New challenges and opportunities for biotech SMEs

VIII Annual Conference of the Biomedical Research Technology Platform

Presented by Constantinos Ziogas on 24 March 2015
Head of SME Office, Stakeholders and Communication Department
Agenda

• Introduction to the Agency
• The SME Office
• Support to SMEs: regulatory assistance and scientific advice
• Outcome
European Medicines Agency - EMA

Responsible for the scientific evaluation of medicines for human and animal use in the EU:

- Scientific advice
- Orphan designation for human medicines for rare diseases
- Paediatric investigation plans
- Centralised procedure for marketing authorisations
- Article 58 with WHO
- Inspections
- Referrals
- Pharmacovigilance
Gatekeepers and Enablers: How Drug Regulators Respond to a Challenging and Changing Environment by Moving Toward a Proactive Attitude

F Ehmann1,2, M Papaluca Amati2, T Salmonson3,4, M Posch5, S Vamvakas6, R Hemmings7,8, HG Eichler9 and CK Schneider10,11

This article analyzes the role of regulatory authorities in facilitating innovation in the pharmaceutical sector. We describe how regulators are expanding their role to be not only gatekeepers but also enablers of development. They have already responded to the challenging and changing environment by moving toward a proactive attitude beyond evaluation of products, thereby more actively contributing to their development. Regulators have to continuously evolve their knowledge and standards alongside evolution in science. Creation of supportive regulatory frameworks and multistakeholder interaction will help address unmet regulatory needs.

Proactive regulatory approach: regulators as “enablers”

- Changing landscape of pharmaceutical R&D
  - Decline in R&D
  - Generic pressure
  - Increasing development costs
  - Increasing regulatory demands
  - Changing markets
  - Multistakeholder involvement

- Creation of supportive regulatory frameworks
  - Innovation task force
  - Procedure for qualification of novel methodologies
  - Support for orphan drugs and SMEs

- Creation of multistakeholder interaction
  - Global regulatory forums and joint scientific advice
  - Dialogue with HTA bodies

Address unmet regulatory needs
- Explore and evolve adaptive licensing
- Quantification of benefit-risk
- Enable innovative clinical trial designs and data analyses
- Enable personalized medicine
SME Office: tailoring assistance to SMEs

A strategic regulatory toolbox to promote innovation and development of new medicines by SMEs:

- A single interface
- SME assignment, public SME register
- Fee incentives, regulatory assistance, translations
- Facilitate communication
- News bulletins, SME user guide, workshops
Assignment of SME status

SME criteria defined in Recommendation 2003/361/EC

**THE NEW THRESHOLDS (Art. 2)**

<table>
<thead>
<tr>
<th>Enterprise category</th>
<th>Headcount: Annual Work Unit (AWU)</th>
<th>Annual turnover</th>
<th>Annual balance sheet total</th>
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<tbody>
<tr>
<td>Medium-sized</td>
<td>&lt; 250</td>
<td>&lt; €5.0 million (In 19% &gt; € 0 million)</td>
<td>or €43 million (In 19% &gt; € 27 million)</td>
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<td>or €10 million (In 19% &gt; € 5 million)</td>
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<td>Micro</td>
<td>&lt; 10</td>
<td>≤ €2 million (previously not defined)</td>
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**Initial Qualifications**

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New challenges and opportunities for biotech SMEs
SME ownership

- Corporate: 25%
- Venture capital: 7%
- Private investment: 11%
- Other: 6%
- Natural persons: 51%
Incentives for SMEs

- Administrative, regulatory and procedural assistance
- Fee reductions and deferrals
- Certification of quality/non-clinical data for advanced therapy medicinal products*
- Translation of product information

* Medicines based on genes / cells / tissues
Regulatory assistance for SMEs

- Direct assistance:
  - Queries dealt with by SME office: e-mail/telecon
  - Briefing meetings/telecon on regulatory strategy
  - Support to emerging therapies through innovation task force
- Published SME user guide on regulatory procedures
- SME news bulletin
- Annual training/workshops tailored for SMEs
Fee incentives for SMEs

- 90% reduction on:
  - Scientific advice & scientific services
  - GMP, GLP, GCP, PhVig inspections
- 100% ‘waiver’ on administrative services
- For MAA, SME fee deferral
  - Orphan medicine: 100% waiver to 1st year post-licensing
  - Paediatric use marketing authorisation: 50% fee reduction
- Conditional fee exemption
  - Subject to EMA scientific advice – payment only for positive outcome
- Post-authorisation activities (variations etc.)
  - 100% waiver for micro enterprises
  - 40% reduction for small, medium sized enterprises
Experience with SMEs (year end 2014)

• 1301 companies assigned SME status
• From 27 countries across EEA
• 45% micro, 38% small, 17% medium
• Majority human (72%), 5% vet, 6% human/vet & 17% service providers
• Public register of companies launched in 2010
A profile of SMEs

- Medical device and technology: 20%
- (Bio)Pharmaceutical: 80%

- Research/Discovery stage: 27%
- Development stage: 34%
- Commercialisation/Marketing stage: 18%
- Manufacturing: 10%
An overview of the product profiles

- Chemicals 44%
- Biologics 15%
- Foods 4%
- Nucleic acids (chemically synthesised) 3%
- Polymers (natural & synthetic - excl. peptides, proteins, nucleic acids) 2%
- Advanced therapy medicinal products 8%
- Vaccines 4%
- Radionuclides 1%
- Allergens 1%
- Polyclonal Immunoglobulins 1%
- Herbal complex substances 5%
- Animal complex substances 2%
- Medical devices 10%
An overview of the products pipelines

**All companies**

- Research/Discovery: 14%
- Pharmaceutical development: 16%
- Preclinical: 15%
- Clinical exploratory: 12%
- Clinical confirmatory: 9%
- Marketing: 20%
- (Pre) Registration: 14%

**Development stage SMEs with biologics and advanced therapies**

- Therapeutics (84%), vaccines (7%), diagnostics/imaging (9%)
- 21% of SMEs developing orphan medicines
- 3% of SMEs in nanotechnology, 3% pharmacogenomics/biomarkers
Biologics in development stage SMEs

- Extracted proteins: 23%
- Monoclonal antibodies: 30%
- Recombinant proteins: 49%

- Tissue engineered products: 30%
- Gene therapy products: 36%
- Somatic cell therapy products: 34%
A more limited number of products in SMEs pipelines

- Clinical confirmatory stage: 1 (0-5)
- Clinical exploratory stage: 2 (0-10)
- Pharmaceutical development & Pre-clinical stage: 2 (0-21)
- Research and Discovery stage: 3 (1-12)
Scientific advice

Strictly confidential

• Scientific advice can be provided on ANY scientific question
  - Quality, non-clinical and clinical

• At any time point of the development
  - Early advice with subsequent follow-up is recommended

• Broad advice, conditional approval/exceptional circumstances
  - On the eligibility or on proposed development

• Qualification of biomarkers and other novel methodologies
Scientific advice

- Voluntary, not mandatory procedure:
- Companies ask questions
- Responses are prepared and discussed
- In 50% of the cases a face-to-face meeting with the company is organised
- **Written responses**, adopted by the licensing committee, sent to the company: scientific advice letter
- short process: 40 days or 70 days
FAQs in scientific advice

Quality/CMC
- comparability, stability, etc.

Non-clinical
- in vivo pharmacology for innovative products
- animal models for products with human specific targets, animal models mimicking the human disease, surrogate molecules
- carcinogenicity and reprotoxicity waivers, etc.

Clinical
- PK/PD, dose-finding, interactions
- exploratory & pivotal trials: study endpoints, population, comparator, blinding, statistics (interim A, adaptive/seamless design), safety DB
Positive impact of SA adherence on MAA outcome

SA Adherence (n=123)
- 88% pos MAA
- 12% neg MAA

SA Non-Adherence (n=53)
- 42% pos MAA
- 58% neg MAA
Scientific advice and protocol assistance 2001-2014

Parallel HTA SA

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<th>Year</th>
<th>Scientific Advice</th>
<th>Protocol Assistance</th>
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Scientific advice and protocol assistance for orphan drugs by SMEs
SME experience in the centralised procedure (human use)

![Bar chart showing SME experience in the centralised procedure (human use) from 2007 to 2014. The chart indicates the number of positive, negative, and withdrawn cases each year.](chart.png)
Origins of new medicines in the EU (2010-12)

Of 94 novel medicinal products authorised

- Large majority marketed by large or intermediate sized companies
- SMEs and academia at the origin of innovation

Most frequent major objections in SME applications

Average number of major objections:
- 6 for positive MAAs (from 0 to 18)
- 12 for negative/withdrawn MAAs (from 8 to 24)
Major objections in quality for SME applications of medicines containing biological entities
Distribution of clinical major objections for SME applications

- General issues on study design: 20%
- Analysis/robustness of pivotal data/selection of submitted studies: 16%
- Choice of endpoint: 12%
- Insufficient long-term follow-up data: 11%
- Inconsistent data on clinical efficacy: 12%
- Clinical efficacy concerns: Pharmacodynamics/pharmacokinetics: 8%
- Other serious AE: 7%
Scientific advice and MA application outcome (2004-2007; N=188)

<table>
<thead>
<tr>
<th>Who requests SA?</th>
<th>Who complies with SA?</th>
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<tbody>
<tr>
<td>• Big Pharma 33%</td>
<td>• Big pharma: 84%</td>
</tr>
<tr>
<td></td>
<td>• Medium pharma: 60%</td>
</tr>
<tr>
<td></td>
<td>• Small pharma: 25%</td>
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</table>

Company size is significantly associated with positive outcome of MA application: OR = 2.96 (95%CI: 1.92, 4.56)

Obtaining and complying with SA appears to be a predictor of outcome [compliant with SA vs. no-SA: OR 14.71, 95% CI 1.95; 111.2; non-compliant with SA vs. no-SA: OR 0.17, 95% CI 0.06; 0.47, p<0.0001]

Thank you for your attention

Further information

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