Conducting Global Clinical Trials
Regulatory’s Piece of the Puzzle

Meredith Brown-Tuttle, RAC

Where to Start

• Work with team and CRO to choose the countries to conduct trials in, based on indication
• Outline requirements for countries chosen
• Put together a “core” package/dossier that will fulfill all country requirements
• Determine if the trial(s) will be conducted under a US IND or not (this effects document collection, retention and submission)
Outlining Requirements

• Use consultants, CRO or regulatory intelligence database to help compile regulatory requirements, across all countries selected
  – What documents needed to begin clinical trials
  – ICF requirements
  – Clinical supply label requirements
Global Regulatory Dossier

- IND/IMPD/CTA
  - Start with a full IMPD and edit down for different country requirements
- Master Informed Consent Form (ICF)
- Investigator’s Brochure
- Protocol
- Advertising

Global Regulatory Dossier

- Protocol signature page
- Other country approval of protocol
- Letter of Delegation of Responsibilities/Power of Attorney (generally needs to be certified by Apostille of the Hague Convention)
- Insurance
- Case Report Forms
- Business license(s)
- TSE/BSE certificates
Translations

- Typical Translations include:
  - ICFs
  - IB
  - Protocol synopsis
  - Protocol
  - Patient diary or questionnaires
  - Clinical supply labels

- Translations need to be translated, back translated and certified

Translations Summary

<table>
<thead>
<tr>
<th>Country</th>
<th>Protocol</th>
<th>IB</th>
<th>Informed Consent</th>
<th>IND Regulatory Filing</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td>English</td>
<td>English (or another language if required to community)</td>
<td>English</td>
<td>English</td>
</tr>
<tr>
<td>Argentina</td>
<td>Japanese</td>
<td>Japanese</td>
<td>Yaami</td>
<td>Yaami</td>
</tr>
<tr>
<td>EU/Eastern EU</td>
<td>English</td>
<td>English</td>
<td>Veritas, depends on country regarding Clinical Trial as use English Master</td>
<td>English</td>
</tr>
<tr>
<td>Australia</td>
<td>English</td>
<td>English</td>
<td>English</td>
<td>English</td>
</tr>
<tr>
<td>Canada</td>
<td>English</td>
<td>English</td>
<td>English</td>
<td>English</td>
</tr>
<tr>
<td>Asia</td>
<td>Translated into local language</td>
<td>Translated into local language</td>
<td>Translated into local language</td>
<td>Translated into local language</td>
</tr>
<tr>
<td>South Europe</td>
<td>Translated into local language</td>
<td>Translated into local language</td>
<td>Translated into local language</td>
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</tr>
<tr>
<td>Saudi Arabia</td>
<td>English</td>
<td>English</td>
<td>English</td>
<td>No</td>
</tr>
</tbody>
</table>
Clinical Labels

- Investigate the requirements of each country for clinical labeling (after countries selected)
- Need to translate into local language(s) and back translate to insure accuracy
- Printing of labels can take a few weeks to a month
- Allow 3-4 months for entire process

Label Summary

<table>
<thead>
<tr>
<th>Language</th>
<th>United States</th>
<th>EU - EEA/EEC</th>
<th>Japan</th>
<th>Australia</th>
<th>Canada</th>
<th>India</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical name and re identification code</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Statement that this drug is for clinical trials or &quot;Investigational Use Only&quot;</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Name and address of the Sponsor</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Manufacturing lot number, batch number or code</td>
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<td>✔</td>
<td>✔</td>
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<td>✔</td>
</tr>
<tr>
<td>Storage conditions</td>
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<tr>
<td>Expiration date</td>
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<td>Package size and code</td>
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<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Dosage form, number of units</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
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<tr>
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<td>✔</td>
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<tr>
<td>Dosage Reference</td>
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<tr>
<td>&quot;Keep out of reach of Children&quot;</td>
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<td>✔</td>
<td>✔</td>
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</tr>
</tbody>
</table>

1. 21 CFR 210
2. 21 CFR 211
3. Direct to Consumer Medicine Product, "Investigational Use Only"
4. Guide to Good Manufacturing Practice
5. Guide to Clinical Trials Towards Clinical Trials Regulations
6. The Drug and Cosmetics Rules, 1981, as Amended up to the 20th November, 2014
SAE Reporting

- SAE requirements and reporting timeframe differ by country
  - Report formats/forms are different (MedWatch, CIOMS, ADR)
  - Some expect reports by mail or electronically
  - Some countries need the MOH, EC and investigator’s informed

Regulatory Packages

- If conducted under a US IND, need to submit the following to the FDA:
  - 1572 (in English)
  - CV
  - EC Approval (biologic only)
  - EC Translation (biologic only)
  - EC translation certification (biologic only)
  - ICF (translated) (biologic only)
  - ICF translation certification (biologic only)
- Also need to collect Financial Disclosure info
Maintaining the Submission

- Annual Reports
- Quarterly Reports
- SAE reporting
- 1572 updates
- Financial Disclosure changes
- Clinical Supply updates
- Protocol Amendments
- Notification that the trial has ended
- Final Clinical Study Report

Determining the Timeline

- EC and MOH review and approval timeframes for each country participating in the trial need to be taken into account
  - Often there is a Central EC committee and a Local EC, the process is sequential
- MOH will typically be on time, EC times will vary considerably
  - Sequential process can delay study start
  - Eastern and Southern EU countries typically take the longest
- Contract delays need to be factored in
### Asia

<table>
<thead>
<tr>
<th>Country</th>
<th>Approval Process (Parallel/Sequential)</th>
<th>Time to Approval (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>MOH</td>
</tr>
<tr>
<td>China</td>
<td>Sequential</td>
<td>240+</td>
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<tr>
<td>Hong Kong</td>
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<td>Japan</td>
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<td>Philippines</td>
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<td>Taiwan</td>
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<td>Thailand</td>
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### Australia

<table>
<thead>
<tr>
<th>Approval Process (Parallel/Sequential)</th>
<th>Time to Approval (days)</th>
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<tbody>
<tr>
<td></td>
<td>MOH</td>
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<tr>
<td>MOH Submission not required</td>
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South Africa

<table>
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<th>Approval Process (Parallel/Sequential)</th>
<th>Time to Approval (days)</th>
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<tr>
<td></td>
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<td>Parallel</td>
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South America

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<th>Country</th>
<th>Approval Process (Parallel/Sequential)</th>
<th>Time to Approval (days)</th>
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</thead>
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<tr>
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<tr>
<td>Brazil</td>
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<td>60 60</td>
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<tr>
<td>Chile</td>
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<td>60 90</td>
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<td>Columbia</td>
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<td>45 90</td>
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<tr>
<td>Guatemala</td>
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<td>45 90</td>
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<td>90 90</td>
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<tr>
<td>Peru</td>
<td>Sequential</td>
<td>60 90</td>
</tr>
<tr>
<td>Venezuela</td>
<td>Sequential</td>
<td>45 90</td>
</tr>
</tbody>
</table>
How Long Does it Really Take?

• MOH Submission 30-180+ days
• EC Submission 7-200+ days

Depends on indication and country

Tips

• Have clinical labeling printed by region or country in some cases
• Some countries have a “No Phase 1/Guinea Pig rule”
• If you administer a drug and it works for a patient, a company will need to continue to provide the drug, at no cost, until the marketing application is approved
Delays to Expect

- Contracts usually take 2-3 times longer than expected
- Printing the clinical supply label in booklet form
- Translations
- Vacation schedules and effect on site initiation or patient recruitment
- Insurance certificates
- Review of regulatory packages for drug shipment

Delays to Expect

- Agency or EC questions
- Import license
- Some countries need a fully executed contract before the MOH will review the IMPD
Recommendations

- Plan early and build in expected delays
- Know the various countries regulatory requirements
- Resource the study appropriately
- Track Agency and EC questions
- Manage CRO closely and company’s expectations
Regulatory Strategy When Outsourcing Global Clinical Trials

Karen Jones

Agenda

• Background
• Key Issues
  – Data acceptability by the FDA?
  – The impact of foreign laws, regulations, guidance documents and practices.
  – Can we get RA and EC approval for a given protocol?
  – What will it take to get RA and EC approval for a given protocol?
  – How long will it take to get RA and EC approval?
  – Regulatory compliance requirements for foreign studies?
  – What will the impact be on the NDA and PI?
• Summary
• Questions
Background

- Traditional regions are saturated, with high costs and low recruitment
- Up to 140 countries now listed on www.clinicaltrials.gov
- CRO business model
  - Growth of the market
- Improved standardization of regulatory governance in emerging markets

Reference: Trends in the globalization of clinical trials
Fabio A. Thiers, Anthony J. Sinskey & Ernst R. Berndt
Nature Reviews Drug Discovery 7, 13-14 (January 2008)

Key Issues:
Data acceptability by the FDA?

- Safe and effective medicines
  - Positive risk to benefit ratio
- If CTs not conducted under IND then study must conform to whichever of the following affords subjects greater protection
  - Ethical principles contained Declaration of Helsinki 1989 version, or
  - The laws and regulations of the country in which the research was conducted

Strategic Outsourcing Decisions:
- Whether to conduct foreign studies under an IND.
- Clearly define the objectives of the study for the CRO & prospectively agree with the CRO any regions to be omitted.
Key Issue: The Impact of Laws, Regulations, Guidance Documents & Local Practices

• It’s all about outsourcing
• Know what you don’t know!
  – 194 countries worldwide
  – Different levels of regulatory sophistication
  – Varying medical and regulatory practices
  – Language barriers
  – Expert knowledge

Strategic Outsourcing Decisions:
- Which CRO - Global, regional or national CRO?
- Type of relationship - Proactive and transparent; hands on?
- Roles & responsibilities – Defined delegation of responsibilities.
- Set expectations - Timeframes & communication plans.
- Governance – Metrics, management and dispute resolution.

Key Issue: The Impact of Laws, Regulations, Guidance Documents & Local Practices

How do we ensure regulatory outsourcing is a success?

1. Define needs
2. Develop process
   - Implement and document consistent selection & evaluation criteria
     - Compliance
     - Experience
     - Capability
     - Capacity
     - Quality
3. CRO management plan
   - Communication plans
   - Management and dispute resolution plans
   - Pre-agreed metrics
   - Feedback
4. Cost
   - Contract defines in-scope activities
   - Pre-agreed process and timelines for out-of-scope activities
   - Bundle up with entire study budget or independent budget
Key Issue:
Can we get RA and EC approval for a given protocol?

• What is acceptable in the US may not be acceptable for foreign RA and ECs
  – Different approaches benefit to risk ratios
  – Acceptability of placebo controlled trials
  – Therapeutic options
• Greatest delays
  – Poor protocol design
  – Local clinical practice & regulatory requirements
  – Poor translation of documents
  – Not adapting documents to local requirements

Strategic Outsourcing Decisions:
• CROs…….. Contractor or consultant?
  • CRO…….. Up-to-the minute expertise is vitally important.
  • Are you actively and proactively listening to the local experts?
  • Can you talk to the local experts / do you want too?

Key Issue:
What will it take to get RA and EC approval?

• Country and site feasibility key
  – Core document package
  – Country specific regulatory requirements
    • Rate limiting documents
    • Lead times for preparation of CTA
    • Special considerations
      – local legal representatives
      – definitions of investigational products, comparators, add-on therapies
      – Import/export requirements
      – Samples & drug analysis

Strategic Outsourcing Decisions:
• Overall RA filing strategy - strategy is essential at project start-up.
  • LPI, LPO – patient enrolment and study completion can be dramatically impacted through RA and EC delays – know your countries.
  • CROs – Exceptional planning skills, proactive communication, “content” plans.
Key Issue: How long will it take to get RA & EC approval?

- Parallel or sequential RA and EC approval?
  - If sequential - staggered or step-wise?
  - Are there meeting dates to adhere to?
- What order of steps?
  - EC then RA, or vice versa?
- Any additional steps?
  - Validation of CTA?
  - Import/export licenses?
- Passive approval or pre-approval process?

Strategic Outsourcing Decisions:
- What is the filing plan & how will the CRO communicate this?
- Do the CRO have the experience and capacity to deliver on the plan?
- Will you define and measure success?

Key Issue: Regulatory compliance requirements for foreign studies?

- Compliance is key to quality!
  - Lifecycle management e.g.
    - Protocol and CTA Amendments
    - Go/No Go decisions for implementation of amendments?
    - Safety Reporting
    - Qualified Person release
    - Trial Master File
  - ALL regulatory activities to be delegated must be captured in the contract / Statement of Work (SOW) / Transfer of Obligations.
    - What oversight and decision making will the sponsor have versus CRO?

Strategic Outsourcing Decisions:
- What activities will the sponsor be delegating?
- Are the CRO to be allowed to sub-contract to other entities and if so does the CRO have an SOP in place?
- In general - make sure the CRO has the relevant SOPS, both global and local and a system for updating them.
- Will you conduct a regulatory specific audit of the CRO?
Key Issue:
What will the impact be on the NDA and PI?

- Regulatory strategy
  - Flexibility of protocol design
  - Balancing scientific objectives with patient recruitment and local medical practices
    - Valid scientific conclusions to support next phase and NDA
    - Target Product Profile (TPP) versus protocol parameters
      - Commercial relevance
- Quality of execution
  - Regulatory oversight

Strategic Outsourcing Decisions:
Where will the regulatory oversight reside?
Who’s accountable and/or responsible for the decisions?
Is there a clearly defined RACI in place?
How much communication and too whom?
Who has control of regulatory go and no/go decisions?

Summary

- Outsourcing global trials is a continuing & increasing trend
- Outsourcing is complex, cross functional and requires advanced matrix management
- Sponsor preparation and clarity is paramount
  - Know what, how, when and who
  - Make no assumptions
  - Know what you don’t know
  - Ask lots of questions
- Select and evaluate CROs then document the decision
- Inspect the CROs
- Define prospectively the type of relationship you want with the CRO
- Define prospectively the goals, expectations, CRO management plan and communication plans
  - Put in place comprehensive contract, SOW and transfer of obligations and review regularly
  - Include start-up AND compliance activities
  - Have a dispute resolution agreement
Questions?

Thank You for Listening
Outsourcing Clinical Trials in Europe

Carla Kikken
MediTech
Strategic Consultants B.V.

MediTech Strategic Consultants B.V.

Outsourcing Clinical Trials in Europe

EU Market Authorization
* CE Mark
* Technical File
* Clinical Trials
  ▶ Notified Bodies
  ▶ Competent Authorities
  ▶ Authorized Representative
EU Market Authorization: CE Mark

- European Directives
  - MDD – IVD – AIMDD
    - Annex I Essential Requirements
- Meddev Guidance Documents
- EN Norms
- ISO Standards
- Transposition EU Member States

EU Market Authorization: CE Mark

- Quality System
- Technical File
- Clinical Data
EU Market Authorization: Technical File

- Required for all classes of devices
- Essential Requirements
- Product description/specifications/verifications
- Manufacturer’s Declaration of Conformity
- Result of Risk Analysis
- Clinical Data
- Quality Assurance System Description


"The manufacturer shall establish and maintain a process for identifying hazards associated with a medical device, estimating and evaluating the associated risks, controlling those risks and monitoring the effectiveness of the control."

- Risk analysis
  - Hazard identification
  - Risk estimation
- Risk evaluation
  - Risk acceptability decisions
- Risk control
  - Implementations
  - Residual risk evaluation
  - Overall risk acceptance
- Post-production information
  - Post-production experiences
  - Risk management experience

Risk assessment
Risk management
EU Market Authorization: Technical File - Product Classification

- Definitions according to MDD
- Device Classification (Annex IX)

- Class I: Self certification
- Class II A and II B: Annex V and Annex VII
- Class III: Annex II

Classification decided by manufacturer
- Based on intended use, risk level, invasiveness in the human body
- Duration (transient, short term, long term)
- Classification determines route to CE Mark
- Devices to comply with Harmonised Standards are presumed to comply with ER’s
- Must go through Conformity Assessment procedure
EU Market Authorization: Clinical Trials Data

- Literature Research
- Literature Research / Clinical Trial
- Clinical Trial
- ISO 14155

Clinical data is data which is relevant to the various aspects of the clinical safety and performance of the device. This must include data obtained from:

- published and/or unpublished data on market experience of the device in question, or a similar device for which equivalence to the device in question can be demonstrated, or
- a prospective clinical investigation (s) of the device concerned, or
- results from a clinical investigation (s) or other studies reported in the scientific literature of a similar device for which equivalence to the device in question can be demonstrated
### EU Market Authorization: Clinical Investigations vs Literature Route

<table>
<thead>
<tr>
<th>Clinical Investigations</th>
<th>Literature Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advantages</td>
<td>Advantages</td>
</tr>
<tr>
<td>Targetted</td>
<td>Less expensive</td>
</tr>
<tr>
<td>Precise provided the study</td>
<td>Fast</td>
</tr>
<tr>
<td>Is sufficiently clear/robust</td>
<td>Low Risk</td>
</tr>
</tbody>
</table>

### EU Market Authorization: Clinical Trials Requirements EU

- Clinical Investigational Plan
- Language
- Patient Information/ Consent format
- Insurance
- Hospital/Investigator Agreements
- EC/ CA submission
EU Market Authorization: Clinical Trials Ethics Committees / IRB's

- Country- or regional specific
- Required submission form
- Clinical Investigational Plan
- Patient Information/Consent (language)
- Insurance

EU Market Authorization: Clinical Trials Country Specific Issues

- Country Specific Issues:
  - Protocol
  - Language
  - Patient Information/ Consent requirements
  - Insurance: local office
  - 60 days waiting period
EU Market Authorization: Clinical Trials Country Specific Issues

- CE – Non CE Marked products
- Germany
- United Kingdom
- Italy
- Spain
- France

EU Market Authorization: Clinical Trials Requirements EU

Requirements for submission of clinical trials to Ethics Committees (IRB) and Competent Authorities in:
- Germany
- United Kingdom
- France
- Spain
- Italy
EU Market Authorization: Clinical Trials Requirements Germany

European law:
- MDD

German Laws:
- MPG
- Radiation law

Guidelines:
- DIMDI-Verordnung

EC submission
- BfArM registered ethic committees
- 1 EC approval is valid for the whole country
  - Local requirements hospitals
  - Submission by investigator/CRO
- Need 1 clinical trial leader/principal investigator for Germany
EU Market Authorization: Clinical Trials Requirements Germany

- CA notification
  - After EC approval
  - DIMDI website
  - Notification complete = start study

EU Market Authorization: Clinical Trials Requirements United Kingdom

- European law:
  - MDD

- Guidelines:
  - Guidance notes MHRA
EU Market Authorization:
Clinical Trials Requirements
United Kingdom

EC submission
- Application by Chief investigator to main Research Ethics Committee (REC)
- 60 day clock
  - Multicenter: local principal investigators submit part C of the submission form to local REC
  - Local REC’s advise main REC on outcome of their assessment within 25 days
- Applicant is invited to attend the REC meeting

CA notification
- Simultaneous with EC submission
- Submit electronically on disk to MHRA
- 60/30 day clock starts when MHRA receives documents
  - No questions or objection: final letter on day 30
  - Final no-objection letter on day 60
  - Study can start after 60 days waiting time, with or without letter
EU Market Authorization: Clinical Trials Requirements France

**European law:**
- MDD

**French law:**
- Date of implementation Aug. 27th, 2006

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**EU Market Authorization: Clinical Trials Requirements France**

**EC submission**
- First request a registration number from AFSSAPS
- Approval from one ethics committee (CPP) is valid for whole country
- Opinion within 35 days after the CPP received the dossier. No answer: negative opinion
EU Market Authorization: Clinical Trials Requirements France

CA notification
- Notification to AFSSAPS can be done simultaneously with EC submission
- Submit files by email to AFSSAPS
- 60 day clock starts when AFSSAPS receives complete dossier
  - No objection: explicit approval before day 30
  - Decision on day 60, no response on day 60: study can start
  - Explicit approval needed for devices of biological origin

EU Market Authorization: Clinical Trials Requirements Spain

European law:
- MDD

Spanish law:
- Real Decreto 561
EU Market Authorization: Clinical Trials Requirements Spain

EC submission
- 1 Positive EC approval for whole country
- Different types of EC’s
  - Not all EC’s are competent to judge multicenter trials
- Need a Spanish translation of the complete protocol

CA Notification
- Simultaneous with EC submission
- Central notification (Agencia Española de Medicamentos y Productos Sanitarios)
  - Currently changing to decentralization
  - Sometimes local requirements
- CA has to come to a decision within 90 days
- The study can only start after explicit approval
EU Market Authorization: Clinical Trials Requirements Italy

**European law:**
- MDD

**Italian law:**
- D.L. vo n. 46/1997
- D.M. 02/08/2005

**EC submission**
- Submit to EC’s of all investigative site(s)
- All sites require a specific list of documents
  - Almost all EC’s require payment in advance
- After notification to CA send a copy to the EC
EU Market Authorization: Clinical Trials Requirements Italy

CA notification
- After EC approval
- Dipartimento dell’Innovazione, Direzione Generale di Farmacie Dispositivi Medici, Ufficio VI
- Send by mail with “return receipt”; date on receipt is start of 60 day clock.
  - Active and implantable devices: wait 60 days
  - Other devices: only advice to wait 60 days

EU Market Authorization: Notified Bodies

- Organisations Designated by National Governments for Independent Judgement
- Product Compliance with CE Marking Directives
- Registered with EU Commission
EU Market Authorization:
Notified Bodies

- Manufacturer to demonstrate intended purpose and claims are achieved
- Safety and Performance
- Assessment of Conformity Essential Requirements and relevant Annexes
- Notified Body: To Evaluate presented data

EU Market Authorization:
Notification to Competent Authorities

- EC Approval Letter
- Approved package as submitted to EC
- Country/regional specific Notification Form(at)
- Status 60 days waiting period
EU Market Authorization: Authorized Representative

- **Definition**

  "Any Natural or Legal Person established in the Community who, explicitly designated by the manufacturer, acts and may be addressed by Authorities and (Notified) Bodies in the community instead of the manufacturer, with regards of the latter’s obligation under the Directive”

- **Tasks**

EU Market Authorization: EU Market Entry

- **Meet Essential Requirements**
- **Follow Clinical Pathway as described in Directives**
- **Obtain CE Mark**
Where 3 countries meet
The MediTech Team

Thank you very much for your attention

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