



# HORIZONS

Think. Challenge. Excel.


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26-28 March 2008 • San Francisco

**Developing Regulatory Strategy**  
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**Regulatory Consultant**



## Developing Regulatory Strategy

- **Drugs & Biologics**
  - Long development timeframe
  - Increasing requirements
  - Differences among markets
  - Resource constraints
  - Technology transfer/testing



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## Global Regulatory Manager Responsibilities

- Leads the global regulatory team
- Identifies internal and external team members
- Establishes close working relationships with global liaisons
- Collaborates in strategic meetings with health authorities
- Delivers effective, persuasive presentations to regulatory authorities

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## Global Regulatory Manager Responsibilities

- Creates clear and concise documents regarding regulatory strategy for senior management
- Directs submission and dossier content
- Identifies and obtains necessary resources
- Defines budgets and timelines

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## Internal Global Regulatory Team

- Representatives from all disciplines involved in product development (research, marketing, medical, regulatory, manufacturing)
- Strong application and working knowledge of drug/device development process
- Sound knowledge of how to compile regulatory dossiers, clinical trial applications, agency responses
- Mastery of global regulatory processes and idiosyncrasies of various global health authorities
- Mastery of competitive climate

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## Help When you Need it- Manage the Contractors

- CROs
  - Clinical trial agreements with investigators
  - Clinical trial material distribution
  - Patient information, informed consent, translations
  - Ethics committee, IRB approvals
- Consultants
  - Assistance with scientific issues
  - Project management
  - Quality assurance
  - Compilation of submissions
  - Establishment and maintenance of regulatory files

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## Help When you Need it- Manage the Contractors

- Former health authority officials
- Attorneys
- Local representation
- Medical Advisory Board
- Scientific Advisory Board
- Marketing Advisors

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## Execution of the Global Regulatory Strategy

- Project in multiple countries
  - country-specific requirements and expectations
  - multiple regulatory deadlines - vary with country and nature of submission
- Manage with:
  - Project plan
  - Organization/designation of responsibilities
  - Systems/SOPs

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## Project Plan

- Detailed, integrated
- Identifies key activities, resources, timing
- Helps to define, implement, and control project
- Gantt charts and project management software useful
- Started early
- Communicated
- Revisited and revised as often as necessary

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## Systems/SOPs

- Internally consistent and mutually supportive
- Optimize quality and efficiency
- Systems, such as
  - Periodic status reports
  - Communication of information to and through the company
- SOPs, such as
  - Obtaining approval for conducting clinical studies
  - Preparing country-specific submissions
  - Documentation systems
  - Gathering, reporting, and communicating of adverse event information

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## Strategy Elements to be Executed and Managed

- Conduct intelligence gathering activities
- Obtain and manage documentation
- Obtain approval (as necessary) to conduct preclinical/clinical studies
- Prepare for and attend regulatory authority meetings
- Plan, prepare, and maintain regulatory submissions/correspondence
- Respond to Agency queries and deficiency letters

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## Elements to be Executed and Managed

- Manage safety reporting throughout product lifecycle
- Prepare for inspections
- Draft/review product advertising and labeling
- Address regulatory aspects of export
- Oversee post-market activities
- Manage product life cycle

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## Post-market Activities

- Compliance
- Additional Markets
- Additional Indications

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## Executing the Strategy

- Dedicated staff for monitoring and interpreting guidance
- Document management
- Internally consistent and mutually supportive systems and actions
- Electronic submissions
- Submission tracking system
- SOPs
- Leverage existing data and submissions
- Post-submission review

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## Adapting to Change

- Evolving regulations and guidance
- New submission reviewers and team members
- Requests for product modifications during the development process
- Unexpected preclinical/clinical study results
- Field issue with a similar product
- Compliance issues that affect regulatory submissions
- Decision to enter additional markets
- Media Blitz

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## Milestones

- Orphan product designation
- Fast track/accelerated review
- Approval to begin pivotal clinical study
- First subject/patient enrolled
- Completion of clinical study
- Submission of approval request
- Successful pre-approval inspection
- Approval to market
- First \$100 million in sales

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## Criteria for Success

- Approval to market in a single country
- Approval to market in several countries
- Expanded product claims or population
- Increased sales and profits

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## Approval Mechanisms

- Orphan Designation
- Fast Track/Accelerated Approval
- Generics
- Centralized procedure
- Electronic submissions
- Common Technical Document
- FDA Oncology Tools

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## Orphan Drugs

- U.S.
- EU
- Japan
- Australia
- Singapore

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## Comparative threshold for Orphan status in USA, EU, Japan and Australia

Table 7-1 Prevalence Limits for Orphan Drugs

	USA	Japan	Australia	Europe
Limit in terms of affected individuals per 100,000 of population.	75	40	11	50
Limit in terms of affected individuals for the country; i.e. maximum size of market in the country.	200,000	50,000	2,000	165,000

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## U.S. Orphan Drugs

- Orphan Drug Act – 1983
- Purpose to stimulate research, development and approval of products to treat rare diseases
- Over 200 drugs and biologics to market

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## U.S. Orphan Drugs

- Incentives
  - 7 years market exclusivity
  - Tax incentives for clinical research
  - Study design assistance OOPD
  - Open protocols
  - Grants for clinical testing

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## U.S. Orphan Drugs

- Process
  - Orphan Designation
    - New product
    - New indication old product
    - New product for designated indication
    - More than one sponsor may hold a designation for a given product/indication

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## U.S. Orphan Drugs

- Process
  - Orphan Designation
    - Rare Disease - <200,000 in U.S.
    - Product intended for diseases or conditions affecting 200,000 or more persons per year in the United States, no reasonable expectation that costs of research and development of the drug for the indication can be recovered by sales of the drug in the United States as
    - Drugs, Biologics, Vaccines, Diagnostic Drug

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## Orphan Drugs - Japanese System

- Orphan drug program in Japan since 1986, codified 1993
- Over 120 candidates, of which over 40 approved as of 2006

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## Japanese System

- Requirements :
  - A rare and serious disease affecting less than 50,000 individuals (= ~4 per 10,000)
  - No alternative product/intervention, or expectation that efficacy/safety much better than existing products
  - High probability of successful development (as assessed by MHW)

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## Japanese System

- Incentives
  - Research grant money
  - Tax incentives
  - Consultation on development
  - Possibility of fast track review
  - 10 years market exclusivity

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## EU - Orphan Medicinal Products

- Adopted 2000 (141/2000)
- Criteria:
  - 1. Indicated for a life-threatening or chronically debilitating condition with a prevalence of no more than 5 in 10,000 persons.
  - 2. Indicated for a life-threatening, seriously debilitating or serious and chronic condition, and without incentives, where insufficient return on investment will prevent marketing the product.
  - 3. When there is no existing satisfactory treatment authorised in the EU (or “significant benefit” over existing treatments)

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## EU - Orphan Medicinal Products

### Incentives:

- 10 year market exclusivity
- Scientific advice and protocol assistance free of charge
- Reduced Market authorisation fees (50%)

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## Orphan Medicinal Products

- Application for orphan status at any time before MA application submitted
- May request orphan indication (new) for currently authorised product - new MA will be required
- Multiple companies may apply for and obtain orphan status for same product in same indication
- Orphan products must use centralised procedure

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## Orphan Medicinal Products 2000-2005

- 458 submissions to COMP- 268 drugs designated
- 22 OD approved
  - 20 through centralised procedure
  - 2 through de-centralised
- 80 protocol assistance procedures conducted

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## Orphan Products

- The number of rare diseases is around 5 000 to 8000
- The number patients suffering from rare diseases is of 24 to 30 Millions in Europe similar number in the USA although the incidence and prevalence may differ between Europe and the USA
- The US and Europe procedures for Orphan designation are similar

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## Orphan Products

- Time to Market could be very significantly reduced through Orphan drug designation in the US and Europe (20 months on average between OD designation and MA)
- Patient population could be small but market can be very attractive e.g Gaucher disease, Fabri, Haemophilia, Oncology, EPO, growth hormone....

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## PATIENT ASSOCIATIONS USA & EU

Patient Associations are playing a key role in the success of the Orphan Drug Act in USA and EU

NORD in the USA and EURORDIS in EUROPE

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## ACCELERATED APPROVAL

- Risk vs Benefit is always a consideration
- Randomized, placebo-controlled trials are optimum – especially when numbers are large
- AIDS crisis prompted a motion to develop alternate strategies – resulting in the implementation of new programs designed to expedite the entry of new therapies.
- Additional programs added in the 90's

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## ACCELERATED APPROVAL MECHANISMS

- ◆ Fast Track (FDAMA – 1997)
- ◆ Accelerated Approval
- ◆ Parallel Track
- ◆ Treatment IND
- ◆ Oncology Initiative
- ◆ Priority Review

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## Accelerating US Approval

- Fast-track Designation
  - For Drugs to Treat ‘Serious Conditions’
  - Surrogate Endpoint That Is “Reasonably Likely” to Predict Clinical Benefit
  - Rolling Review of Submission
- Accelerated Development
  - Proceed Directly From a Phase 1 Trial to One Phase 2 Pivotal Trial to Support Product Approval
  - Post-marketing Studies Required

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## Accelerating US Approval

- Priority Review
  - Assigned to a Product Based on an Estimate of Therapeutic, Preventive or Diagnostic Value
  - Submission Review of 180 Days Compared With Standard 300 Days

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## ACCELERATED APPROVAL

*The Oncology Initiative*

- Designed to reduce development by a year and review to 6 months :
  1. Accelerated Approval for cancer drugs
  2. Greater access to non-US drugs
  3. Patient representation at Advisory Committees
  4. Clarification of the Policy for Studies of Marketed Cancer Drugs

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## Accelerating EU registration

- EU maximum timeframe for evaluation Marketing Authorisation Application under Centralised Procedure is 210 days
- In exceptional cases, an accelerated evaluation might be initiated for major public health need:
  - Seriousness of the disease
  - Absence of alternative therapy
  - Anticipated high therapeutic benefit

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## Accelerating EU registration

- Conditional approval is part of the European Pharmaceutical Legislation (2004/27/EC) applicable November 2005:
  - Rolling approval (like the US)
  - Post-approval commitments(Phase II or IV)
  - Authorization will be reviewed every year

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## HYPOTHETICAL

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## Developing Regulatory Strategy

William F. Greenrose  
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## Developing Regulatory Strategy

- DEVICES
- Think Globally
  - Can Save Time and Resources
  - Major markets are moving to harmonization
  - Stay competitive

BUT....



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## Developing Regulatory Strategy

- Global Harmonization does not mean identical processes or documentation
- Some requirements are the same
  - e.g. Documented Quality System
- But virtually all markets have unique requirements
  - e.g. US Predicate Device
  - EU Clinical Information

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## Developing Regulatory Strategy

- Just because terminology is similar does not mean strategies are also similar
  - e.g. EU Class I, IIa, IIb, III virtually the same as Canadian I, II, III, IV
  - BUT, very different from FDA Class I, II, III
  - US Class III and EU Class III mean very different things!

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## Developing Regulatory Strategy

- It is possible to develop parallel submission/device approval strategies for various local markets.
- Just be aware of the sometimes subtle differences

**ASSUME NOTHING!**

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## Developing Regulatory Strategy

- Hip Implants
  - US: From Class III to Class II
  - EU: From Class IIb to Class III
- Anti-Snoring Throat Spray
  - EU: Class IIa
  - US: New Drug

**Do Your Homework!**

Small effort up front saves major headaches later

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## Developing Regulatory Strategy

- In the end it is a business decision
- All business decisions involve conflict between short-term and long-term goals
- Multi-Market Regulatory Strategy
  - Short Term: Increased Costs
  - Long Term: Increased Revenue
- “There are infinite ideas but finite resources” – Bill Greenrose

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## Developing Regulatory Strategy

- If you embark on a multi-local market regulatory project be sure to:
  - Protect IP
  - Be sensitive to language issues within and without the organization
  - Understand Resource Costs
    - Money
    - Time
    - People

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## Developing Regulatory Strategy

- Intellectual Property
  - US patent is not global
  - All markets are not created equal
    - Patent integrity is interpreted differently around the world
    - Applies to:
      - End product distribution
      - Manufacturing
  - Can you ensure security/integrity/quality?

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## Developing Regulatory Strategy

- Language
  - “I’m sorry, but what you heard was not what I said.”
  - Not everyone who speaks English is fluent
    - A head bob does not necessarily mean “I understand”
  - Applies both externally and internally
  - Keep It Simple, Simon (KISS Principle)
  - Write it down

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## Developing Regulatory Strategy

- Resource Costs
  - Compare apples to apples or you end up with fruit salad.
    - Currency differences
    - ROI differences
  - People/cultural/time zone differences
  - TIME: the most fleeting of resources
    - All workdays are not created equal

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## Developing Regulatory Strategy

- Time
- Time assumptions can be deceiving
  - e.g. “Regulatory approval time is quicker for devices in Europe than in the US.”
    - Depends on the Class
      - US Class III it is probably true
        - » IDE
        - » PMA review
        - » Site Inspection

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## Developing Regulatory Strategy

- Time, continued
  - US Class II

### US

- Write 510(k)
- Submit
- Respond
- Clearance

### EU

- Write Technical File
- Submit
- Respond
- Schedule Site Audit
- Respond
- Certification

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## Developing Regulatory Strategy

- Time, continued
  - Quality System Development

### US

- Comply with 21 CFR 820

### EU

- Select Annex (Annex II)
- Comply with ISO 13485
- Schedule Site Audit
- Respond
- Certification

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## Developing Regulatory Strategy

- Steps
  - Identify Markets
  - Determine Resource Needs
  - Get Senior Management Buy In
  - Create Team
    - Make it a team and not a herd of cats
  - Standardize where appropriate e.g. STED

THINK PROJECT MANAGEMENT

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## Developing Regulatory Strategy

- Steps, continued
  - COMMUNICATE REGULARLY
    - When dealing with regulatory entities
      - NEVER ask an open-ended question
      - Propose a solution and provide the logic
    - Authorities want to know that YOU know what you're doing
  - Keep Management in the loop
  - Keep Team in the loop

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## Developing Regulatory Strategy

- Establish realistic milestones
  - Obtaining 510(k) clearance one month post submission is NOT a realistic milestone
  - May need to cross swords with PTB (Powers That Be)
- Follow established procedures and....
- Document everything
- Obtain Market Approval(s)
- Celebrate

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## Developing Regulatory Strategy

- Post-Approval
  - Besides the regulatory requirements (e.g. Post Market Surveillance)
  - Have a debriefing meeting
    - What went right
    - What went wrong
  - Learn from mistakes (or be doomed to repeat)
  - Thank the participants
    - You will probably need their help again

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## Developing Regulatory Strategy

- In conclusion
  - Thinking globally can save time and money
    - But be aware of the challenges/differences
  - Do your homework
  - Think project management
  - Utilize all your available resources
  - Keep the lines of communication open
  - Work with people, not against them
  - Learn from the process

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## Developing Regulatory Strategy

# THANK YOU!

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