



# HORIZONS

Think. Challenge. Excel.

**2008 RAPS HORIZONS CONFERENCE & EXHIBITION**  
26-28 March 2008 • San Francisco • The Fairmont

## Post-approval Considerations for Drugs & Biologics (US & EU Perspective)

**Shamim Ruff: Executive Director, Global Regulatory Affairs; Amgen**  
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## Learning Objectives: To Enable Regulatory Professionals to:

- Expand regulatory perspective to include post-approval lifecycle management activities
- Develop and present the strategies needed to ensure regulatory compliance and improve risk management



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## The Times They Are a Changin'

The line it is drawn  
 The curse it is cast  
 The slow one now  
 Will later be fast

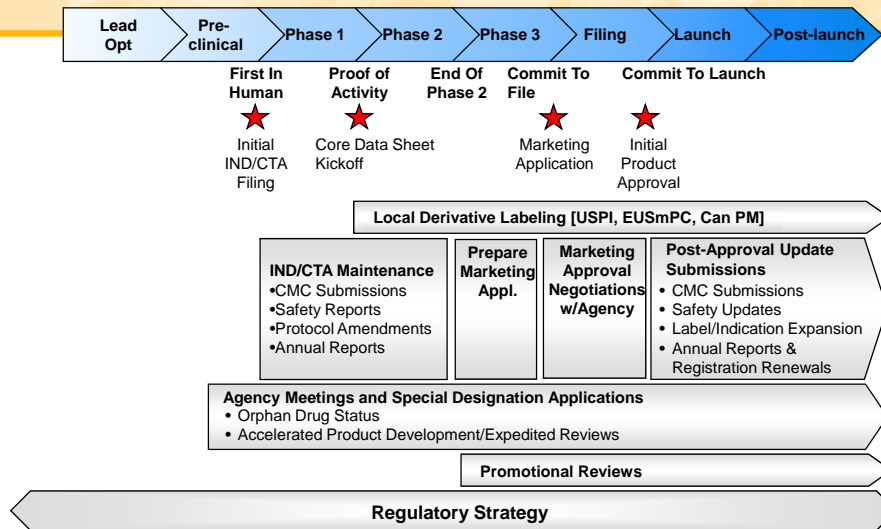
As the present now  
 Will later be past  
 The order is  
 Rapidly fadin'

And the first one now  
 Will later be last  
 For the times they are a-changin'

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## Traditional Regulatory Affairs Activities within Commercialization

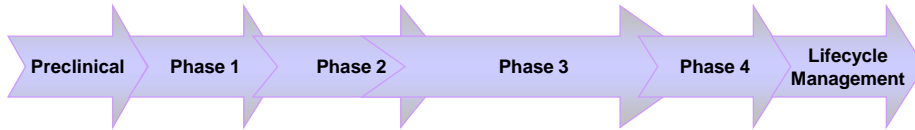


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## Product Development: Traditional Approach vs. New Paradigm

### Traditional Approach:



### New Paradigm: **It doesn't end with approval**



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## Begin With the End in Mind



Timeline: Five to Ten Years

- Robust target product profile → Focused product development programs
- Increased focus on clinical benefit and outcomes endpoints
- Strong supporting data/analysis → best position to support optimal labeling & Pricing
- Optimal labeling → best position for product in the market
- Greater cross functional working in planning for Post Marketing Commitments and communications at launch with commercial function
- Best position in the marketplace → commercial success & reaching the optimal patients who will benefit

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## Commercialization In Today's Market Place

- Responsibilities to Health Authorities
  - Conditional Approvals
  - Pharmacovigilance
  - Risk Management/Risk Maps/Controlled distribution
  - PLR Label Conversion
  - Regulatory Compliance
  - Non Traditional Health Authorities
- Responsibilities to Our Patients
  - Pediatrics
  - Life Cycle
  - Expanded Access/Compassionate Use

**Approval Is Just the beginning**

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## Responsibilities to Health Authorities Conditional Approvals

When is an approval not an Approval?

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## Accelerated Approval Models in US

- FDA Accelerated Approval Process
  - Subpart H
    - Serious or life-threatening disease
    - Improvement over available therapies
    - Surrogate endpoint reasonably likely to predict clinical benefit
    - Confirmation of clinical benefit required to maintain approval

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## Accelerated Approval Model in US: Iressa

- **Case Study**
- **Iressa (giffitinib) AA granted in 2003 - AstraZeneca**
- **Indication: use as single agent in third line NSCLC**
  - IRESSA is indicated as monotherapy for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of both platinum-based and docetaxel chemotherapies
- **Accelerated Approval based on P2 studies and surrogate endpoint of ORR**
- **Post marketing confirmatory studies for evidence of clinical benefit:**
  - P3 studies in both refractory disease and 1<sup>st</sup> Line in combination with chemotherapy
  - Defined timelines for SPA and FPE
  - Primary endpoints of clinical benefit
- **2005: confirmatory studies did not demonstrate an increase in OS**
- **Limit distribution of drug under a risk management plan (Iressa Access Program) to:**
  - Patients currently receiving and benefiting from Iressa;
  - Patients who have previously received and benefited from Iressa
  - Previously enrolled patients or new patients in non-IND clinical trials approved by an IRB prior to June 17, 2005

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## Conditional Marketing Authorization Commission Regulation (EC) 507/2006 Finalized, 29 March 2006

- **Introduces a legal basis for conditional marketing authorization for medicinal products for human use**
- **Concept: Early access to 'promising' medicines for patients**
  - Orphan drugs, emergency threats, serious, chronic, life-threatening, unmet need
- **Mechanism Concessions:**
  - None in terms of Pharmaceutical or Non-clinical data except for medicines for emergency use
  - Limited clinical evidence availability permitted
    - 'Incomplete clinical data package'
- **Eligibility: (EMA Scientific advice available)**
  - Drugs intended to treat life threatening conditions;
  - Drugs intended for emergency situations;
  - Orphan drugs
- **Eligibility Assessment made at granting of opinion**
  - **Positive risk benefit balance** (EMA assessment of risk exposure from permitting access to the product with incomplete data)
  - **Ability to complete data package**
  - **Unmet need** (advantage over existing treatment or first treatment available)

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## Conditional Marketing Authorization A new filing mechanism in Europe

- **Obligations:**
  - **Complete the limited data package** (otherwise Exceptional Circumstance mechanism) within a defined/agreed timeframe to confirm the positive risk benefit assessment
  - **Additional Pharmacovigilance** requirements
  - **Annual Benefit/Risk assessment**
  - **Annual Renewal** (6m prior to expiry) inc. progress update to completing data package
  - **Transparency**
    - Commitments will be publicly available
    - Use of mechanism will be reflected in the labelling
  - Once complete CMA converts approval to a 'full approval'

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## Conditional Marketing Authorization A new filing mechanism in Europe

- **Case Study:**
- First product gained a positive opinion  
April 2006 - Sutent (Sunitinib malate)- Pfizer
- **Indication:** GIST & Renal cell carcinoma
- 'for the treatment of unresectable and/or metastatic malignant gastrointestinal stromal tumours (**GIST**) after failure of imatinib mesylate treatment due to resistance or intolerance, and advanced and/or metastatic renal cell carcinoma (**MRCC**) after failure of interferon alfa or interleukin-2 therapy'
- **Post authorization commitments:** 'further evidence related to the product's effect in terms of progression-free survival in patients with MRCC, for which a study is being conducted. The European Medicines Agency will review new information within one year and update the product information as necessary'



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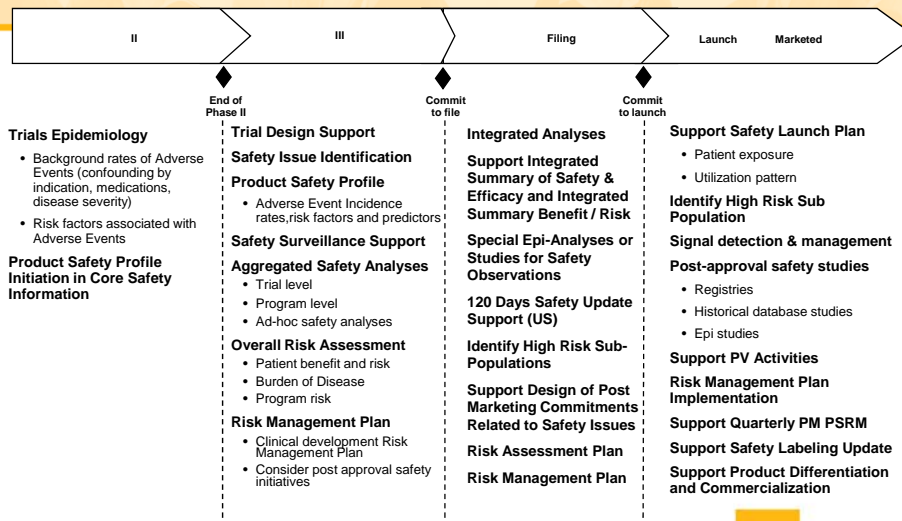
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  - **Pharmacovigilance**
  - **Risk Management/Risk Maps/Controlled distribution**
  - PLR Label Conversion
  - Regulatory Compliance
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## Safety Epidemiology Across Product Lifecycle



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## FDAAA: Enhanced Authorities Regarding Post-Market Safety of Drugs

### Postmarket Studies and Surveillance:

- Sponsors may be required to conduct a post-approval study/trial of the drug, on the basis of scientific data deemed appropriate by Secretary, including information regarding chemically-related or pharmacologically-related drugs
- Assess a known serious risk
  - Assess signals of serious risk
  - To identify an unexpected serious risk when available data indicates the potential for a serious risk
- Sponsor required to submit a timetable for completion of the study and periodically report to the Secretary on the status of the study
- Sponsor in violation if unmet timeline and other mandatory PMC-related provisions
  - Such failure may result in the sponsor incurring substantial CMPs. Dispute Resolution as established in regulation/guidance

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## Enhanced Authorities Regarding Post-Market Safety of Drugs

### Risk Evaluation and Mitigation Strategy (REMS):

- **Prior to approval:** REMS required if it is “necessary to ensure that the benefits of the drug involved outweigh the risks”
- **Post approval:** REMS may be required (including when acting on a supplemental application seeking approval for a new indication for use) “if the Agency becomes aware of ‘new safety information’ and determines that it is necessary to ensure that benefits outweigh risks”.
- **Timetable for submission of assessments of the REMS:**
  - Assessment by the date that is 18 months after strategy initially approved.
  - By the date that is 3 years after approved
  - By the date that is 7 years after approved

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## Enhanced Authorities Regarding Post-Market Safety of Drugs: REMS

- Additional Potential Elements –
  - MedGuide; Patient Package Insert; Informed Consent
  - Communication plan to healthcare providers & patients
  - Elements to Assure Safe Use (i.e. Restrictions on distribution or use)
  - Implementation system - Sponsor to take reasonable steps to:
    - Monitor and evaluate implementation by healthcare providers, pharmacists and other parties in the healthcare system and
    - Work to improve implementation of such elements by such persons

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## Enhanced Authorities Regarding Post-Market Safety of Drugs

- Overall, new regulatory burden on products pre- and post-approval
- FDA could impose REMS on a drug at any point in lifecycle based on new safety information. Agency may act retrospectively on any approved product
- New Authorities for Agency which may exercise at any time
- Abbreviated timelines for review/negotiation
- Highlights importance of Benefit : Risk data and communication
- If restrictions imposed, will require Sponsors to monitor its wholesalers, providers and others

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## Risk Management Is an Iterative Process with Clear Objectives

- Assess a product's benefit-risk profile
- Develop and implement tools to maintain or enhance benefit-risk profile
- Evaluate tool effectiveness and reassess the benefit-risk profile
- Adjust available tools to further improve the benefit-risk balance

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## Risk Minimization Action Plan (RiskMAP) is a Strategic Program for Overall Risk Minimization

### • Routine PV Tools • RiskMAP Tools

Similar

Unique

- |   |  |
|---|--|
| <ul style="list-style-type: none"> <li>–Product Label</li> <li>–Education</li> <li>–Adverse event reporting and monitoring</li> </ul> | <ul style="list-style-type: none"> <li>–Product Label</li> <li>–Education</li> <li>–Adverse event reporting and monitoring</li> </ul>                  |
| <ul style="list-style-type: none"> <li>–Post-marketing surveillance</li> </ul>  | <ul style="list-style-type: none"> <li>–Targeted surveillance</li> <li>–Reminder systems (Informed consent)</li> <li>–PLAS (Restricted Use)</li> </ul> |

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## Cialis (Tadalafil)\*

- A phosphodiesterase type 5 (PDE5) inhibitor for the treatment of male erectile dysfunction approved in November 2003.
- RMP to decrease the concomitant use of tadalafil with nitrates
- The RMP includes:
  - labeling
  - a call center
  - postmarketing surveillance studies
- ODS also recommended the following actions:
  - Dr Health Care Professional letter at the time of product launch emphasizing specific safety aspects of the product
  - Commitment to conduct a US observational cohort study to determine the level of co-prescribing with contraindicated drugs, and
  - Revision of the sponsor's educational materials to include relevant labeling issues
    - Annual review to assess whether the objectives of the educational program are being met

\*Center for Drug Evaluation and Research  
Food and Drug Administration  
Office of Drug Safety Annual Report FY 2003

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## US Labeling Format & Content Requirements Revised Regulations & Guidances

- **21 CFR 201.56 and 201.57**
  - New revisions issued January 24, 2006
  - Effective June 30, 2006
  - “Physician Labeling Rule (PLR)”
- **Associated Guidance**
  - Final
    - Adverse Reactions Section of Labeling
    - Clinical Studies Section of Labeling
  - Draft
    - Implementing the New Content & Formatting Requirements
    - Warnings & Precautions, Contraindications, Boxed Warning Sections of Labeling
    - Dosage & Administration Section of Labeling
  - Additional labeling guidance's expected

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## Purpose of New Labeling

- **Improve the quality of information**
  - More objective presentation of facts
  - Include sources of information
  - Identify new information
- **Make it easier to find critical information**
  - Summary
  - Outline
- **Assist the health care professional in**
  - Evaluating the drug
  - Understanding the pros and cons of its use
  - Informing the patient of benefits and risks
- **Decrease drug related errors due to misunderstanding of information**
- **Facilitate implementation of electronic labeling initiatives**

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## First Approved PLR Conversion Label: Oncaspar®

- Approved by Oncology Review Division in July 2006
- Based on approval of a new indication for an existing product

### HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to prescribe Oncaspar® safely and effectively. See full prescribing information for Oncaspar®.

Oncaspar® (*pegaspargase*)  
Intravenous or Intramuscular Injection  
Initial U.S. Approval: 1994

### RECENT MAJOR CHANGES

Indications and Usage, 07/2006  
First line acute lymphoblastic leukemia (ALL) (1.1)  
Contraindications, 07/2006  
History of serious thrombosis with prior L-asparaginase therapy (4)

### INDICATIONS AND USAGE

Oncaspar® is indicated as a component of a multi-agent chemotherapeutic regimen for treatment of patients with:

- First line acute lymphoblastic leukemia (1.1)
- Acute lymphoblastic leukemia and hypersensitivity to asparaginase (1.2)

### DOSAGE AND ADMINISTRATION

- 2,500 IU/m<sup>2</sup> intramuscularly (IM) or intravenously (IV) no more frequently than every 14 days. (2.1)
- For IM administration, limit the volume at a single injection site to 2 mL; if greater than 2 mL, use multiple injection sites. (2.2)
- For IV administration, give over a period of 1 to 2 hours in 100 mL of sodium chloride or dextrose injection 5%, through an infusion that is already running. (2.2)
- Do not administer Oncaspar® if drug has been frozen, stored at room temperature for more than 48 hours, or shaken or vigorously agitated. (2.3)

### DOSAGE FORMS AND STRENGTHS

- 3,750 IU/5 mL single-use vial. (3)

### CONTRAINDICATIONS

- History of serious allergic reactions to Oncaspar® (4)
- History of serious thrombosis with prior L-asparaginase therapy (4)
- History of pancreatitis with prior L-asparaginase therapy (4)
- History of serious hemorrhagic events with prior L-asparaginase therapy (4)

### WARNINGS AND PRECAUTIONS

- If the following occur - discontinue Oncaspar:  
Anaphylaxis or serious allergic reactions (5.1)  
Thrombosis (5.2)  
Pancreatitis (5.3)
- Glucose intolerance, in some cases irreversible, can occur (5.4)
- Coagulopathy can occur. Perform appropriate monitoring. (5.5)

### ADVERSE REACTIONS

Most common adverse reactions (≥2%) are allergic reactions (including anaphylaxis), central nervous system (CNS) thrombosis, coagulopathy, elevated transaminases, hyperbilirubinemia, hyperglycemia, and pancreatitis. (6)

To report SUSPECTED ADVERSE REACTIONS, contact ENZON PHARMACEUTICALS, INC at 1-800-836-4301 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 7/2006

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## First Approved PLR Conversion: Oncaspar®

- Existing Indication narrowed
- Pediatric specific D & A information removed
- New spotlight on known (but “hidden”) safety information
  - Old label: Recommended lab tests under precautions
  - New label: now presented as stand alone Warning
- Comparator safety information permitted; however, adverse reactions in comparator study were pre-identified
- “Off label” maintenance regimen information moved from efficacy to safety sections
  - Old label: duration of maintenance therapy presented in “clinical activity” section (no efficacy presented)
  - New label: duration of maintenance therapy presented in “Adverse Reaction” section
- Previous extensive drug interaction section removed
  - Based on theoretical concerns only?

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## Responsibilities to Health Authorities: Regulatory Compliance

- Traditional Post Approval Regulatory Activities
  - Post Marketing Commitments
  - Site Inspections
  - Advertising & Promotional activities
  - License Maintenance
- Increasing complexity
  - Global manufacturing
  - Internet based advertising
- Increased Enforcement
  - Increased transparency to public
  - PMC status postings

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## Responsibilities to Health Authorities: Non Traditional Regulatory Agencies

- “New” regulatory bodies
  - e.g. NICE; CMS; Private Payers (eg. BCBS, AETNA etc)
  - Third-party payer involvement in market entry “beyond” safety, efficacy, and quality
- Regulatory agencies and payers controlling access to products on a global level are converging
  - Increased cost containment & budgetary controls
  - Increased price controls, greater transparency; reference pricing
  - Greater reliance on Health Technology Assessments
- Regulatory needs to be an integral team member
  - Incorporate Reimbursement needs in regulatory strategy

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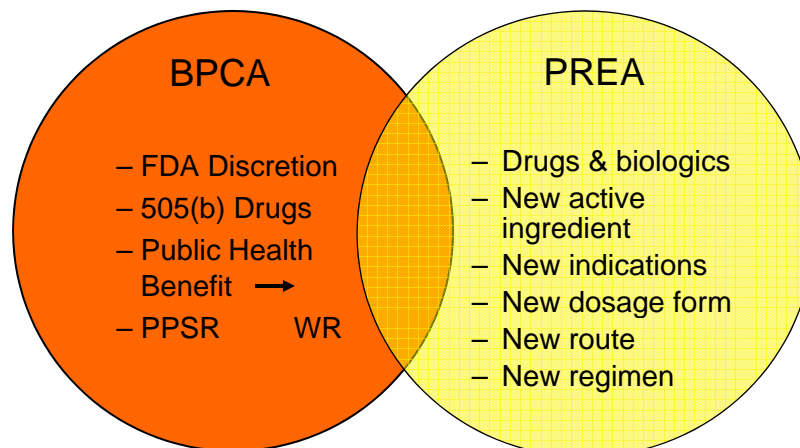
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## Responsibilities to our patients: Pediatrics



**2 Statues - Different Scope**

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## Pediatric Drug Development: US 2 Statues - Different Scope

### BPCA

- **Earn Exclusivity**
- Discretionary
- Any use(s)
- 505(b)(1) Drugs only
- Drugs with market protection
- Triggered by sponsor PPSR

### PREA

- **Doesn't Earn Exclusivity** (*usually*)
- Mandatory
- Only sought ( or app'd) indications
- Drugs & biologics
- Multiple use
- Protected & unprotected
- Automatically triggered by certain actions

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## “Simon Says” vs. “Mother May I”

- Effective use of BPCA pediatric exclusivity for Life Cycle Management
  - Understand studies required to support PREA
  - Evaluate the possibility for additional uses in children
- FDA will reserve written requests to encourage studies of uses in children not covered by PREA
- Begin planning pediatric strategy early in development
- Discuss pediatric plan with FDA at EOP2

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## EU Pediatric Regulation

- Legislative process was initiated in 2000, and came into effect in January 2007
- Aim of regulation is to improve the health of Europe's children by increasing research, development and authorization of medicines for use in children
- >50% of medicines used in children in the EU have not been tested or authorized for use in children
- Regulation will bring both opportunities and liabilities for industry, however there is little clarity as yet on specific impact

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## Opportunities, Liabilities

### • Opportunities

- 6 months additional patent protection (for drugs still protected by patent) if compliance with Pediatric Investigation Plan (PIP) is demonstrated
- Additional incentives for non-patent protected drugs (thought to be difficult to implement) and orphan drugs

### • Liabilities

- New MAA or line extension application must comply with agreed PIP or considered invalid
- Must either have data, waiver, or deferral at time of filing
- PIP/waiver/deferral must cover all subsets of pediatric population (includes indications not sought in adults?)
- For line extensions – must cover indications already approved

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## Pediatric Committee and PIP

### PC

- Formed 6 months after legislation published
- Assess PIPs, waiver/deferral requests
- Assess compliance of eventual submission with PIP

### PIP

- Contains proposed development plan or waiver/deferral request
- Submitted when adult PK studies completed
- Review process – 4-7 months (depending on clock stop)

### Issues

- Bureaucracy, transparency, length of review process?

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## Similarities/Differences EU vs US?

Similar?	Different?
Significant incentives (6 months additional patent protection) available for compliance with FDA/EMEA request	EU – Requirement for pediatric plan to be submitted and agreed at defined stage of development
Opportunity to obtain product waiver, class waiver or deferral (EU industry view/expectation is that deferrals will be easily obtained in early years)	EU – requirement for PIP to contain development plan, or waiver/deferral request, for pediatric indications not being sought in adults (not a requirement in US, though company can choose to study indications not being sought in adults in order to benefit from incentives through “written request”)
Data doesn't need to support a paediatric indication in order to qualify for incentive (as long as studies are conducted in line with agreement)	<b>How will any differences between views of FDA and EMEA be addressed without 1) requiring unnecessary duplication of studies 2) without delay to program?</b>

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## Responsibilities to our patients; Life Cycle Management

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## Commercialization In Today's Market Place

- Formulation & Process Development
  - Exclusivity
  - Enhanced patent protection
  - Patent Expiry
  - Increased Compliance
  - Increased convenience
  - Reduce Safety Risk
- New Indications
  - Label Expansion within the same broad indication
    - Statins
  - Label extension into MOA related Indications
    - TNF's

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## Responsibilities to our patients Expanded Access/Compassionate Use

- Not a typical post approval activity
  - Lottery approach for products with manufacturing constraints
- Incorporate into strategic regulatory plans

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## The Regulatory Landscape Is Evolving

- Environment is influenced by several factors, including:
  - Industry reputation—big pharma not trusted
  - Reputation of regulatory agencies
- This has resulted in a regulatory environment that is:
  - Risk averse
  - Higher hurdles in demonstrating benefits
  - Greater focus on benefit:risk
  - Approvals increasingly influenced by cost concerns

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## It's No Longer All About Drug Approval

- Increased scrutiny on drug safety in all phases of development and postapproval
- Marketing authorization (approval) is part of the step
  - Higher development cost
  - Postmarketing commitments extend duration of investment
  - Evolving towards approval based on effectiveness, not only efficacy

External Environment:  
Globally Progressively Restrictive

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