ARNOLD & PORTER (UK) LLP

Deal Making and Product Development in Europe: Changes and Trends You Need to Know About: Regulatory Strategy

Lincoln Tsang
Amanda Wearing
Jeremy Willcocks

November 19, 2004

Key Issues

- Coupling of good science and understanding of regulatory environment is important
  - Defining key milestones in product development
  - Shaping the regulatory strategy for timeliness of commercial launch of a product
- Post-approval product life-cycle management to optimize wider IP issues including data exclusivity and market exclusivity
- Regulatory landscape across the world continues to evolve
  - Convergent regulatory standard (policy) for product assessment
  - For approval of clinical trials and marketing authorization

EU-US Information Sharing Agreement

- Regular cycle of EU-FDA bilateral meetings has been ongoing since 1989
- 12 September 2003 agreement signed between US FDA and the EU for greater co-operation between the two authorities
- Heralded as important milestone in the sphere of global pharmaceutical development
- Agreement not intended to create any legal obligations under international or other law on the USA and the EU

Scope

- Initially run for 2 years and review the effectiveness at least annually
- Arrangement to be implemented stepwise according to priority
- Applies only to pharmaceuticals, including biological products and orphan drugs for human and veterinary use
- Devices and nutritional products are excluded

Impact on the Product Life Cycle

- Pre-approval and post-approval regulatory activities
- Pending legislative proposals
- Transfer of information between the two authorities

Pre-approval and Post-approval

- Exchange information relating to evaluations of marketing applications and post-marketing surveillance
  - scientific advice
  - orphan drug designations
  - inspections reports (quality defects, product recalls and good manufacturing and clinical practice reports)
  - approvals
  - post-approval pharmacovigilance
- Reinforcing ongoing co-operation between FDA and EMEA

Intended Effects

- Accelerated access of patients to new and innovative medicines
- Savings in resources to reduce duplication of assessment
- Improve performance and safety by mobilizing the best regulatory expertise from both sides of the Atlantic

October 2004 Announcement

- Implementation of agreement
- Pilot program for companies to obtain “parallel advice” from two agencies for
  - novel breakthrough drugs not covered by existing guidelines (or divergent views between FDA and EMEA in the guidelines)
  - orphan drugs and pediatric indications
- Platform to exchange views in the beginning of the life cycle
- Voluntary and at the request of a sponsor- milestone meetings

Current EU regulatory position - Pediatric Studies

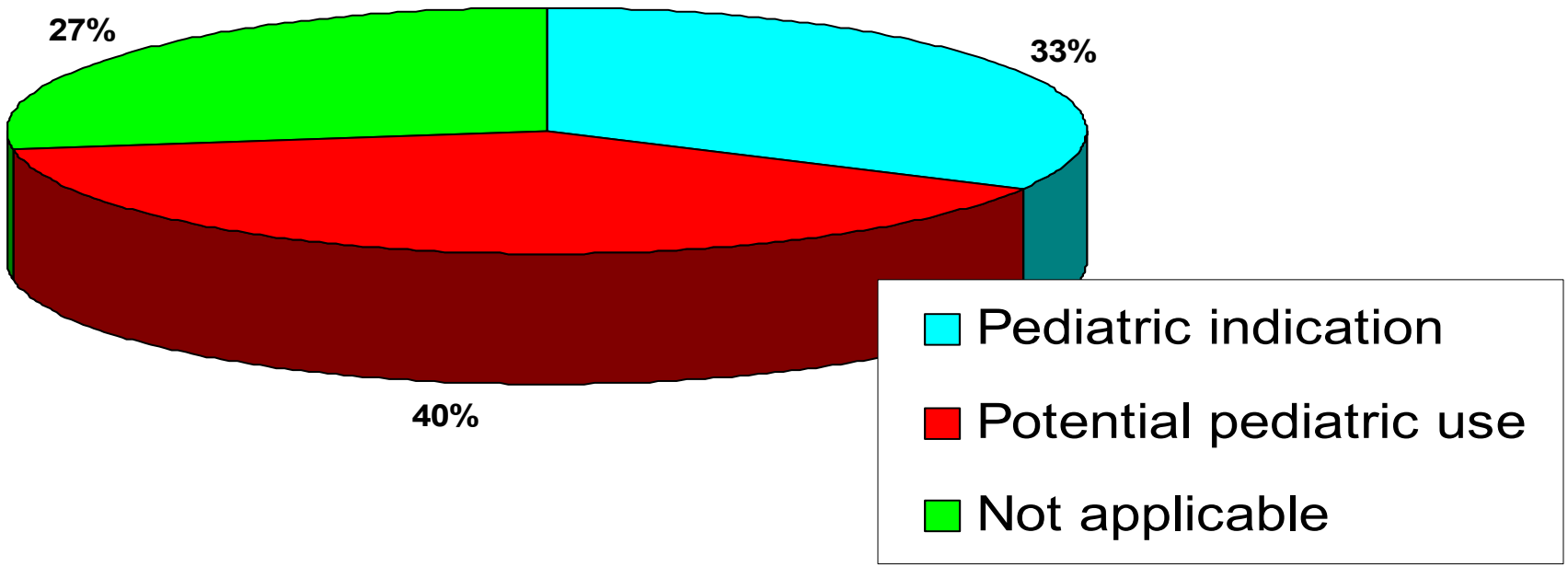
- No regulatory requirement to
  - study use of product in particular patient groups or indications
  - apply for a license in patient groups or indications outside target patient population or indications
- No regulatory incentive for pediatric product development

Current EU regulatory position

- ICH guideline on development of medicines for children (1999)
  - Pediatric patients should be given medicines that have been appropriately evaluated (and formulated) for their use
  - Drug development plans should include the pediatric patient population when anticipate product use in under 18s

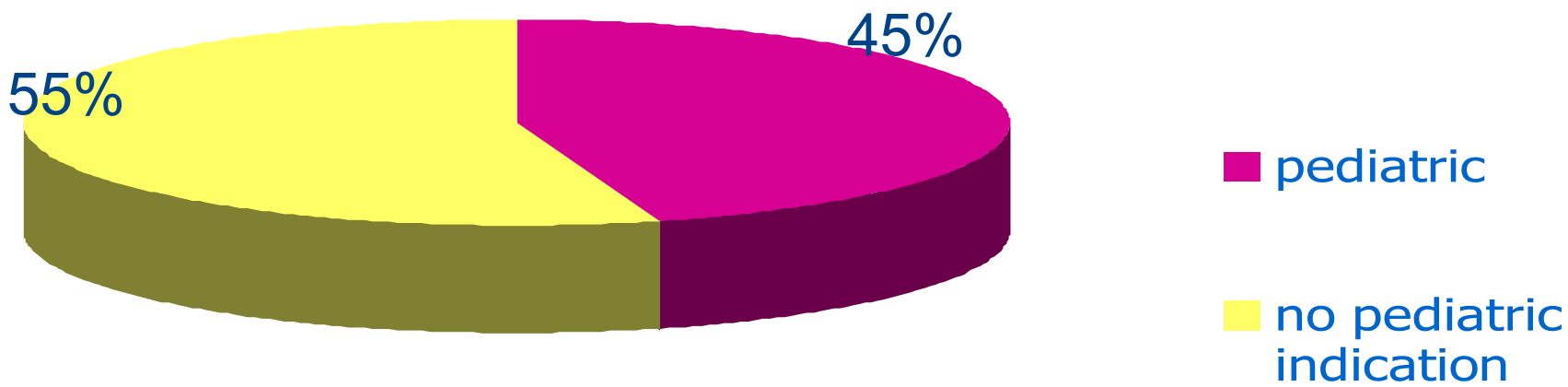
Experience with the centralized procedure Approval for Pediatric Use

Total number of approved substances: 210 (April 2004)



Experience with the centralized procedure Approval for Pediatric Use

Total number of approved substances with potential pediatric use: 152 (April 2004)



Pediatric Rules - History of Proposal

December 1997	Expert meeting of EMEA and Commission
July 1998	Report of experts' meeting proposes legislation and initiatives
December 2000	Council of Ministers Resolution calls for Commission to act
November 2001	Commission announce public consultation and proposal mid-2002
February 2002	Consultation launched
July 2003	Informal drafts of two Regulations
March 2004	Final Proposal in one Regulation
October 2004	Revised Proposal

EU Legislative Proposal: Pediatric Use

- Proposed Regulation released for public consultation in March 2004
- Revised text published in October 2004
- New regulatory requirements and incentives for development of pediatric medicines

Objectives of Proposal

- Improving health of children
  - increasing availability of pediatric medicines
  - increase high quality research that follows the guiding ethical principles
  - improving information on medicines for pediatric use
  - specific post-authorization product monitoring for efficacy and safety

Proposed Regulation - Framework

- New products
  - obligation to provide pediatric data based on Pediatric Investigation Plan (PIP) in return for extension of SPC
- Orphan medicinal product
  - conduct of studies according to PIP leading to SmPC wording regarding data on use in children fully met reflective of the study results
  - extension to 12 years market exclusivity
- Existing products
  - right to seek Pediatric Use MA based on PIP and in return data exclusivity
  - obligation to supply existing relevant data
- New advisory body
  - Pediatric Board (PB)

Definitions

- Pediatric population includes 0-18 years of age, but will be sub-divided following implementation
- Pediatric Investigation Plan relates to research & development to generate data to support use in target population. Can be subject to modifications
- Pediatric Use Marketing Authorization granted under centralized or decentralized procedures covering only indications relevant to pediatric populations

Pediatric Board

- PB - new expert committee of EMEA
- Representation from CHMP, member states, pediatricians and patient groups with Commission/EMEA attendees
- Consider and provide opinion to EMA on the Pediatric Investigation Plan
- Consider whether proposed studies can be expected to be of “significant therapeutic benefit” to pediatric population
- competent authorities may ask PB to assess compliance with P.I.P. and/or consider safety, quality, efficacy implications of data

Existing Products - Existing Information

- Research incentives exclude pediatric studies completed before the date of entry into force outside EU
- Submit results to competent authority within 1 year of entry into force of Reg for update to SmPC and leaflet
- But some CAs treat Annex 1 as requiring this now
  - Para 11 of Introduction: “any new information … and all pharmacovigilance information ” to be submitted to monitor b/r assessment;
  - Para 7 requires completed trials for indications not covered by application

Existing Products - "PUMA" - Pediatric use MA

- Authorized product may be developed for pediatric use
- Application in accordance with Article 8.3 of Directive 2001/83 with data from agreed P.I.P.
- Authorization for pediatric use indications only
- Can apply centrally or nationally (MR)
- Same trade name with "P" superscript
- 10 years' protection

Pediatric Investigation Plan (PIP)

- PB assesses whether:

  "the proposed studies will … ensure the generation of data on the expected and practical use of the product" and whether "the expected therapeutic benefits do not justify the studies proposed"
- Positive Opinion leads to Letter of Acceptance from EMA and obligation to conduct according to PIP
- PB may also give Opinion on whether completed study complies
- Negative Opinion may be "appealed"
- Re-examination of opinion

New Products - New obligations for pediatric data

- Unless waiver or deferral granted, requirement to include results of studies from agreed P.I.P. in:
  - application for MA for new active substance (not approved when Regulation enters in force)
  - application for new indications, pharmaceutical forms, routes of administration for authorized product covered by patent or SPC
- Defining new active substance, indications, pharmaceutical forms etc
- Does not apply to products approved under Article 10 or 10a i.e. generics/biogenerics or "well-established use" exemption

Waivers

- Apply to requirement for pediatric data in first place, or after submission of P.I.P.
- Class (or part-class) or particular product advance where
  - product(s) likely to be “ineffective or unsafe” in pop
  - “disease or condition” for which product indicated exists only in adults
- Post-consideration waiver where:
  - as above, or
  - product does not represent “significant therapeutic benefit over existing treatments”
- Specific waiver
  - applicant may apply; PB has 60 days to give opinion, subject to “re-examination”

Deferrals

- Applicant may make reasoned application to EMA/PB for deferral of initiation or completion of studies
- PB may recommend deferral in a positive opinion, specify time-limits to initiate or complete some or all of the measures in the investigation plan
- Justification must be based scientific and technical grounds or public health
- PB can recommend deferral of its own volition
- PB opinion subject to “re-examination” procedure

Pediatric Use Marketing Authorization

- Products with no patent or SPC protection
- Authorized according to the provisions for centralized and decentralized procedures
- Covering only those indications for pediatric use
- Application must be in accordance with article 8(3) of Directive 2001/83 and an agreed pediatric investigation plan
- When approved, can use the same trade name as the ‘sister’ product but a superscript “P” to indicate pediatric use

Modification of agreed PIP

- If before submission of application for MA, applicant finds plan unworkable or inappropriate, applicant can propose changes/deferral to PB
- Review/re-examination by PB as before
- Refusal or revised letter of acceptance/deferral from EMEA

PMS

- Applicant must explain in the application its specific plan for follow-up on efficacy/safety
- CHMP, or CA may propose risk management system on optimizing efficacy/safety or impose condition for specific post-marketing studies
- PSUR will report on above
- Annual Reports on progress in relation to deferrals

Future guidance/initiatives

- Procedures for co-ordination between PB, CHMP, COMP
- Commission Guidance on format and content of applications for submission, modification, waiver, deferral of P.I.P.
- EMEA to provide guidance on pediatric pharmacovigilance
- Commission guidance on database of all trials started as part of a P.I.P. and all results and what is to be public
- PB to draw up inventory of therapeutic needs in each therapeutic area to identify priorities
- PB to provide guidance on content and format of data to be collected within 2 years by MSs on pediatric use of products

Pre-existing Studies

- Any pediatric studies completed before the 30th day following publication of the Regulation and subject to assessment in a non-EU country
- No SPC extension granted
- But, still a need to submit the data to authorities for assessment for updating the SmPC and PIL

ARNOLD & PORTER (UK) LLP

Deal Making and Product Development in Europe: Changes and Trends You Need to Know About: Regulatory Strategy

Amanda Wearing

November 19, 2004

Changes and Trends in the regulation of medicines in the EU

- Background: new developments
- Key strategic issues
  - Who will hold the marketing authorization(s) for the product in the EU?
  - What role will the other party have?
  - Authorization procedures: what options do you have for filing?

Specific regulatory developments

- Current authorization system came into effect in 1995
- Extensive review of EU pharma legislation, leading to major changes to the rules
  - Directives 2001/82/EC and 2001/83/EC amended
  - new Regulation 726/2004/EC to replace 2309/93
  - rules in the process of being phased in

Broader Regulatory Developments

- Increase in size of EU (25 members from May 2004)
- New members: Czech Republic, Estonia, Hungary, Latvia, Lithuania, Poland, Slovak Republic, Slovenia, Cyprus and Malta
- Nine new languages
- Another 75 million people (old EU was 380 million)
- General characteristics: low price, generic driven

Who will hold the marketing authorization?

- Marketing authorization holder must be “established in the EU”
- Now a choice of 25 Member States
- What does “establishment” mean?
  - Effective control, permanent presence, able to fulfil responsibilities
  - Not just a name on a door

What are the consequences of being a marketing authorization holder?

- New rules say that the MAH shall be responsible for the marketing of the product. The designation of a representative shall not relieve the MAH of his legal responsibility
- MAH may contract out day to day role, e.g.:
  - advertising
  - adverse event reporting
- But it is the MAH who will be prosecuted if things go wrong

Partnering Arrangements

- EU rules permits a variety of partnering arrangements (subject to anti-trust considerations)
- The Commission and Member States have generally recognized co-marketing and co-promotion
- New rule will require Member States to permit co-promotion as an option
- Other less visible partnering arrangements permitted

Features of EU Co-Marketing

- Separate products, separate MAHs. Two applications filed in parallel, or second filed later. Often a continued obligation on the original MAH to support partner with subsequent changes to the product (e.g. new indications).
- MAHs have separate regulatory responsibilities, have different advertising, set separate prices, etc

Features of EU Co-Promotion

- Single product, single MAH
- The other partner may be very active, but does not have direct regulatory responsibilities
- MAH will usually impose strict terms to enable it to comply with its regulatory responsibilities

Points to consider where there are two companies but only one MAH

- The MAH (or applicant) must be the principal point of contact for the regulators
- Non-MAH may have day to day responsibility for adverse events or advertising but must:
  - keep MAH informed promptly of any issues
  - not do anything without MAH approval
- Limitations on mentioning non-MAH on label
- Generally no limitations on mentioning non-MAH in promotion

Authorization procedures in the EU: The Options

- Two procedures for the registration of medicines
  - Centralized: single authorization, valid for whole EU
  - Decentralized: series of national authorizations underpinned by principle of “mutual recognition”

How does the centralized procedure work?

- Single filing to the EMEA
- Compulsory for products developed by listed biotech processes; optional for new active substances and innovations (e.g. significant new indications)
- Timing:
  - 210 days to CHMP opinion (+clock stop)
  - Approx 90 days to Commission decision
- Single authorization, valid for whole EU unless the applicant withdraws

Good and bad points of the centralized procedure

- Faster time to market in whole EU
- But lack of flexibility for licensing arrangements
  - co-marketing has to be justified in advance
  - cannot grant a MA for part of the territory
  - EMEA insists on single trade mark
  - need to translate documents into ALL EU languages, whether or not you intend to market

How does the decentralized procedure work?

- Application in Reference Member State, followed by “mutual recognition” in Concerned Member States
- Timing
  - 210 days to RMS authorization (+clock stop)
  - 90 days for CMSs to consider
- Arbitration process where CMSs and RMS disagree (objections based on risks to public health)

Good and bad points of the decentralized procedure

- Allows a phased approach: expand market gradually
- Greater flexibility for licensing out part of territory
- Practical problems if you want to access the whole EU quickly
- Arbitration process will involve a delay to market of approx one year

How are things changing? The centralized procedure

- The good news
  - accelerated process for products with major public interest
  - faster Commission decisions
- The bad news
  - less flexibility: will be required for ALL NASs for the treatment of AIDs, cancer, neurodegerative diseases, diabetes; autoimmune diseases and viral diseases
  - language requirements (9+ new languages)
  - single trade mark: now expressly mentioned

How are things changing? The decentralized procedure

- The good news
  - buy-in from Member States earlier in the procedure
  - greater focus on limiting scope of Member State objections
- The bad news
  - arbitration will be compulsory if resolution is not possible (but will not block marketing in the interim)

To sum up

- The two authorization procedures are changing
- Greater scope of centralized procedure means less flexibility for doing deals
- Need caution where non-MAH involved in “regulatory” activities
- Bigger EU:
  - greater regulatory bureaucracy
  - how do you manage your presence in the new Member States?

ARNOLD & PORTER (UK) LLP

Deal Making and Product Development in Europe: Changes and Trends You Need to Know About

Jeremy Willcocks

November 19, 2004

Deal Making in Europe

- Current Trends
  - Public markets
  - Private companies
- Documenting the deal

Deal Making in Europe

- Public markets
  - Belgium-based UCB's acquisition of Celltech ($2.8 billion)
  - Further consolidation of public companies
  - Climate for fund-raising remains depressed
  - Weak IPO market

Deal Making in Europe

- Private companies
  - Funding gap
  - Lack of exit and listing opportunities
  - Consolidation
  - Leading to more M&A

Deal Making in Europe

Region	1999-2003 Financings completed	1999-2003 Value (US$bn)	2004 Financings 'outstanding'
United Kingdom	114	1.4	36
Germany	95	1.2	39
Scandinavia	63	0.6	16
Rest of Europe	94	1.3	27
Total	366	4.4	118

EXCLUDING first round financings

Source: Dunhaw Capital

Deal Making in Europe

Exited / Refinanced

v

Further funding required

$511m
$27m

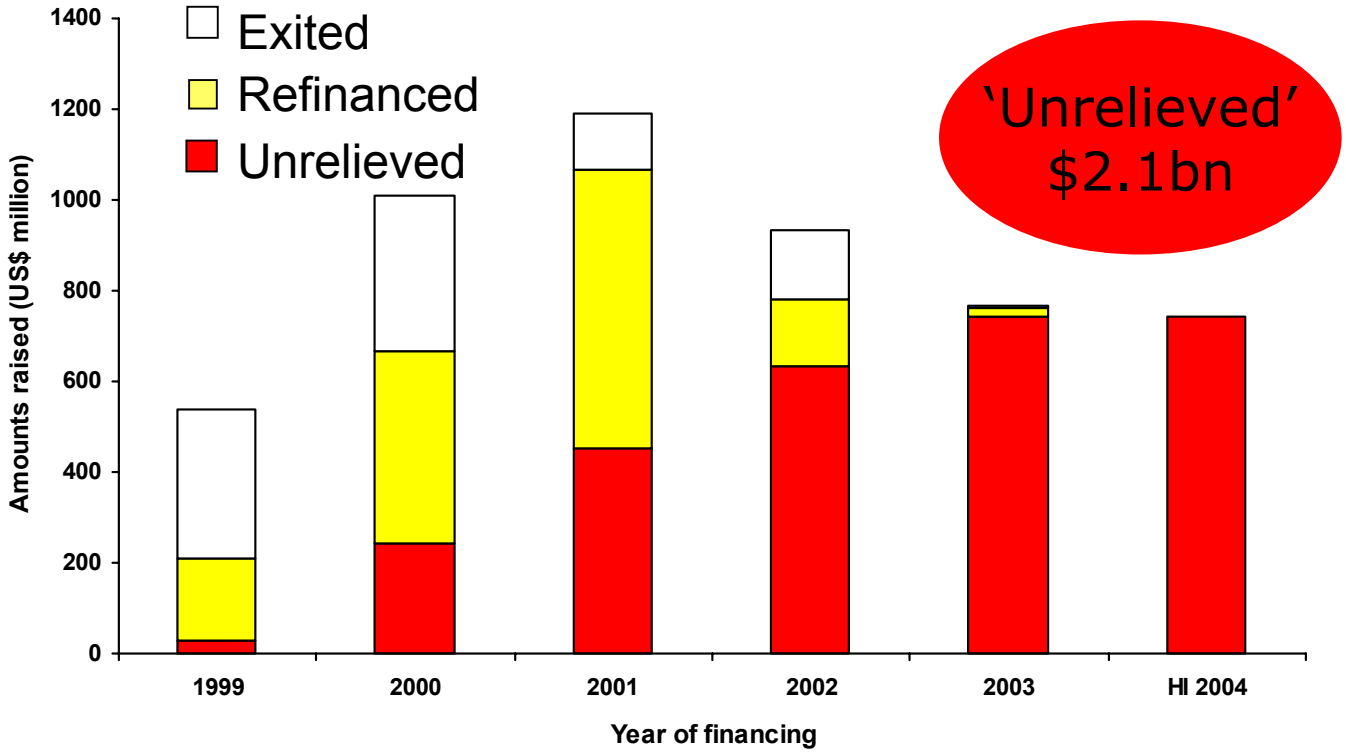
$765m
$245m

$741m
$451m

$299m
$634m

$24m
$741m

-
$743m



Deal Making in Europe

- Documenting the deal: Points to note:
  - Warranties - who will give them?
  - Break fees
  - Liquidation preferences
  - Drag rights
  - Employment issues

Deal Making in Europe

To sum up

...a buyer's market