EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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

An agency of the European Union

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

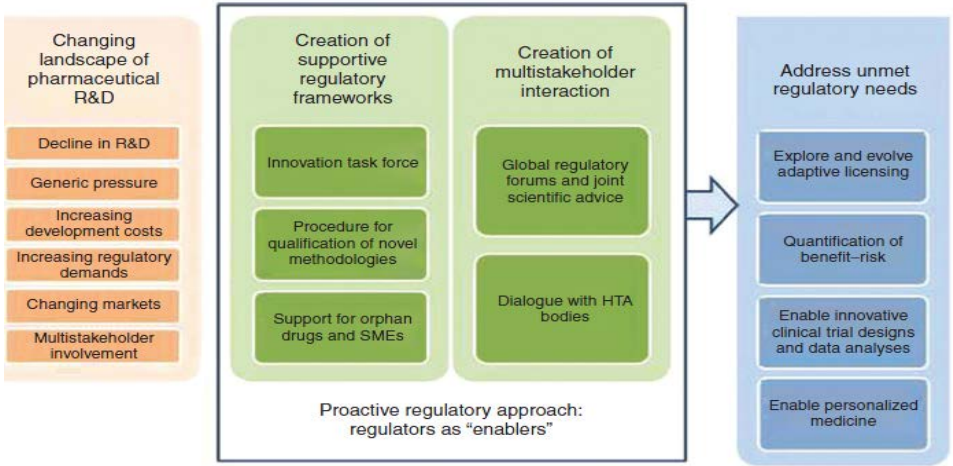
Gatekeepers and Enablers: How Drug Regulators Respond to a Challenging and Changing Environment by Moving Toward a Proactive Attitude

F Ehmann[1,2], M Papaluca Amati[2], T Salmonson[3,4], M Posch[5], S Vamvakas[6], R Hemmings[7,8], HG Eichler[9] and CK Schneider[10,11]

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.

A proactive regulatory approach:

"Be part of it and shape it together."



SME Office: tailoring assistance to SMEs

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

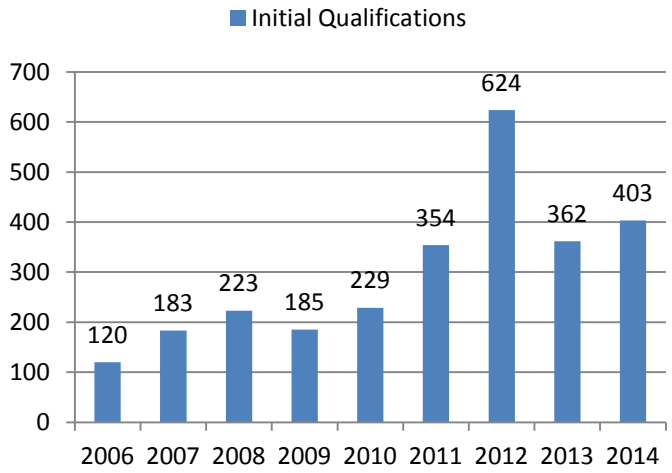
- A single interface
- SME assignment, public SME register
- Fee incentives, regulatory assistance, translations
- Facilitate communication
- News bulletins, SME user guide, workshops

Assignment of SME status

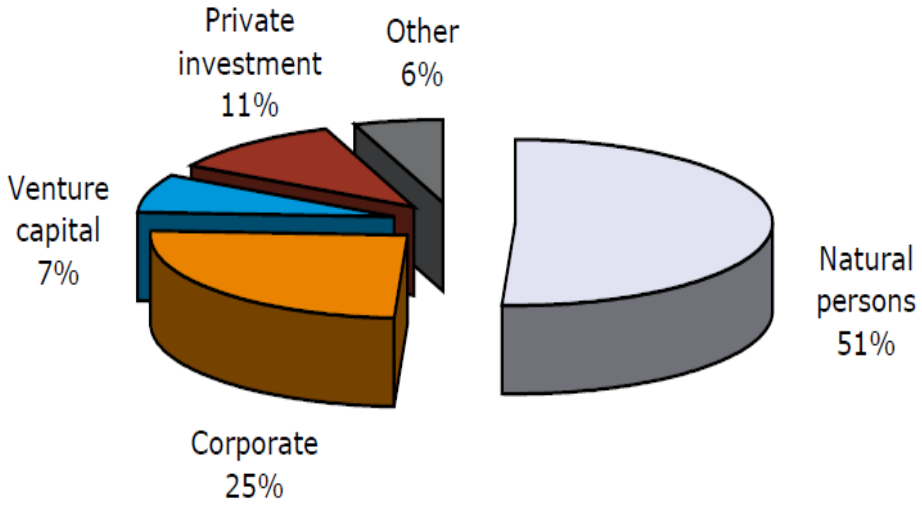
SME criteria defined in Recommendation 2003/361/EC

THE NEW THRESHOLDS *(Art. 2)*

Enterprise category	Headcount: Annual Work Unit (AWU)	Annual turnover	or	Annual balance sheet total
Medium-sized	< 250	≤ €50 million (In 1996 € 40 million)	or	≤ €43 million (In 1996 € 27 million)
Small	< 50	≤ €10 million (In 1996 € 7 million)	or	≤ €10 million (In 1996 €5 million)
Micro	< 10	≤ €2 million (previously not defined)	or	≤ €2 million (previously not defined)



SME ownership



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

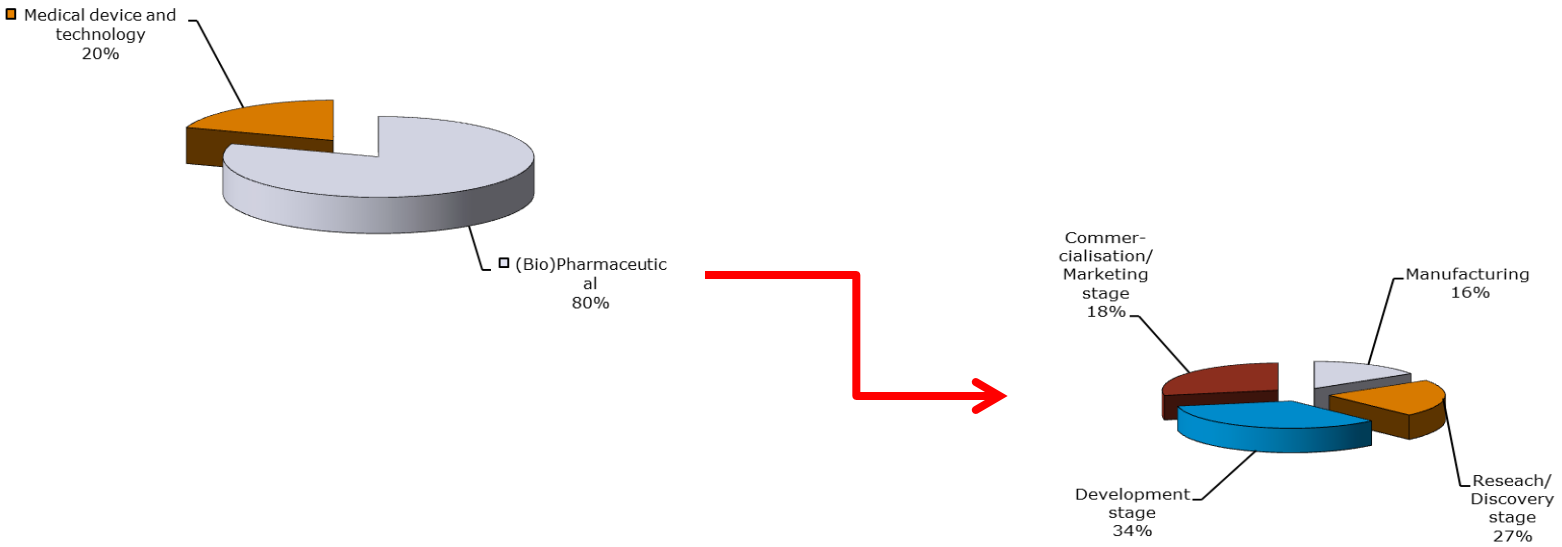
Fee incentives for SMEs

- 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

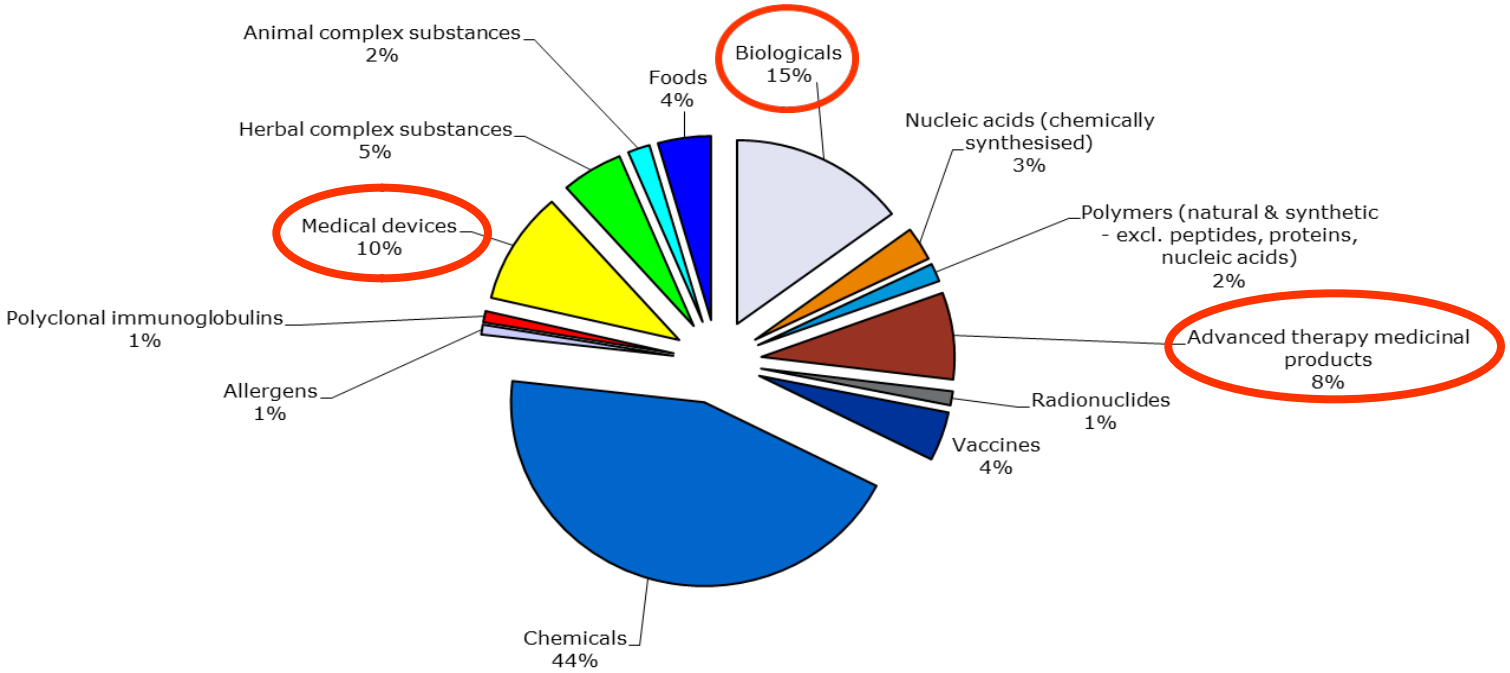
Experience with SMEs (year end 2014)

- 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

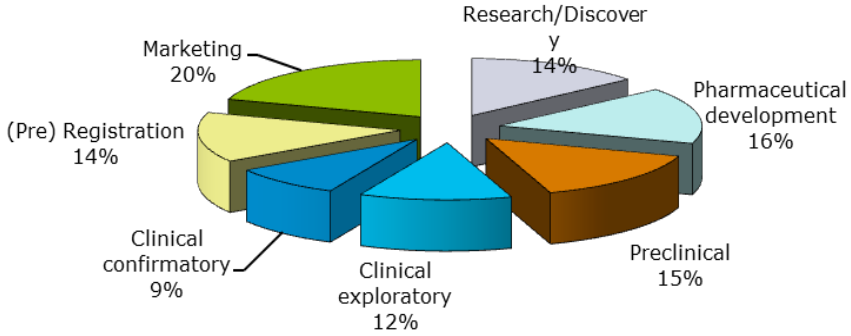


An overview of the product profiles

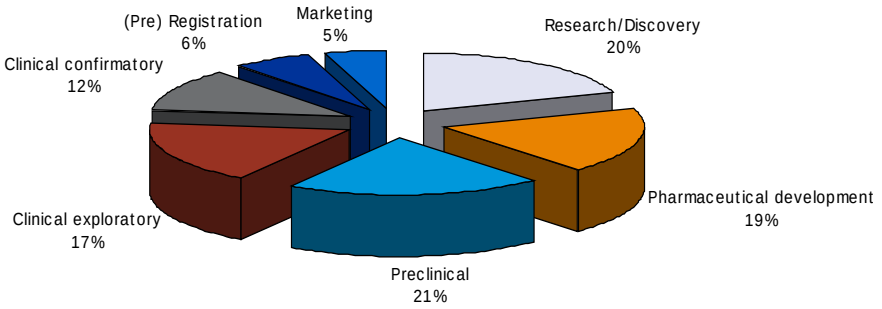


An overview of the products pipelines

All companies



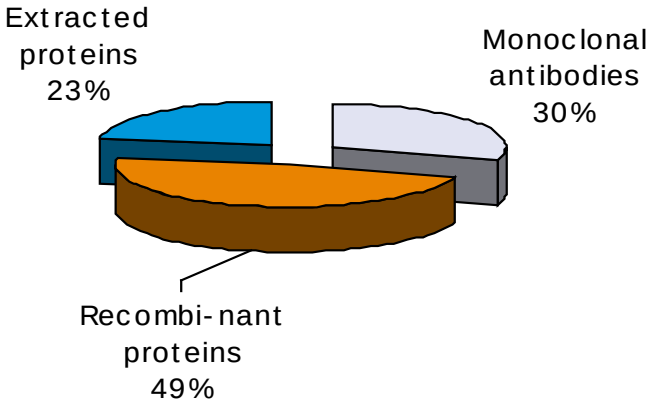
Development stage SMEs with biologics and advanced therapies

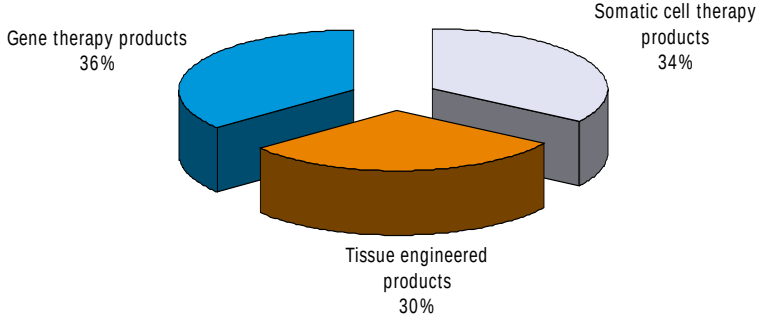


Therapeutics (84%), vaccines (7%), diagnostics/imaging (9%)

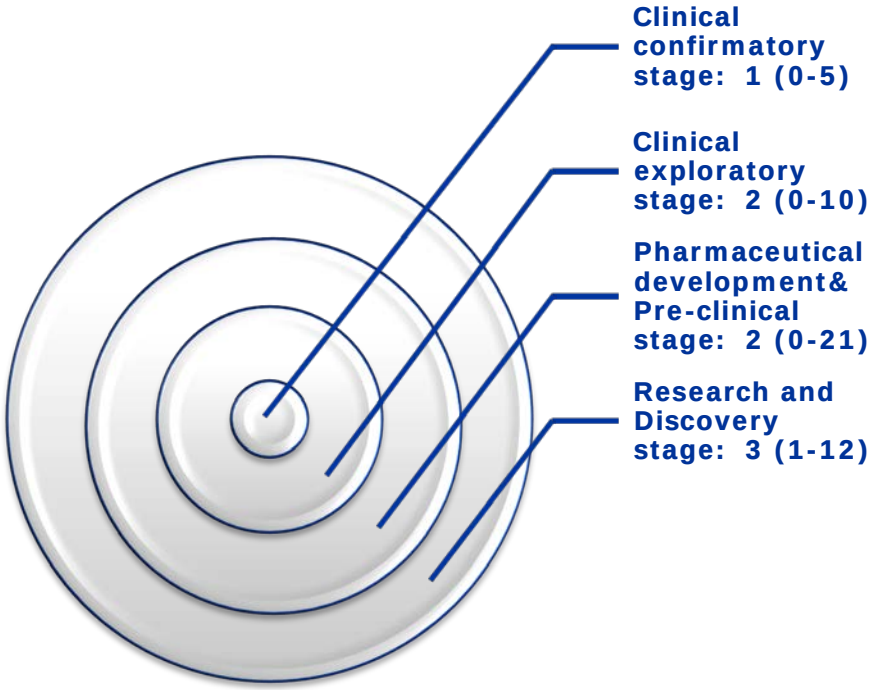
- 21% of SMEs developing orphan medicines
- 3% of SMEs in nanotechnology, 3% pharmacogenomics/biomarkers

Biologics in development stage SMEs





A more limited number of products in SMEs pipelines




Support to SMEs


Success
Failure

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.

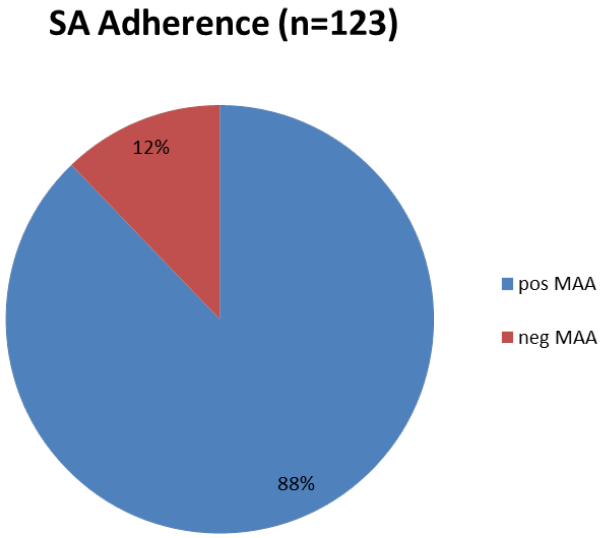
Non-clinical

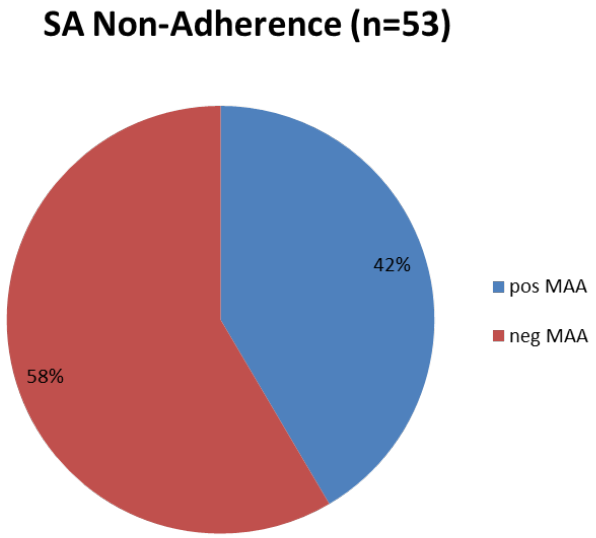
- in vivo pharmacology for innovative products
- animal models for products with human specific targets, animal models mimicking the human disease, surrogate molecules
- carcinogenicity and reprotoxicity waivers, etc.

Clinical

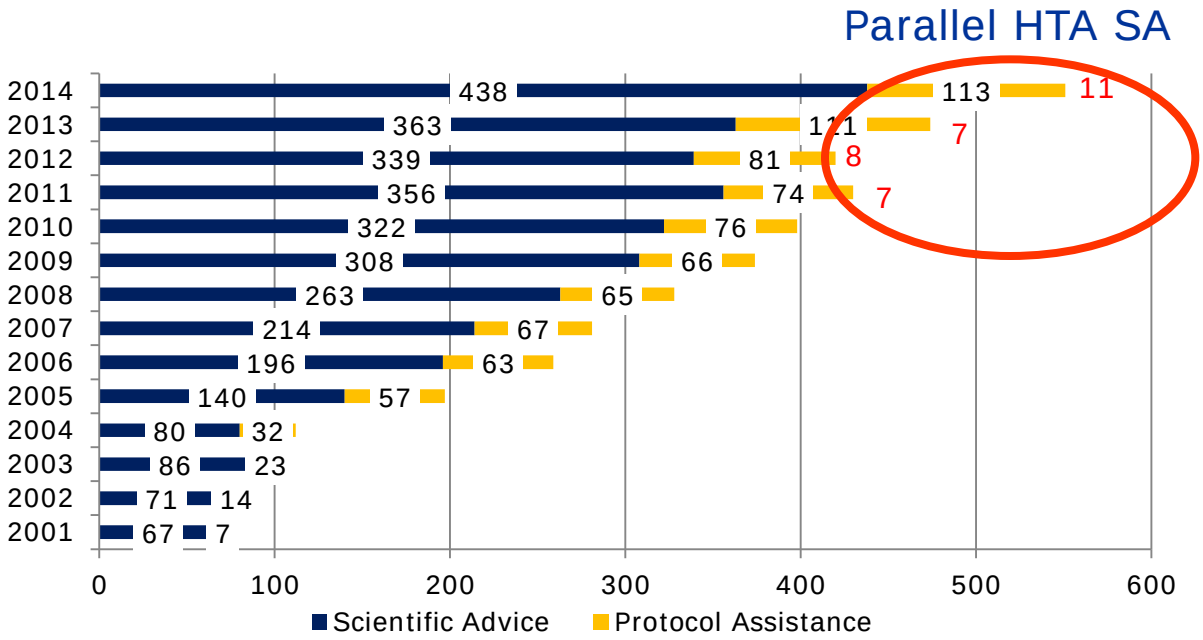
- PK/PD, dose-finding, interactions
- exploratory & pivotal trials: study endpoints, population, comparator, blinding, statistics (interim A, adaptive/seamless design), safety DB

Positive impact of SA adherence on MAA outcome

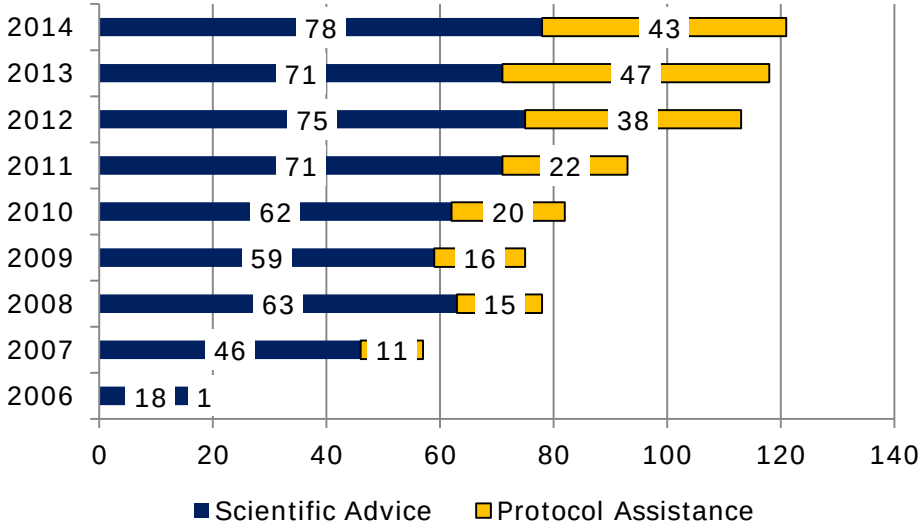




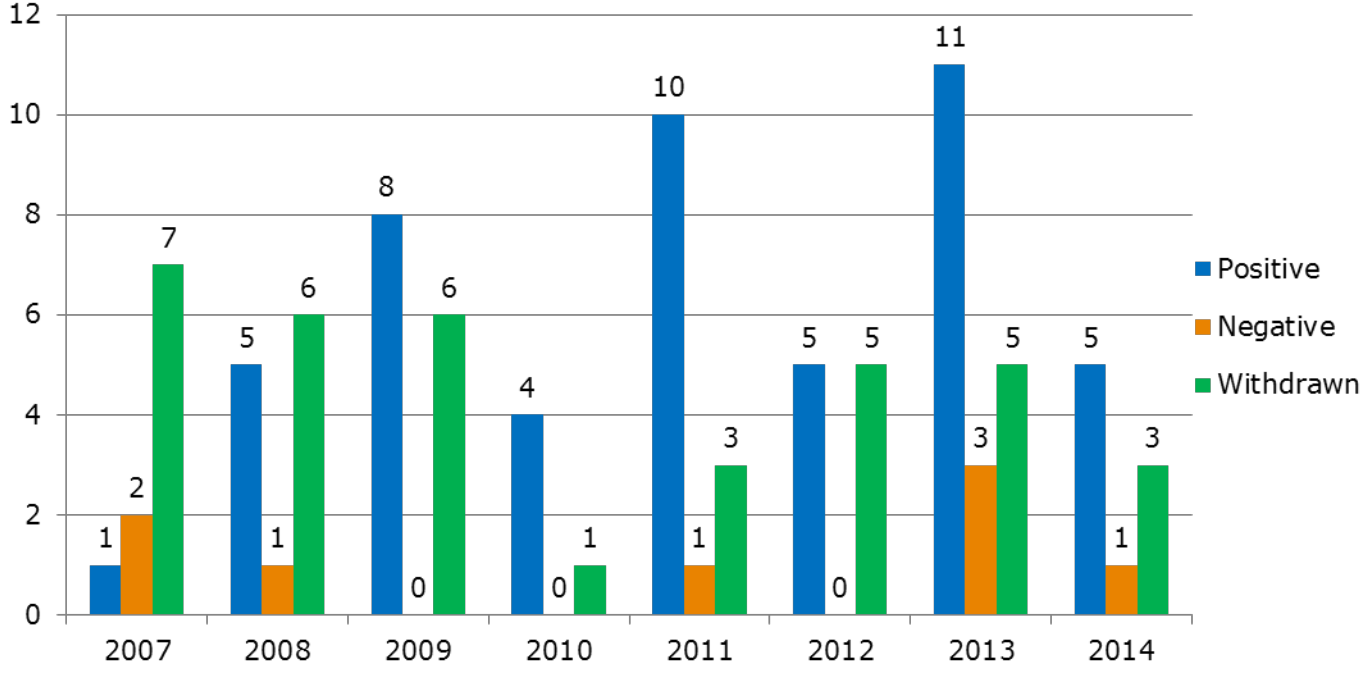
Scientific advice and protocol assistance 2001-2014



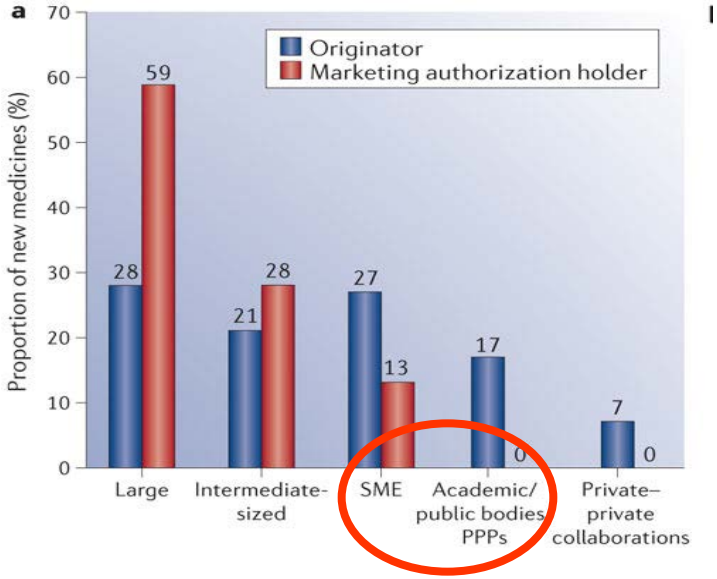
Scientific advice and protocol assistance for orphan drugs by SMEs



SME experience in the centralised procedure (human use)



Origins of new medicines in the EU (2010-12)



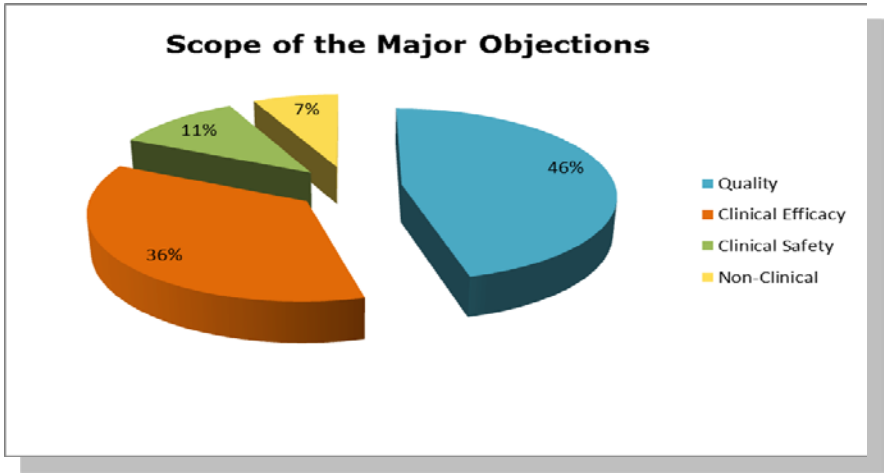
Of 94 novel medicinal products authorised

Large majority marketed by large or intermediate sized companies

SMEs and academia at the origin of innovation

H. Lincker et al; Nature Reviews Drug Discovery Vol: 13, pp. 92–93 (2014)

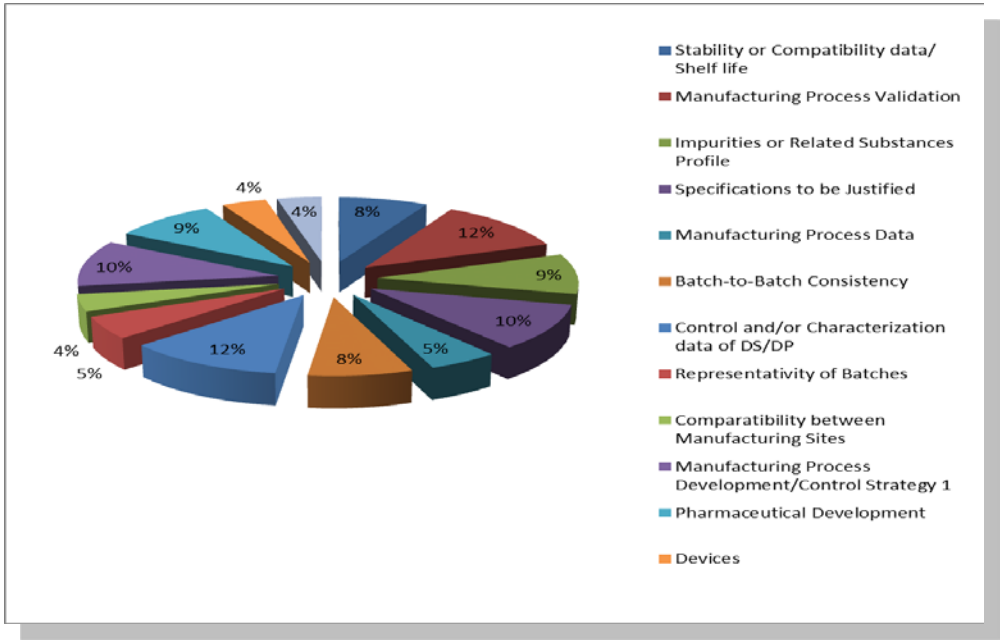
Most frequent major objections in SME applications



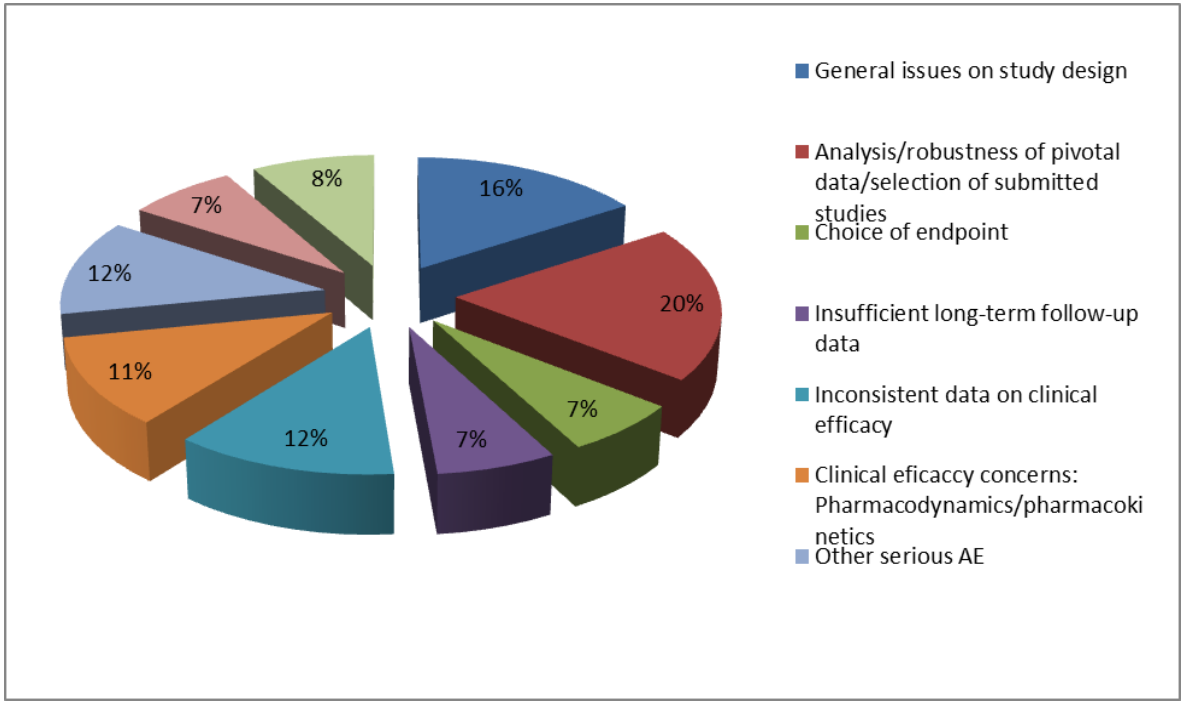
Average number of major objections:

- 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



Scientific advice and MA application outcome (2004-2007; N=188)

Who requests SA?	Who complies with SA?
•Big Pharma 33%	•Big pharma: 84% •Medium pharma: 60% •Small pharma: 25%

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)]

Regnstrom et al; Eur J Clin Pharmacol. 2010 Jan;66(1):39-48

Thank you for your attention

Further information

www.ema.europa.eu

European Medicines Agency
30 Churchill Place • Canary Wharf • London E14 5EU • United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
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