GHTF Final Rule – 7
  - EU Class III

- Submission to Centro para el Control Estatal de Medicamentos, Equipos y Dispositivos Médicos (CECMED)
  - CFS required – must have CE mark prior to submission
  - Review time 1 month
  - Alert: BIS (Bureau of Industry and Security) License
    - Required to export into Cuba
    - No fees for BIS
  - Fee – US$ 300

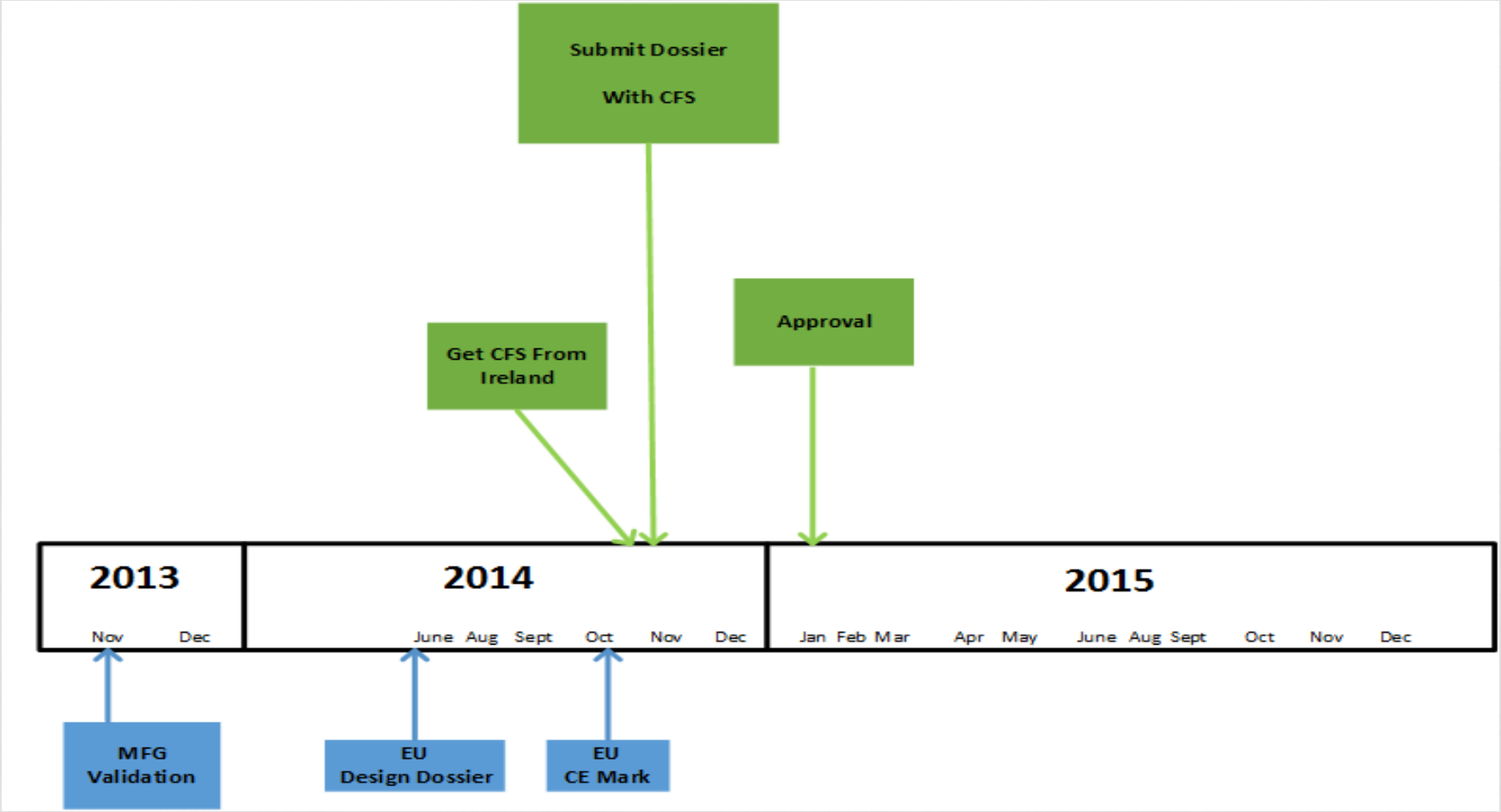
CUBA TIMELINE



EGYPT

- Catheter Device Classification
  - GHTF Classification - D
  - GHTF Final Rule – 7
  - EU Class III
- ISO 13485 certificate
- Appoint Egypt Registration Holder (ERH)
  - Use distributor
- Submit Registration to Central Administration of Pharmaceutical Affairs (CAPA)
  - CFS required – must have CE mark prior to submission
  - 2 months review time
  - Alert: A lot of technical questions from reviewers
  - Fee – US$ 550

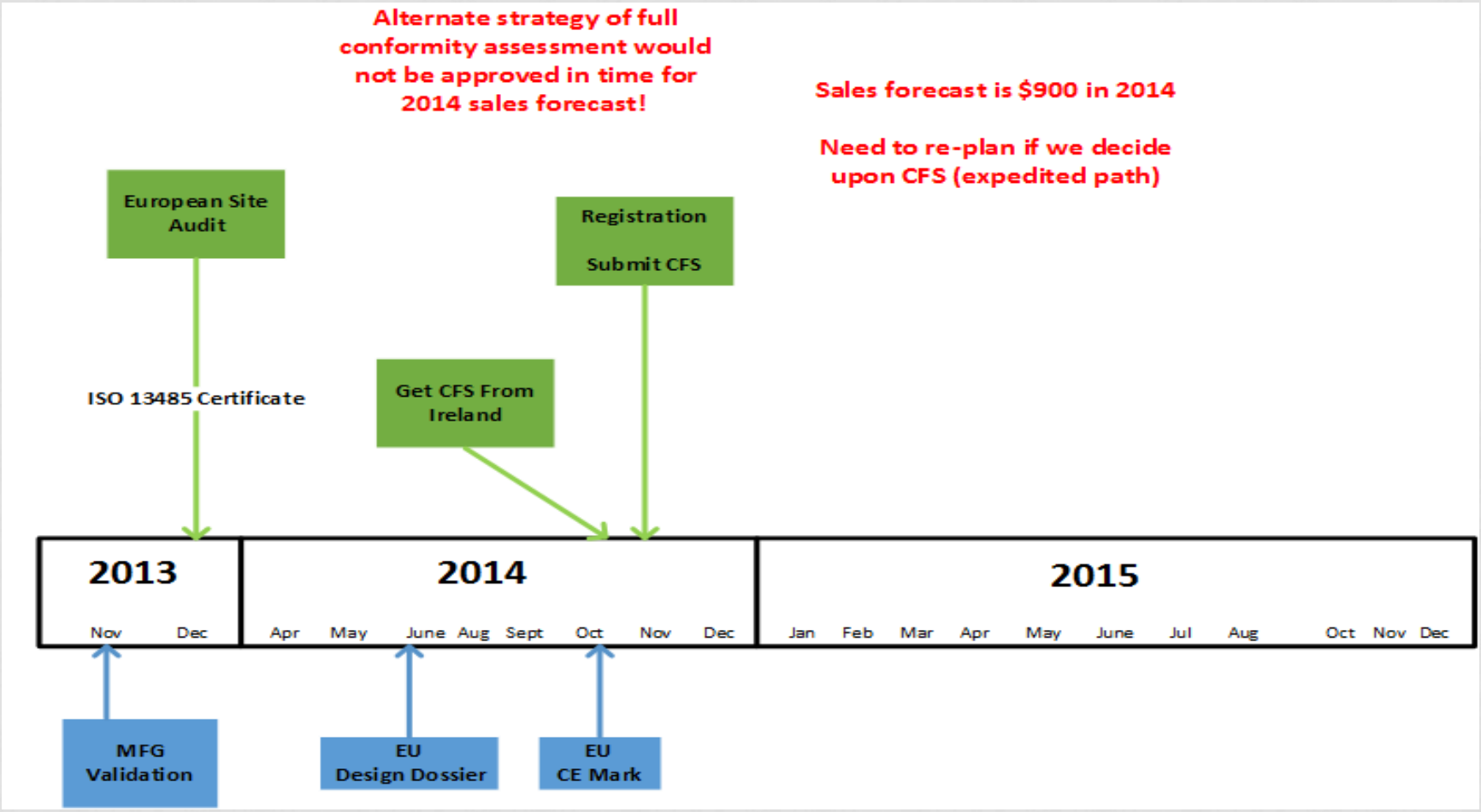
EGYPT TIMELINE



HONG KONG

- Registration is voluntary
- Catheter Device Classification
  - GHTF Classification - D
  - GHTF Final Rule - 7
- Submit Registration to Medical Device Control Office (MDCO) with CFS
  - CFS from a GHTF results in abbreviated process for approval with no need for a conformity assessment audit

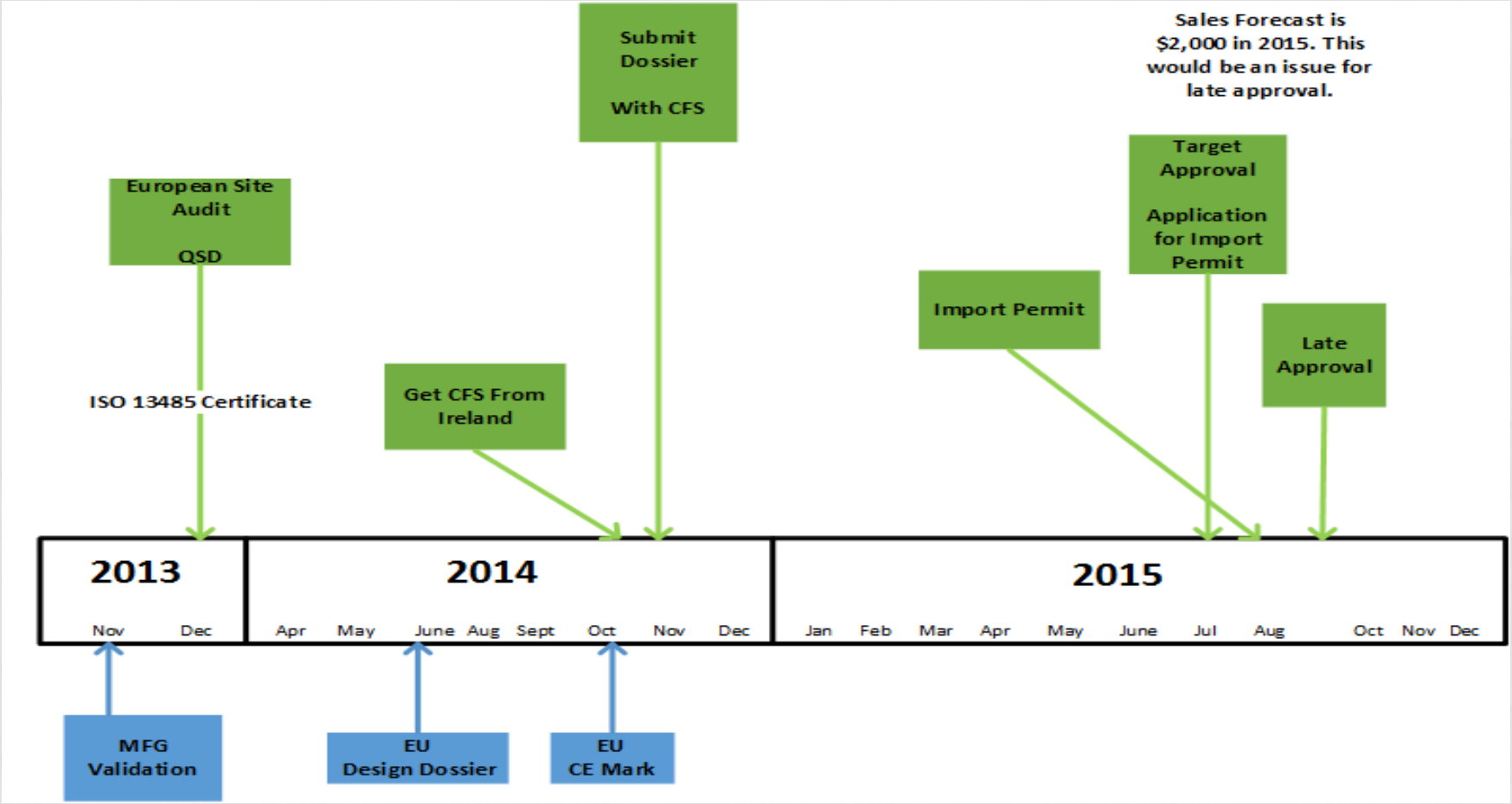
HONG KONG TIMELINE



INDIA

- Catheter is on notified list / register with Central Drugs Standard Controls Organization (CDSCO)
- ISO 13485 certificate
- Submit Registration to Drug Controller General India (DCGI)
  - CFS required – must have CE mark prior to submission
  - Review time 8-10 months
  - Register as Old Device (Rule 21) since Baverick is approved
  - Fee - US$ 1,500 for new MFG site
  - Fee - US$ 1,000 for new Cutter device
- Apply for Import Permit (1 month)

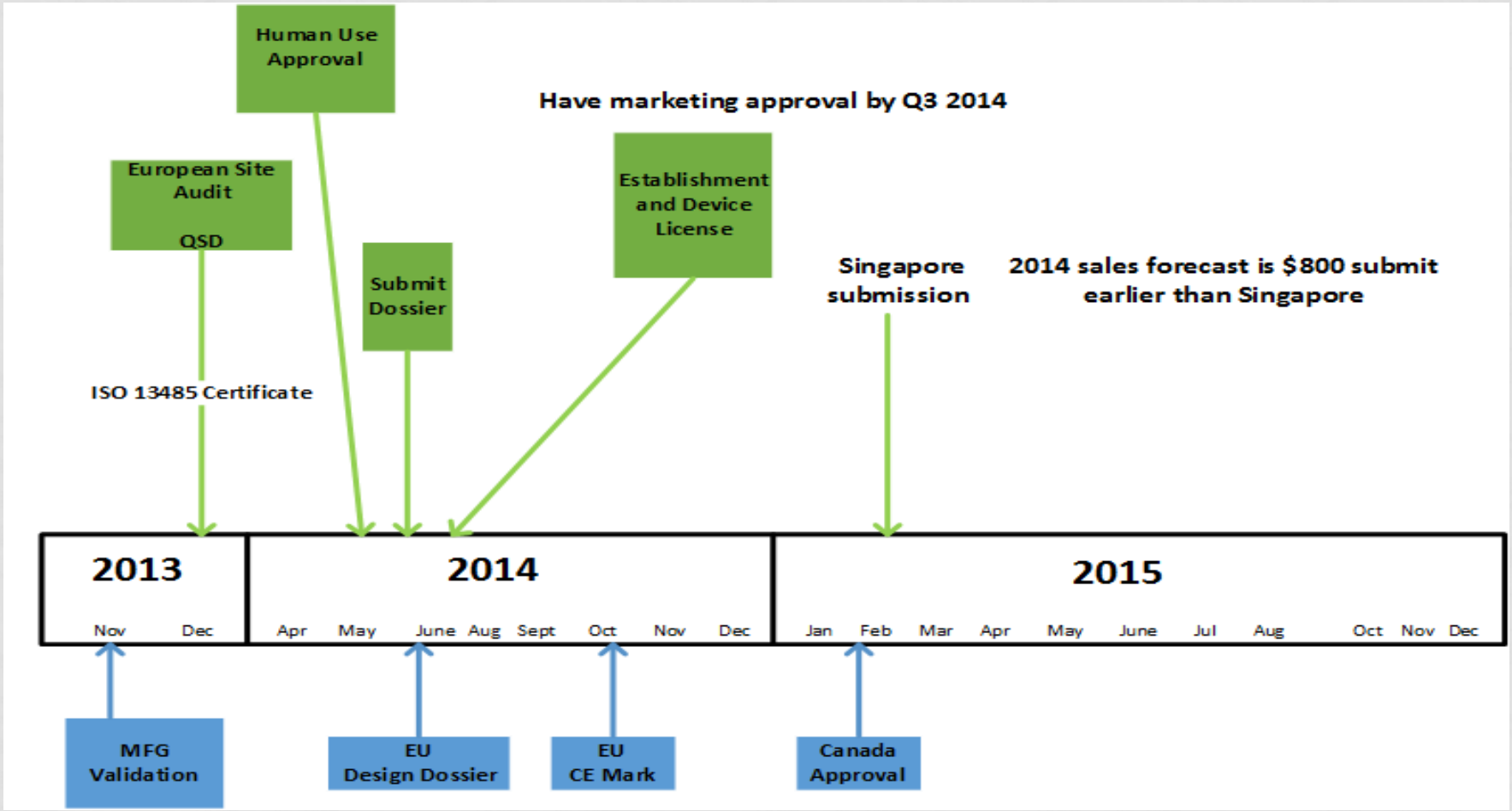
INDIA TIMELINE



MALAYSIA

- Catheter Device Classification
  - GHTF Classification - D
  - GHTF Final Rule – 7
- Registration is voluntary
- Submit Registration to Ministry of Health
  - No fees
- Need device license and establishment license prior to marketing

MALAYSIA TIMELINE



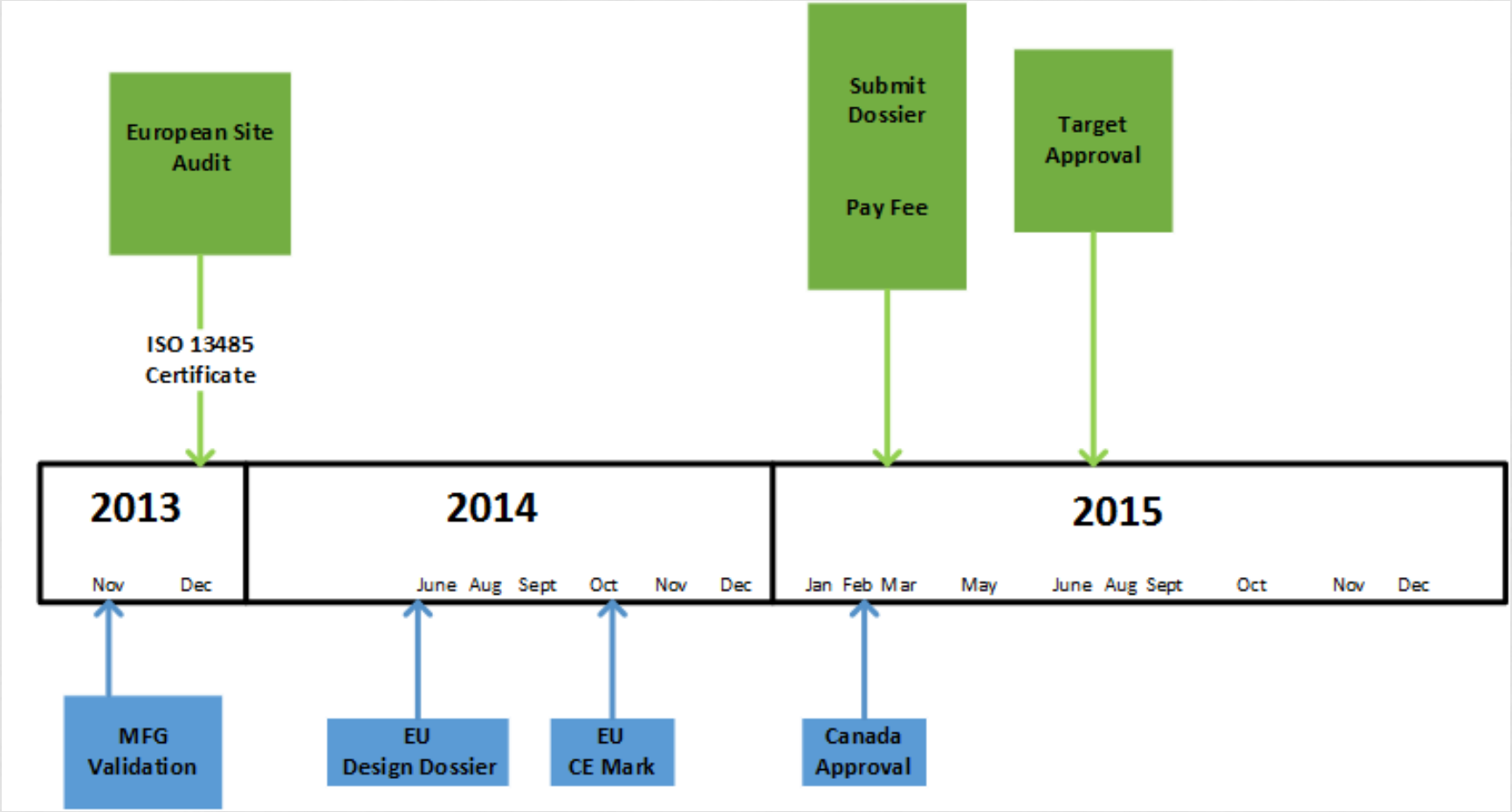
MEXICO

- Catheter is a Class III device

- Appoint Local Responsible Person
  - Use same one as Baverick approval

- Submit Registration to COFEPRIS
    - Use Canada Fast Track
      - Copy of Canadian product license
      - Certificate of accreditation from CMDCAS
      - ISO 13485
      - Mexico supplemental package
    - Review time 3-4 months
    - Labeling in Spanish
    - Fee - US$ 954

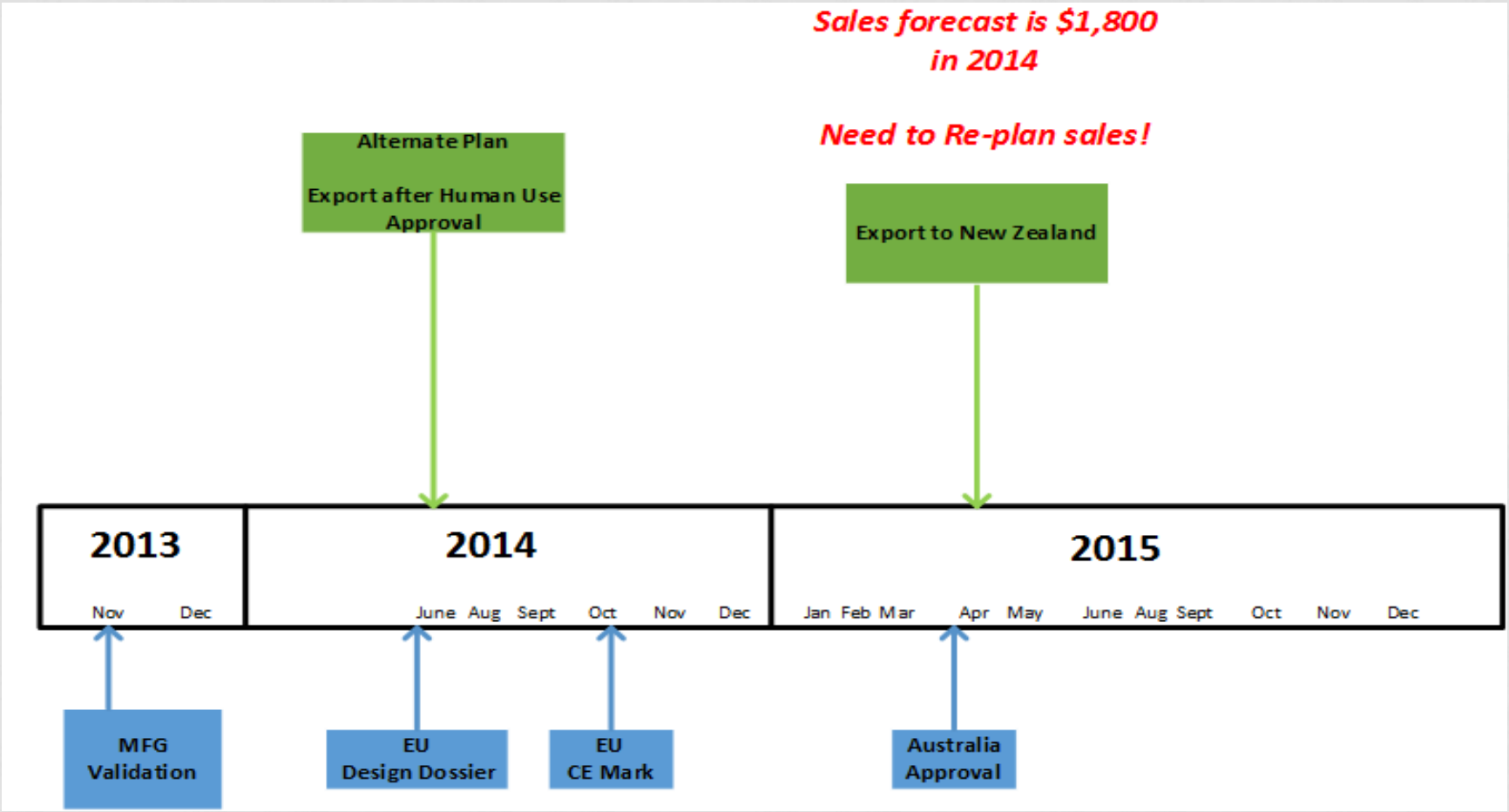
MEXICO TIMELINE



NEW ZEALAND

- Unregulated
- If ship from Australia, requires TGA approval

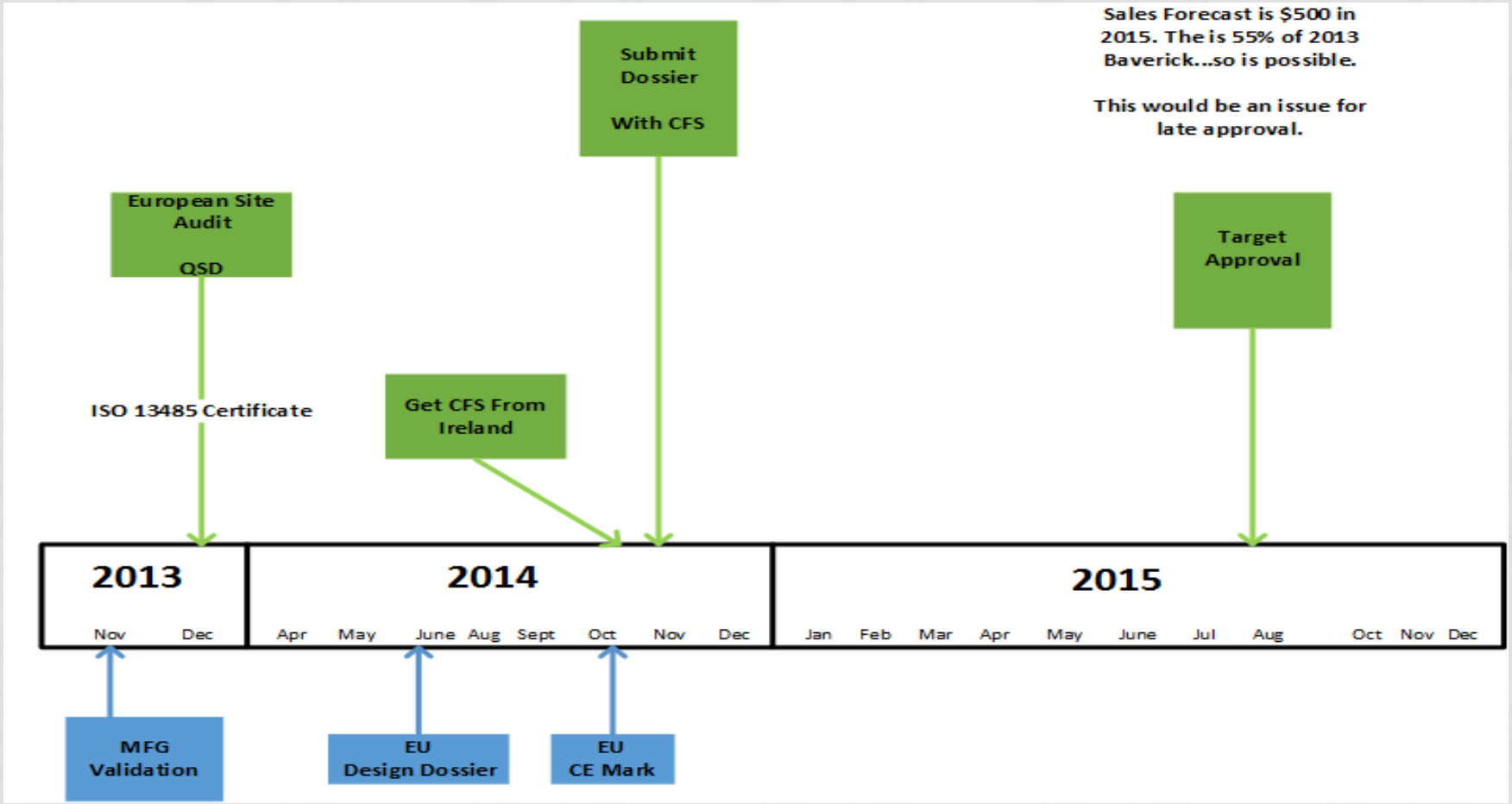
NEW ZEALAND TIMELINE



PHILIPPINES

- Catheter is Class III device
- ISO 13485 certificate
- Submit Registration to BFAD
  - Review time 6-18 months
  - CFS required – must have CE mark prior to submission
    - With CFS approval time 9 months
  - Fees – US$ 35
- Local Company Registration
  - Fees – US$ 100-$300
  - Use same local sponsor as Baverick approval

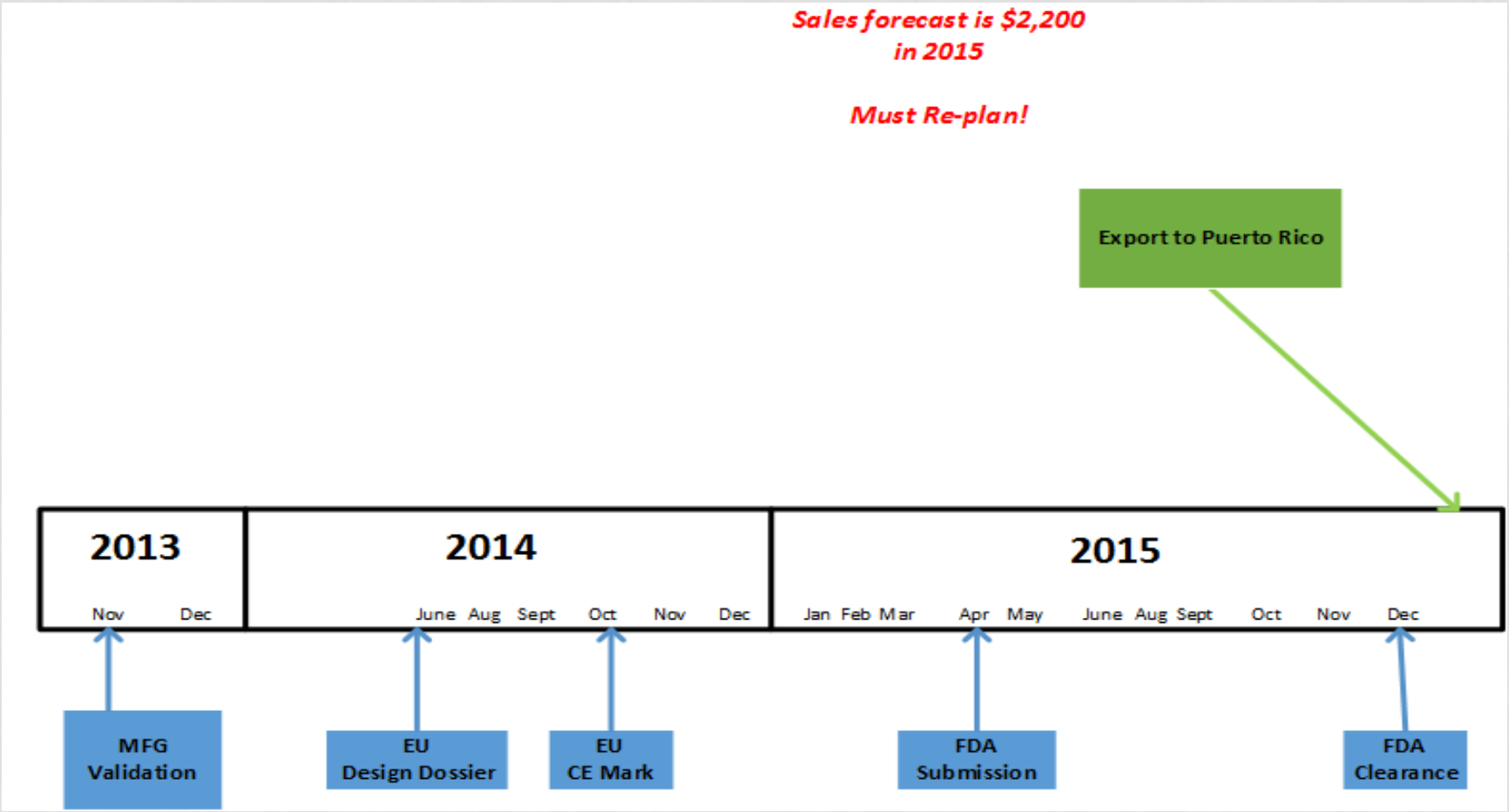
PHILIPPINES TIMELINE



PUERTO RICO

- U.S. Common Wealth
- Meet all FDA requirements

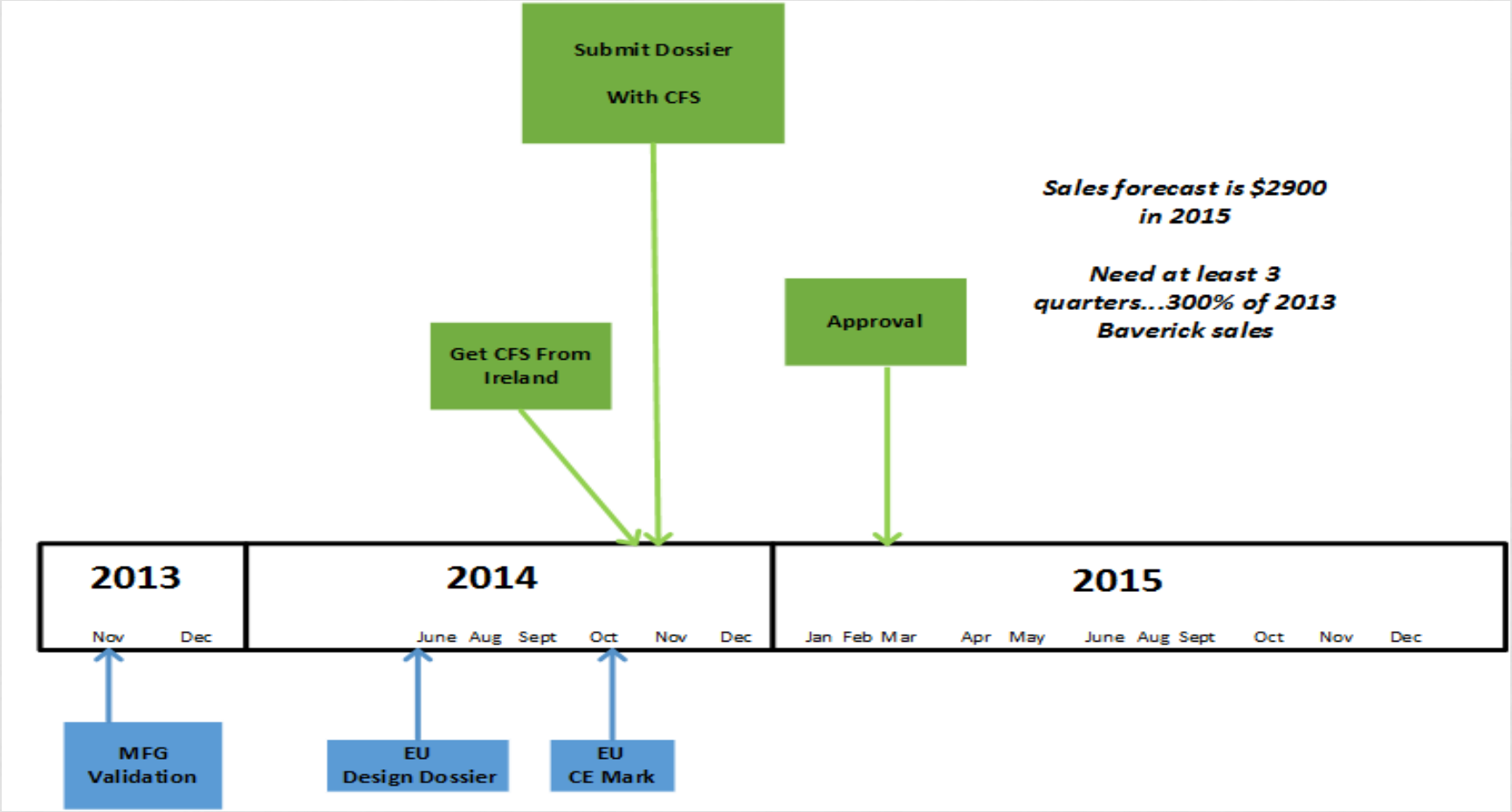
PUERTO RICO TIMELINE



SAUDI ARABIA

- Catheter Device Classification
  - GHTF Classification - D
  - GHTF Final Rule – 7
  - EU Class III
- Appoint Local Responsible Person
  - Use same one as Baverick approval
- Submit Registration to Saudi Food and Drug Authority (SFDA)
    - CFS required – must have CE mark prior to submission
    - Review time 4 months
    - Approval in 1 GHTF Country
    - Fee - US$ 10,000

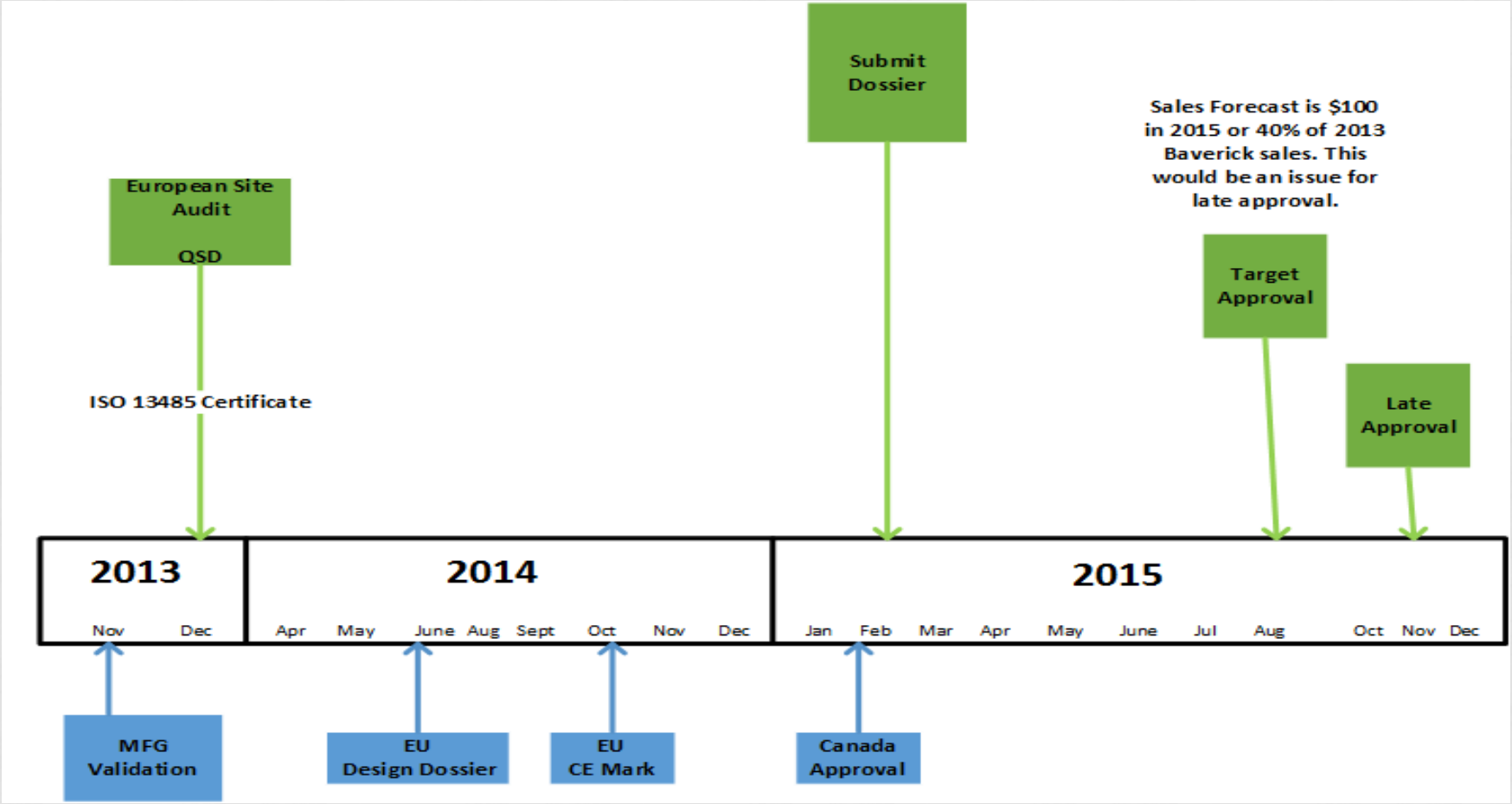
SAUDI TIMELINE



SINGAPORE

- Catheter is Class C device
- ISO 13485 certificate
- Submit Registration to Health Sciences Authority (HSA)
  - Review time 4-5 months
  - Abridged Submission based on 2 GHTF countries
    - EU
    - Canada
  - Application fee - S$ 500
  - Evaluation fee - S$ 2,800
  - Annual License fee - S$ 1,000

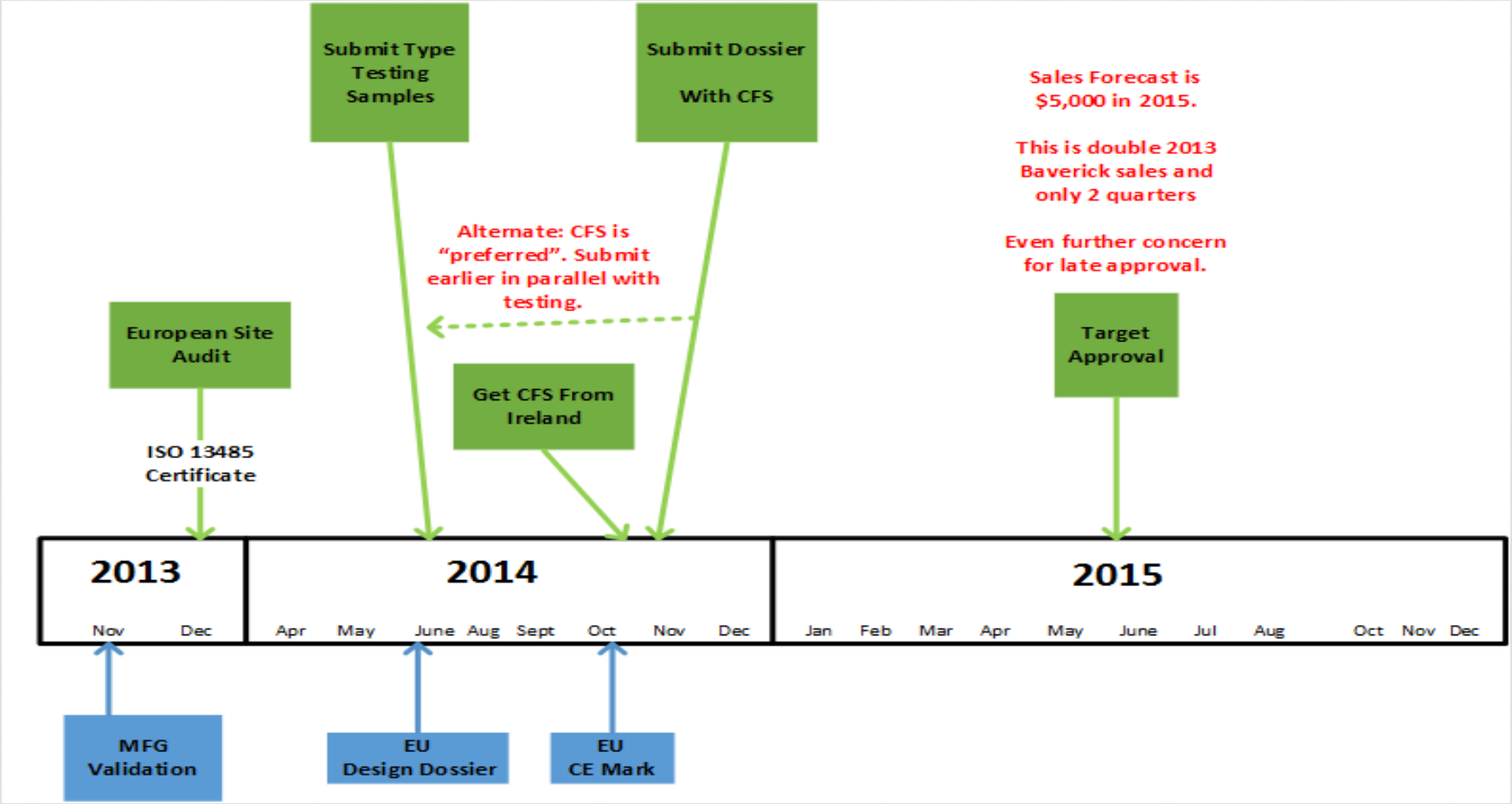
SINGAPORE TIMELINE



SOUTH KOREA

- Catheter Device Classification
  - GHTF Classification - D
  - GHTF Final Rule – 7
- ISO 13485 certificate
  - Alert: GMP audits coming soon
- Complete Type Testing (3-4 months)
  - Fee - US$ 2-10k (KFDA certified 3rd party)
  - Alert: Work with lab in advance to mitigate failures
- Submit Registration to State Food and Drugs Administration (KFDA)
  - CFS preferred – would need CE mark prior to submission
  - 7 months review time
  - Fee - US$ 30

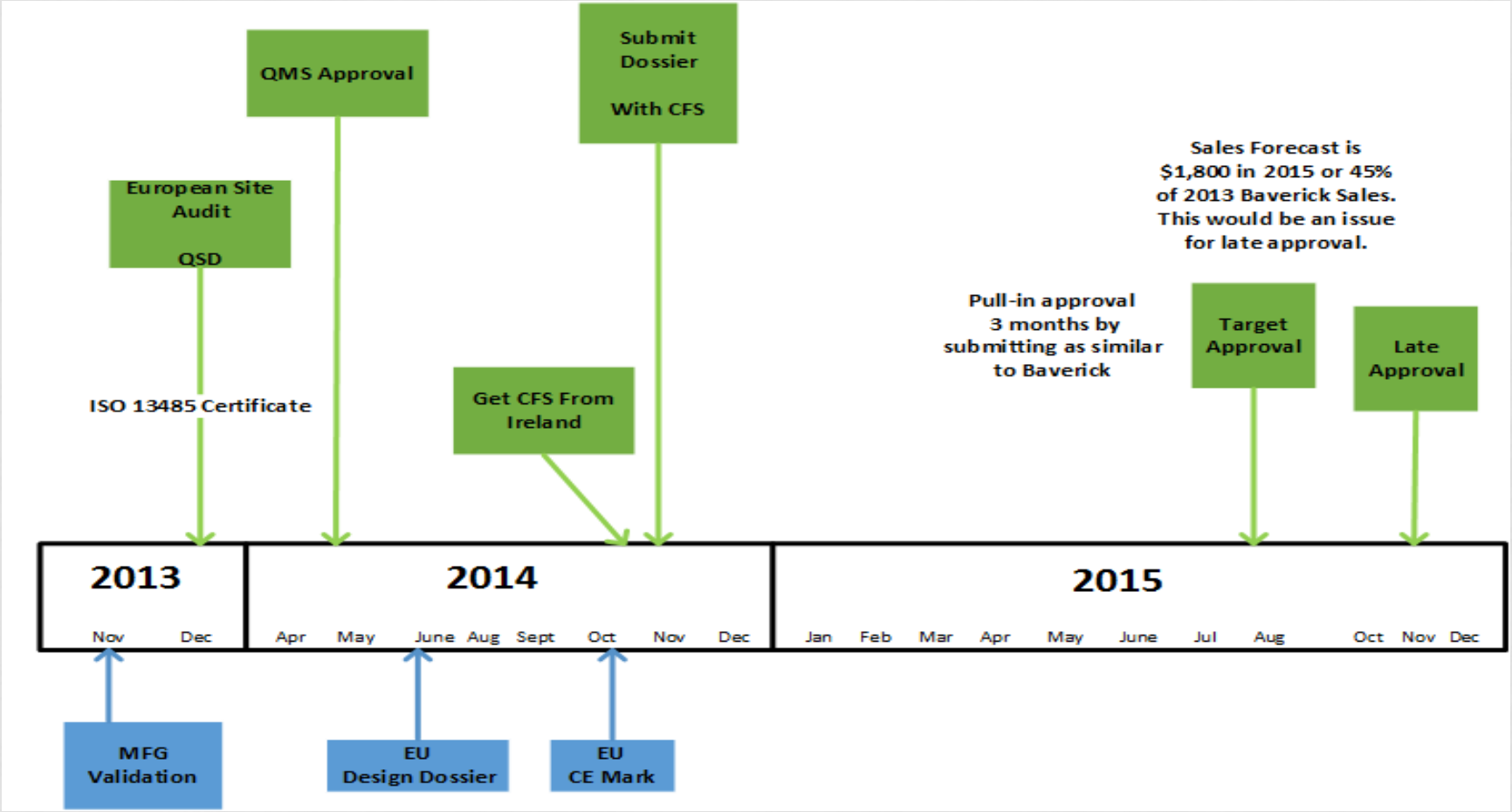
SOUTH KOREA TIMELINE



TAIWAN

- Catheter is Class III device
- QMS Certification (3-6 months)
  - QSD Simplified Process-EU
  - Fee – US$ 750
- Submit Registration to Taiwan
  - CFS required – must have CE mark prior to submission
  - Review time 9-12 months
  - Fee – US$ 1,125

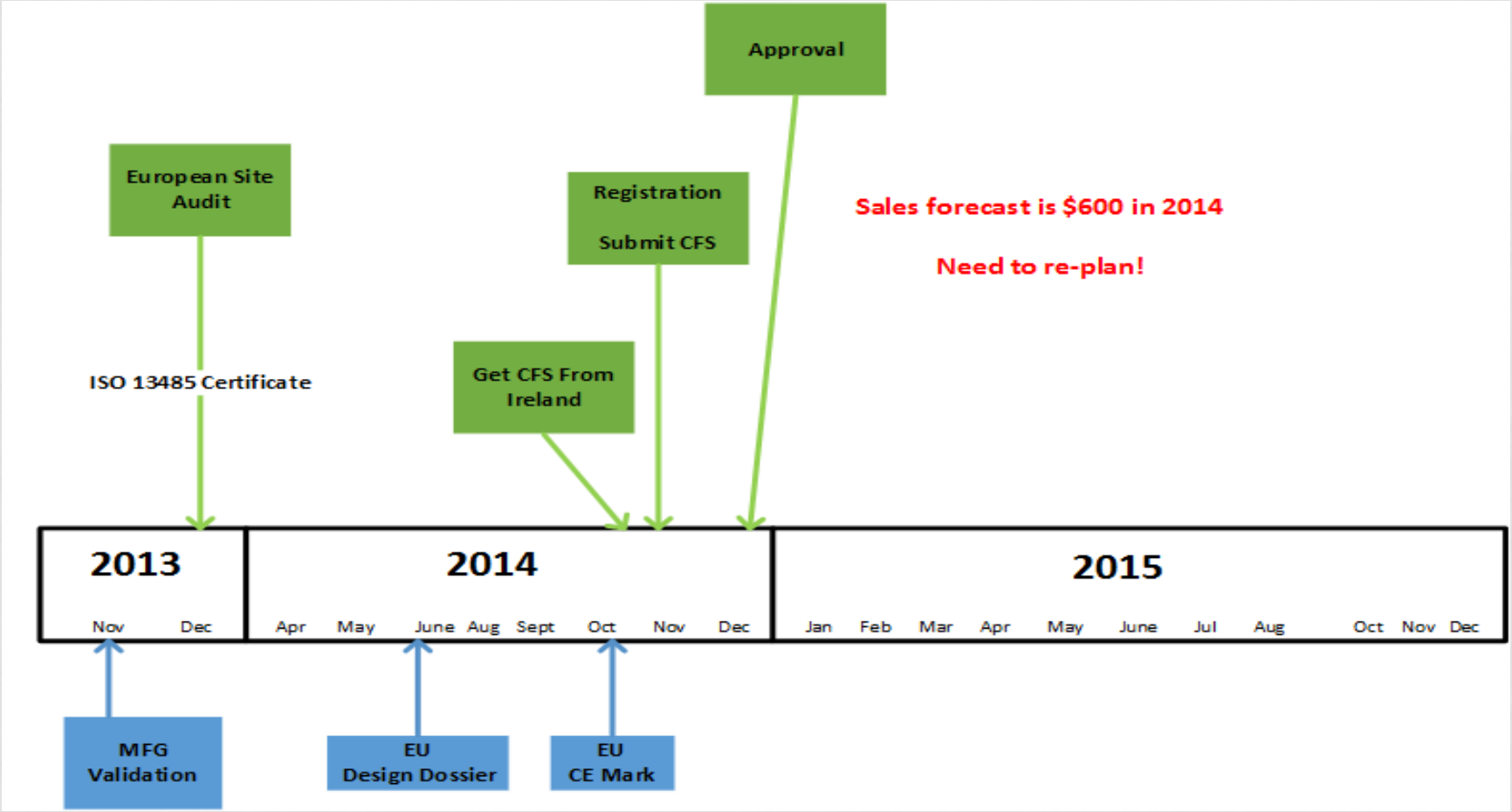
TAIWAN TIMELINE



THAILAND

- Catheter is Class III
- Simple and fast process
  - No fees
- Submit registration
  - CFS required – must have CE mark prior to submission
  - Review time 1 month
- Alerts – customs violations can be criminal fines
  - Product labeling must match content on:
    - CFS
    - ISO Certificate
    - Directions for Use
    - Approval Document

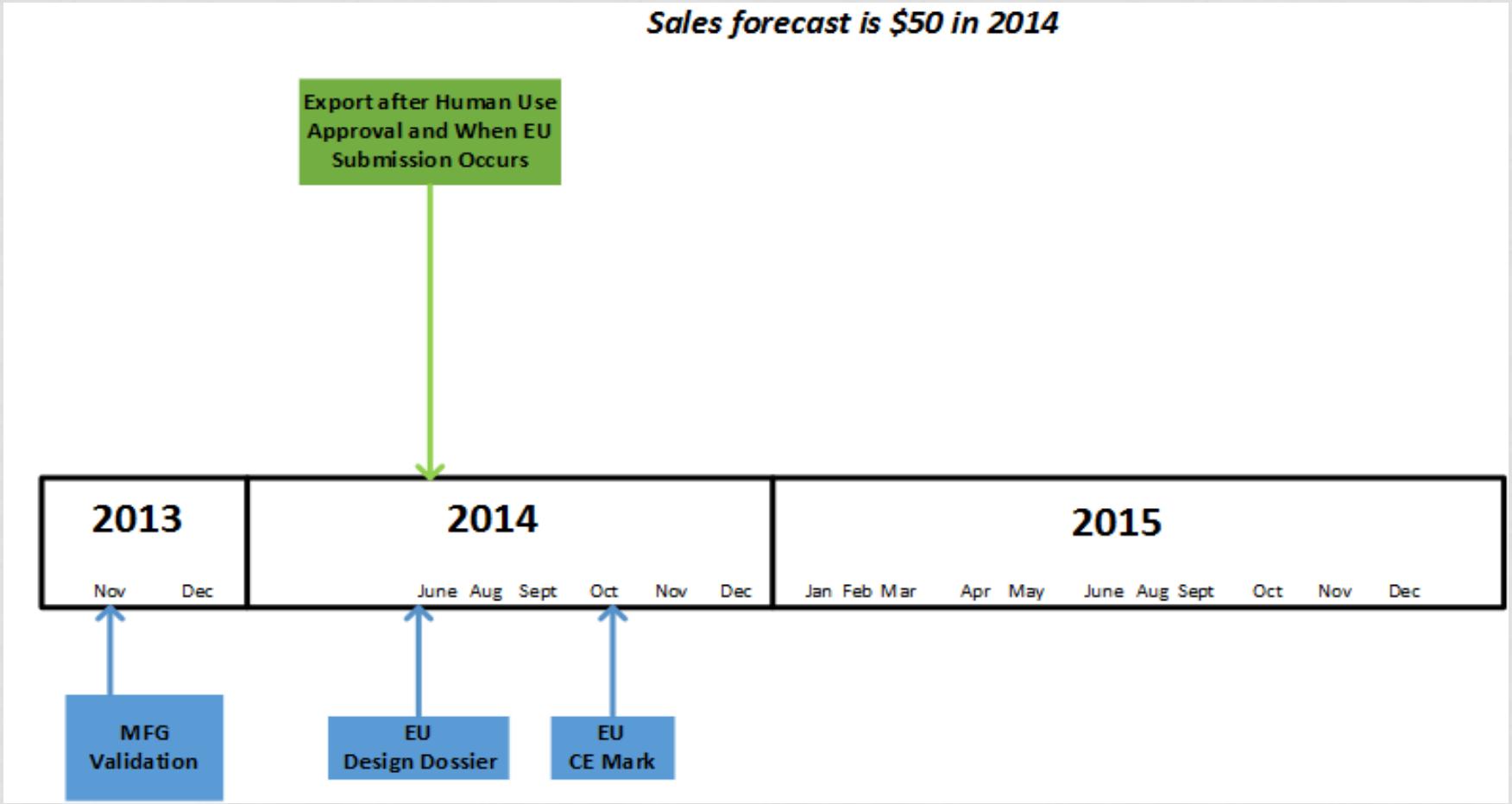
THAILAND TIMELINE



TRINIDAD

- Unregulated
- Sell through distributor after Neuco's internal safety requirements are met

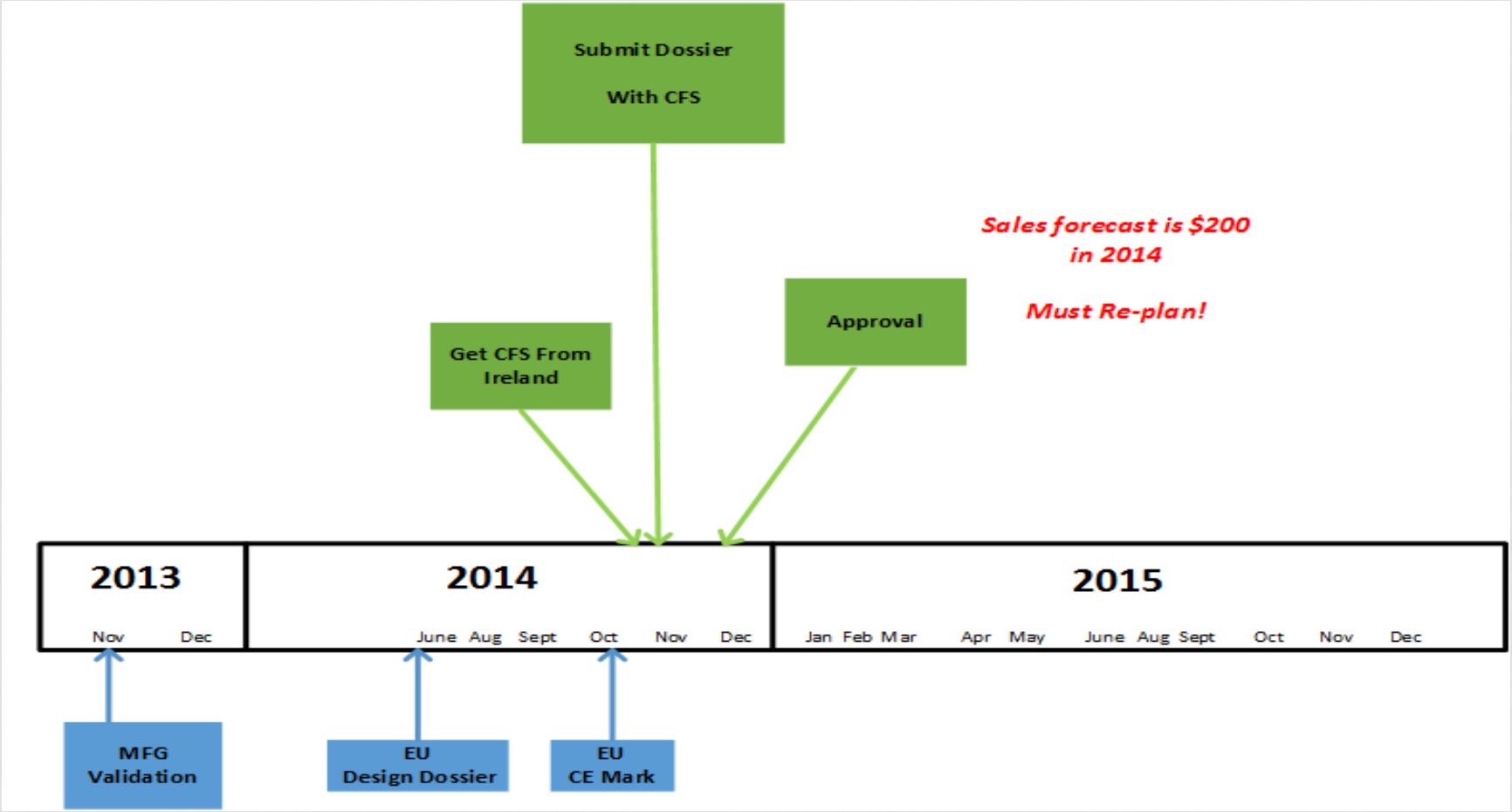
TRINIDAD TIMELINE



VENEZUELA

- Catheter Device Classification
  - GHTF Classification - D
  - GHTF Final Rule – 7
  - EU Class III
- Appoint Local Responsible Person
  - Use existing distributor
- Type Testing
- Certificate of Analysis (CoA)
  - Alert: – Need to create CoA from product specifications that meet specific requirements
- Submission to OICEM
    - CFS required – must have CE mark prior to submission
    - Review time 3 weeks
    - Local distributor labeling
    - Fee - US$ 300

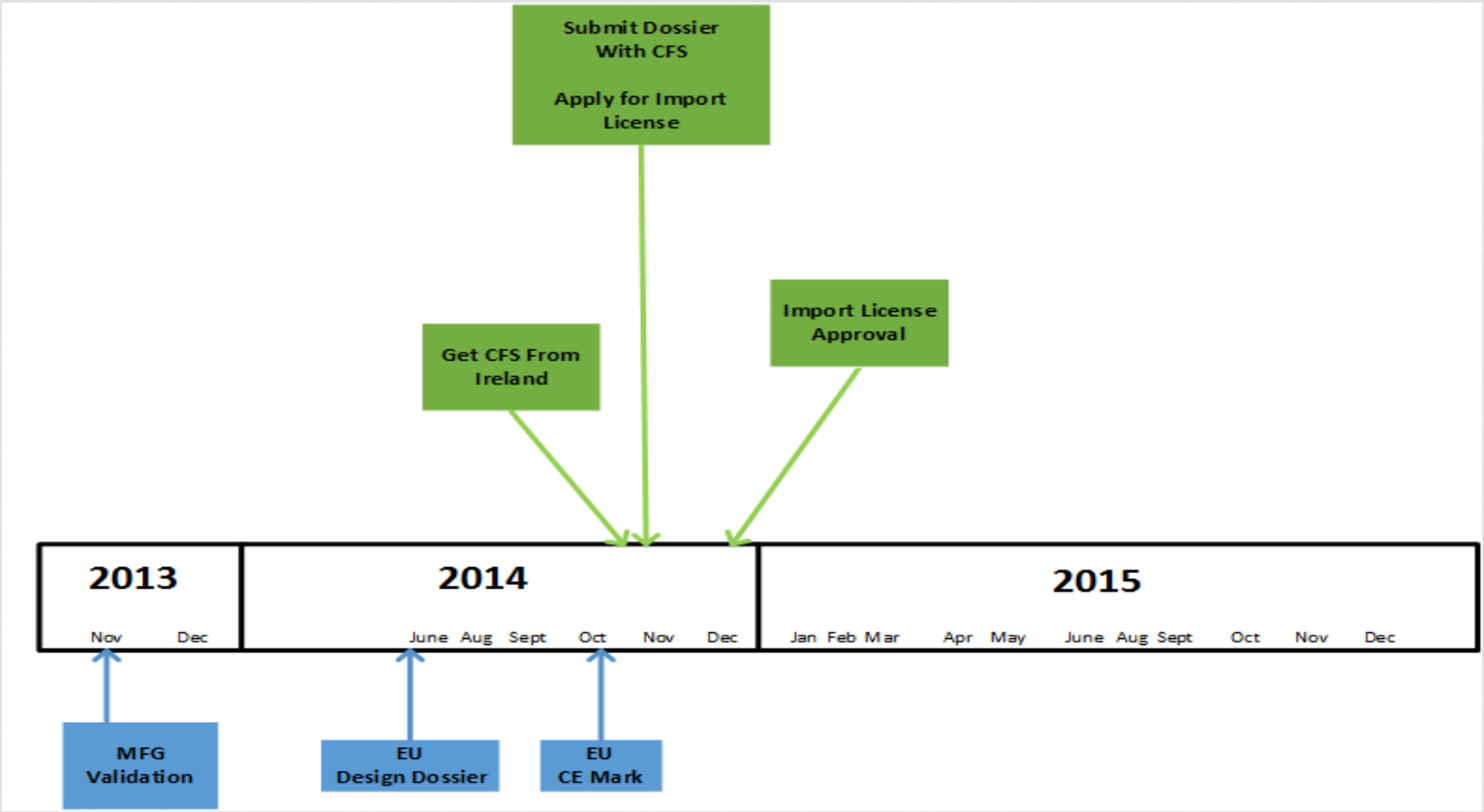
VENEZUELA TIMELINE



VIETNAM

- No device classification
- No registration fees
- Submit to Department of Medical Equipment and Health Works (DMEHW)
- Import license
  - CFS required – must have CE mark prior to license request
  - Processing time - 1 month
  - License fee - US$ 60

VIETNAM TIMELINE



PROPER COMPREHENSIVE RISK ALERTS - LABELING

- Products can be rejected in customs
  - Product labeling must match content on:
    - CFS
    - ISO Certificate
    - Directions for Use
    - Approval Document
- Local language requirements
  - Korea, Thailand, Vietnam, Brazil, India, Taiwan, China, Mexico, and Spanish Latin America
  - Most are not safety related, thus strict manufacturing controls not necessary
    - Mitigation: Handled using local control measures

COMPREHENSIVE RISK ALERTS

- Loss of intellectual property
  - Distributor
  - Regulator
- Mitigation
  - Use European (CE Mark) Dossier
    - Remove diagrams
    - Detailed specifications

COMPREHENSIVE RISK ALERTS

- Incomplete Dossiers
  - Understand the list of necessary documents
  - Submission should be as close to sample docs as possible
- Human Factors
  - Reviewers have work hours and not concerned with our urgencies
- Regulatory Red Tape
  - Cooperate, don’t fight the system

SUMMARY

- Use of Standard Technical File
- 75% of submissions in parallel leverage CE Mark (November, 2014)
- Approximately US$ 75,000 in fees (testing, manufacturing audits, registrations)
- Sales Plan Concerns
  - Argentina, Brazil, S. Korea
- Sales Re-Plan Necessary
  - Columbia, Hong Kong, New Zealand, Puerto Rico, Thailand, Venezuela
- Sales Plan Opportunities
  - Canadian approval in time to generate income in 2015