European Medicines Agency’s SME Office

- the services and fee reductions offered to SMEs
SME Initiative at EMA

Objective:
To promote innovation and development of new medicines by SMEs

SME Office:
- A single interface
- Advise on regulatory issues
- Facilitate communication
- Organise workshop/training sessions
Assignment of SME Status

Applicant must be established in the EEA
Meet SME criteria defined in Recommendation 2003/361/EC:

Headcount < 250 and annual turnover not more than € 50 mil or balance sheet not more than € 43 mil

Submit information to show comply with criteria

Incentives for SMEs

- Administrative 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
Fee Reductions for SMEs

90% reduction on:
- scientific advice
- inspections
- scientific services
- maximum residue limits (veterinary medicines)

100% ‘waiver’ on administrative services (except for parallel distribution)
SME fee incentives for centralised MAA

Fee deferral for SMEs, plus for

Advanced Therapies:
50% reduction for SME/hospitals
- centralised MAA where public health interest in EU until 2011-2012
- reduction of 1st year post-authorisation fees

Orphan medicines:
100% waiver for SMEs
- waiver of 1st year post-authorisation fees
Fee Deferral & Conditional Fee Exemption

Granting of the Marketing Authorisation

Marketing Authorisation Application

Payment deferred until the end of the procedure

Time

IF scientific advice used:

=> Payment only in case of success
(Marketing Authorisation Granted)
### Example

<table>
<thead>
<tr>
<th>Service</th>
<th>Standard application non-SME</th>
<th>Standard application SME</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scientific Advice</td>
<td>75 000 EUR</td>
<td>7 500 EUR (-90%)</td>
</tr>
<tr>
<td>Inspection</td>
<td>19 000 EUR</td>
<td>1 900 EUR (-90%)</td>
</tr>
<tr>
<td>Marketing Authorisation</td>
<td>252 000 EUR</td>
<td>252 000 EUR if success</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0 EUR (-100%) if failure</td>
</tr>
<tr>
<td>Total</td>
<td>346 000 EUR</td>
<td>261 400 EUR if success</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9 400 EUR if failure (-97%)</td>
</tr>
</tbody>
</table>

Payment deferred until end of the procedure
Experience with SMEs at end of 2009....

460 companies assigned SME status in total

24% increase from 2008 to 2009

37% micro, 34% small, 29% medium

Majority human, 25 vet, 16 human/vet & 47 consultants
Support to SMEs

Regulatory assistance:

• > 260 SMEs received direct regulatory assistance
• Published SME User Guide on regulatory procedures
• SME News bulletin to update companies
• Annual training/workshops tailored for SMEs
Support to SMEs

Scientific advice (SA):

- >220 SME’s in scientific advice

Applications for marketing authorisation (MAA)

- 45 submitted MAAs (human & vet medicines)
- Provision of translations for 16 SMEs
# Status of SME Applications for Marketing Authorisation for Human Medicines

<table>
<thead>
<tr>
<th></th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. of applications submitted</strong></td>
<td>10</td>
<td>11</td>
<td>12</td>
<td>4</td>
<td>37</td>
</tr>
<tr>
<td><strong>Positive</strong></td>
<td></td>
<td></td>
<td>5</td>
<td>8</td>
<td>14</td>
</tr>
<tr>
<td><strong>Negative</strong></td>
<td>-</td>
<td>1</td>
<td>2</td>
<td>1*</td>
<td>4</td>
</tr>
<tr>
<td><strong>Withdrawals</strong></td>
<td>1</td>
<td>3</td>
<td>6</td>
<td>6</td>
<td>16</td>
</tr>
</tbody>
</table>

* Negative opinion currently under re-examination

Dec 2005 - Dec 2009
MAA outcomes over time for SMEs

For medicines for human use

Overall success rate for SMEs 41% vs 75% for all companies
Fourteen positive SME Marketing Authorisation Applications

- Soliris for paroxysmal nocturnal haemoglobinuria
- Firazyr for hereditary angioedema
- Evicel for improvement of haemostasis in surgery
- Ceplene for acute myeloid leukaemia
- Mepact for osteosarcoma
- Ixiaro for immunisation against Japanese encephalitis
- Qutenza for peripheral neuropathic pain
- Ellaone for emergency contraception
- Vedrop for vitamin E deficiency due to malabsorption
- Grepid for prevention of atherothrombotic events (generic)
- ChondroCelect for repair of symptomatic cartilage defects
- Resolor for chronic constipation
- Zenas for Lambert-Eaton Myasthenic Syndrome (LEMS)
- Tepadina for conditioning prior to haematopoietic progenitor cell transplant
Overview clinical studies in positive opinions
(Jan 2006-Sep 2009)

10 of 12 applications – at least one pivotal phase III, 1/3 with 2 or more

All but 2 contained data from randomised controlled trials
(generic excluded)
Overview clinical studies in negative/withdrawals (Jan 2006-Sep 2009)

Smaller proportion 1/16 (6%) with 2 or more pivotal phase III studies
Companies filing earlier in development >50% in phase II/III
Higher proportion based on non-controlled trials
Questions raised & response time

Average number of major objections:

- 5 for positive MAAs (from 0 to 10)
- 12 for negative/withdrawn MAAs (from 1 to 34)

Response time on average: 222 days
Examples of Major Objections “Quality”

- Process documentation incomplete
- Process validation incomplete
- Levels of impurities too high
- Setting of specifications not justified
- Lack of demonstrated consistency of lots
- Comparability between different sites not addressed
- Lack of GMP Certification
- Stability data lacking
Examples of Major Objections “Clinical”

- Discrepancy between studied patients & proposed indications
- Insufficient clinical package – one pivotal study
- Inadequate trial design
- Efficacy not demonstrated to significantly robust level
- Primary endpoint is not statistically significant
- Choice of dose not sufficiently justified
- Predefined criteria for clinical relevance not met
- Inconsistency in statistical methods between protocol & report
- Multiplicity issues
- Data do not allow comprehensive evaluation of safety profile
Closing Remarks

Observations:

– Limited experience to date
– Main areas objections raised quality and clinical efficacy
– Element of premature filing

Recommendations:

– If MAA based on one pivotal trial, results should be compelling
– EPARs/WPARs are useful source of information
– Early Scientific advice is strongly encouraged