FDA - EMEA Interaction Implications for the Pharmaceutical Industry

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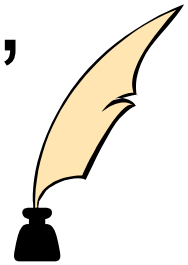
Competetive global environment and high development costs

demand for one

efficient global drug development program appropriately proving safety and efficacy and providing access to all major markets

Information-Sharing Agreement FDA/EU signed by FDA, EMEA, and EC September 2003

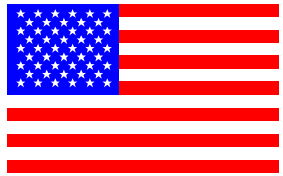


- EU-FDA bilateral meetings since 1989
- PhWG/FDA monthly videoconferences on Pharmaco-vigilance
- Now strengthening communication in step wise approach to include - orphan drug designation
  - inspection reports
  - marketing approvals
  - post-authorisation surveillance information
  - parallel scientific advice

EMEA perspective

- Confidentiality of non-public information will be protected
- Industry benefit: opportunity for parallel Scientific Advice
  [EMEA Press release Sep 2003]
- More focus on global development is required, but very resource intensive [T.Lönngren at DIA March 2004]
- Parallel SA only when the company is volunteering
  [D.Brasseur at DIA March 2004]
- Company may potentially be involved immediately after conference [M.Toivonen at DIA March 2004]

FDA perspective



- Share important information about
  - pending approvals
  - post marketing surveillance
  - enforcement actions
- To build understanding and mutual confidence [FDA Report 2003]
- Joint Advice can occur in a number of ways, including ...a videoconference...with company representatives

[M Lumpkin, RAJ Nov 2003]

- Joint policy development [S.Hirschfeld DIA, March 2004]

Parallel Scientific Advice (pSA)

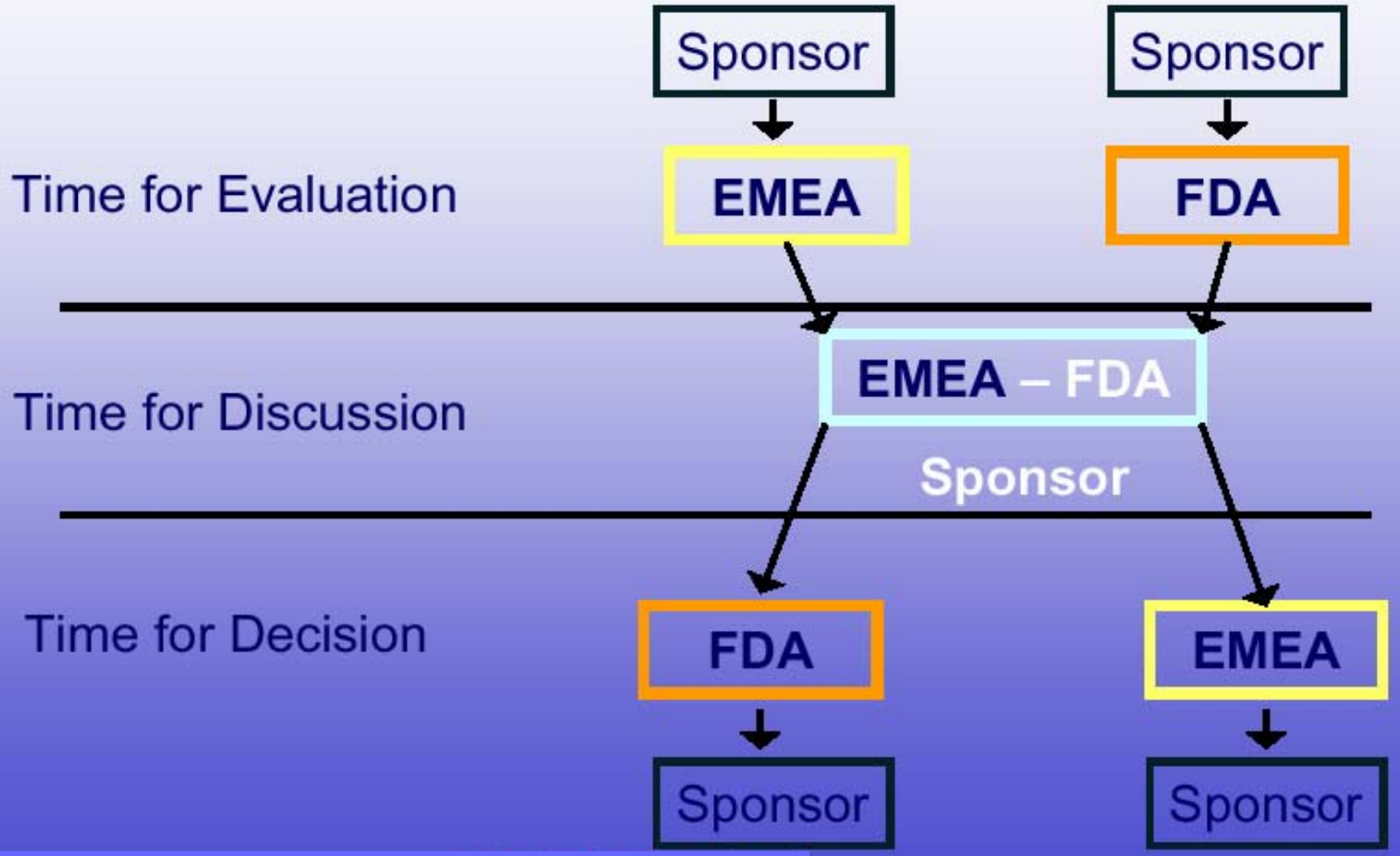
- First experience
- Background: Current advice procedures EMEA/FDA
- Benefits of pSA from industry perspective
- Risks of pSA from industry perspective
- When should Industry use pSA
- What industry would really need

First parallel EMEA-FDA Scientific Advice procedure (pSA)

September 2003

- For orphan drug at request of the sponsor
- During Protocol Assistance (PA) after oral EMEA hearing
- Prior to EoP 2 meeting at FDA
- Videoconference of EMEA and FDA assessors
- Chaired by M.Toivonen, observer T.Lönngren, M. Lumpkin
- On scientific issues on the proposed development plan
- FDA / CPMP continue to adopt advice independently

HARMONISED SCIENTIFIC ADVICE



M. Papaluca Amati, CMR Workshop Sept. 15/16 2003, Washington

pSA experience from EMEA perspective

- High expectations/interest from sponsors
- EMEA already before requested FDA advice from sponsor
- Each agency remains responsible for its own advice

  [M. Papaluca Amati, at CMR Sept 2003]
- Parallel SA provides arena for agency discussion but outcome is not binding for any side [T.Lönngren at DIA March 2004]
- Two further requests for parallel SA received
- Points for discussion on preclinical and clinical issues

  [M.Toivonen at DIA March 2004]

EMEA Scientific Advice - survey 2003

Jan - Sep 2003
n=41 questionnaires, 36 SA and follow up, 6 PA

58 % Clinical questions (thereof 56 % Phase III related)
26 % Preclinical questions

12 % found advice very different from the one received from other authorities

19% had to devise a completely different development plan after the advice

[Prof M Toivonen, DIA meeting March 2004]

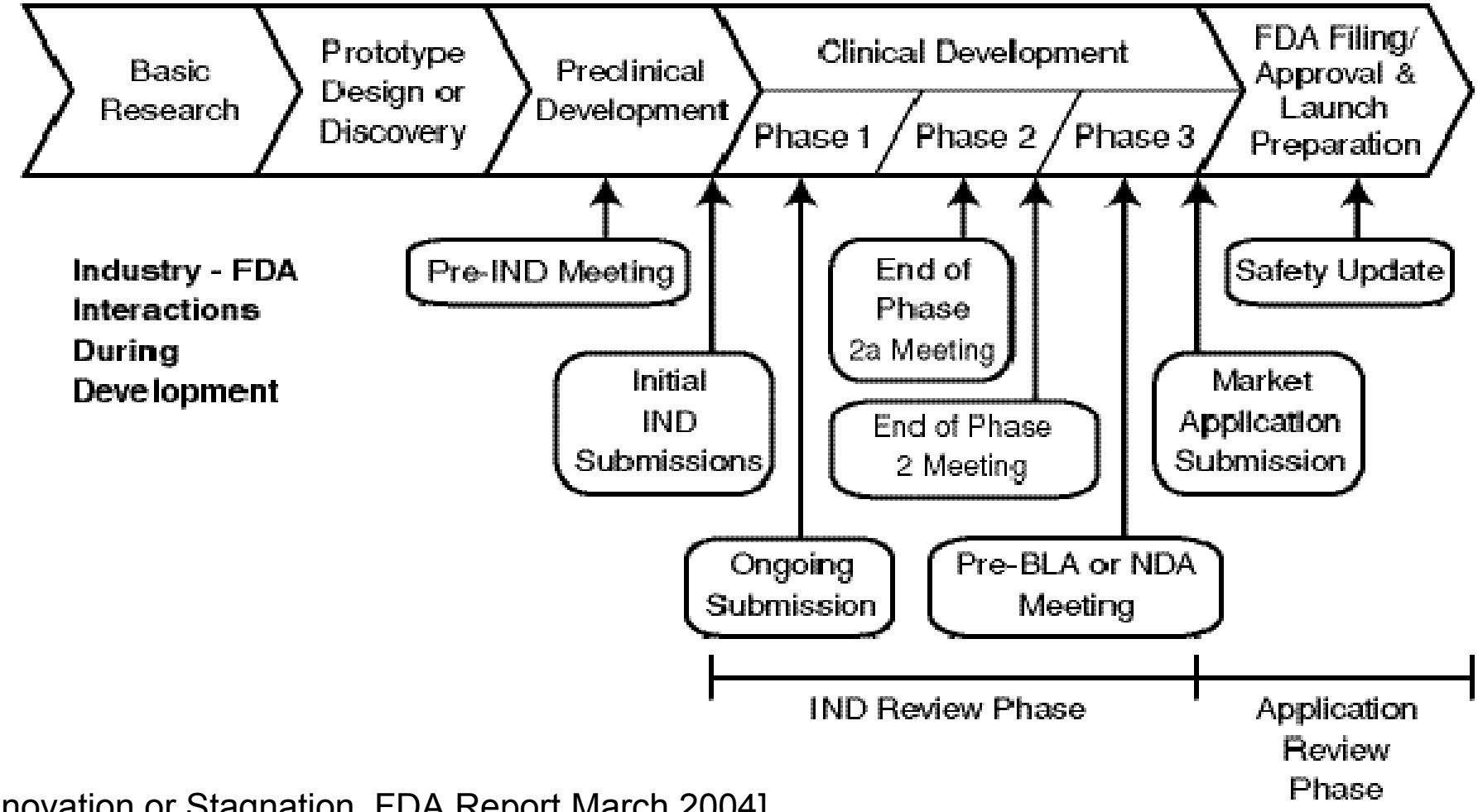
Impact of EMEA Scientific Advice on approval chances

In 2003, up to 45 % of applicants for Marketing Authorisations received prior Scientific Advice or Protocol Assistance

Chances of favourable outcome at the time of the opinion of the CPMP show positive correlation with prior SA / PA

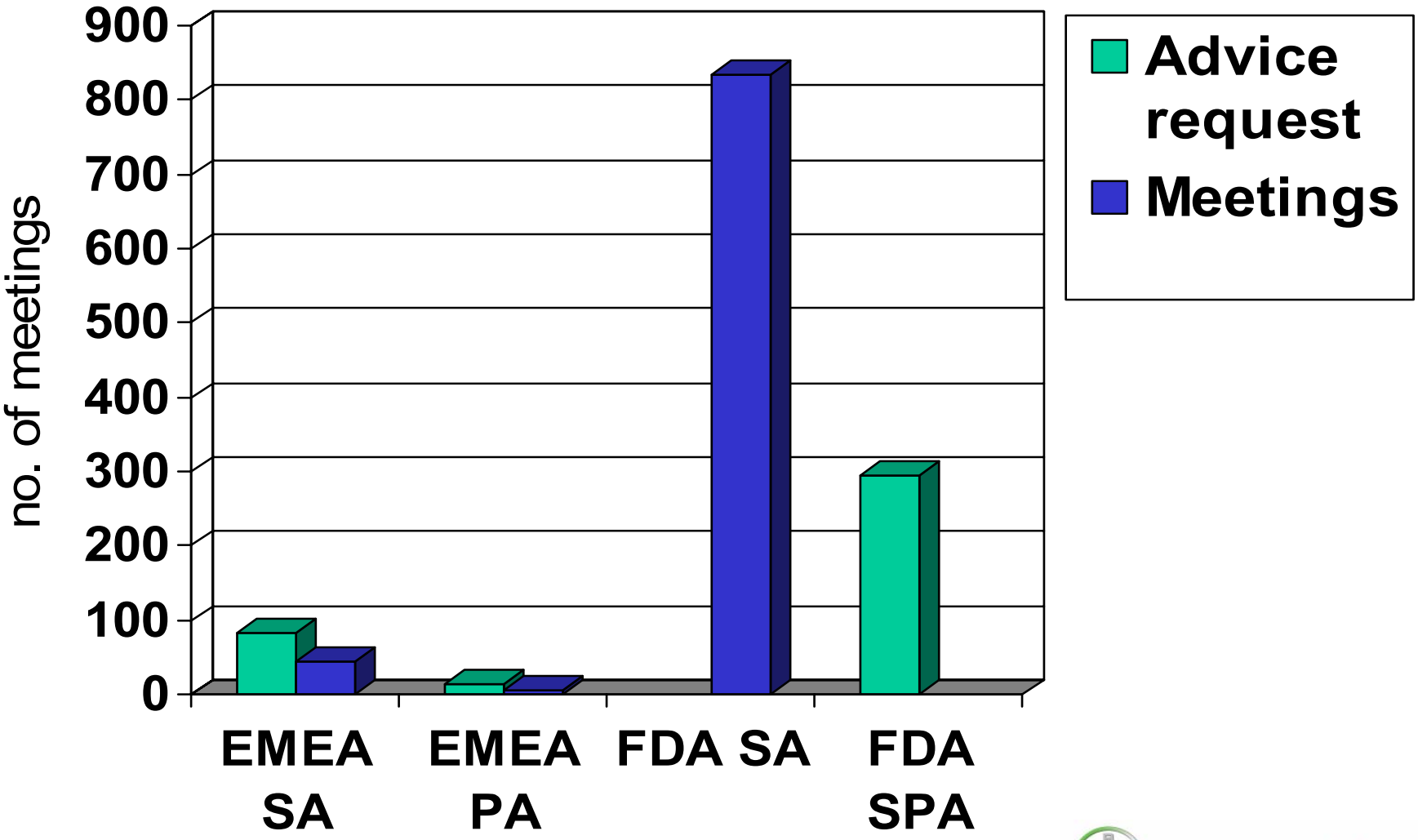
[9th Annual report EMEA activities 2003]

FDA Scientific Advice during drug development

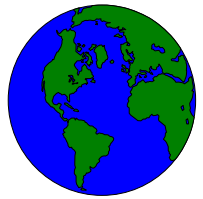


[Innovation or Stagnation, FDA Report March 2004]

2003 EMEA SA, PA and FDA SA meetings, SPA requests

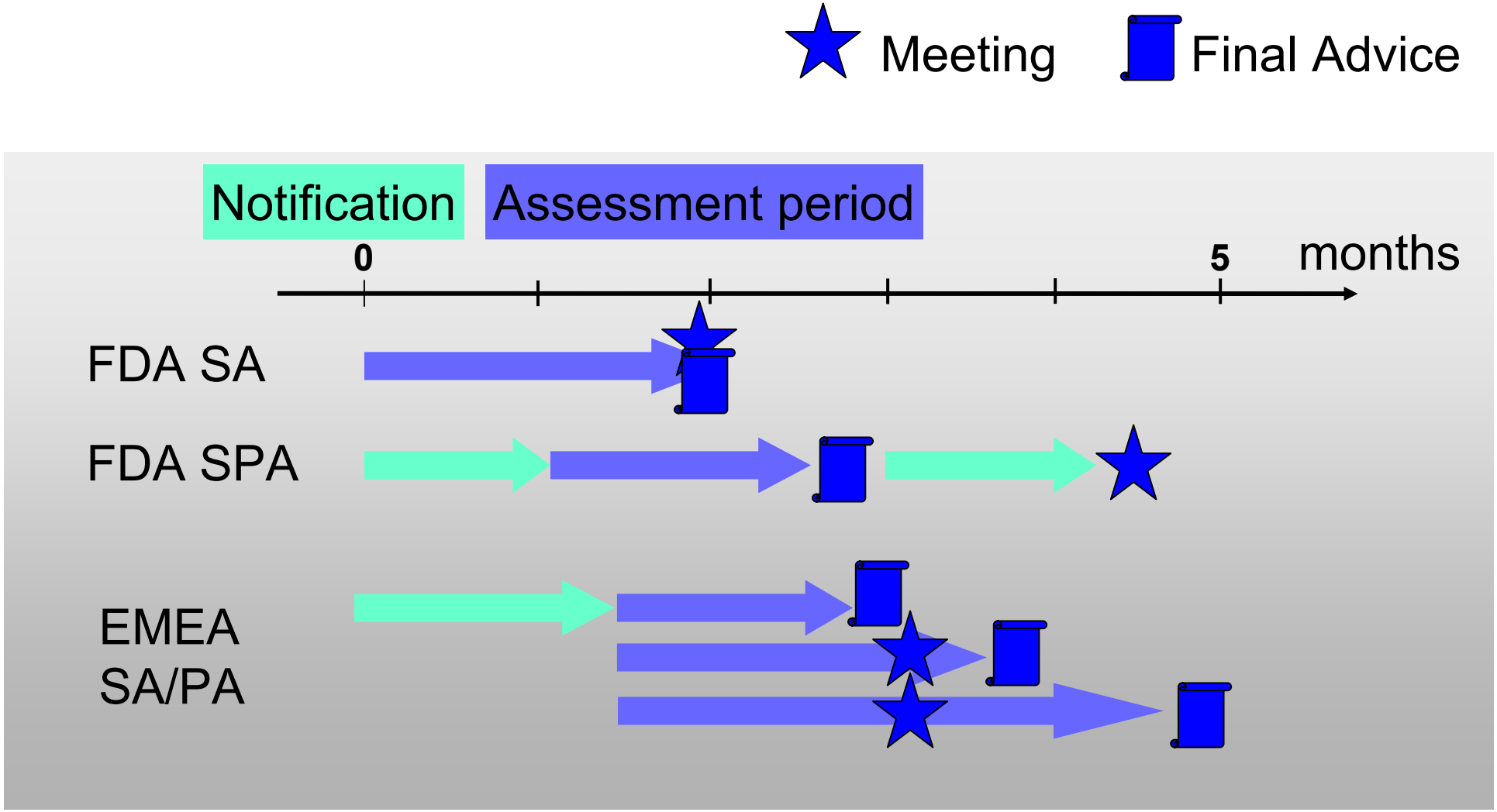


Industry perspective - Benefits pSA



- Allows for discussion and maximal information exchange on scientific issues
- Fills gaps if no guideline or precedent is available (see also announced shared guideline development)
- Strengthens Regulators guidance / impact during development
- Avoid unnecessary study replication in the two regions if agreement can be reached on an appropriate level - one efficient global development plan

Scientific Advice timelines FDA/EMEA



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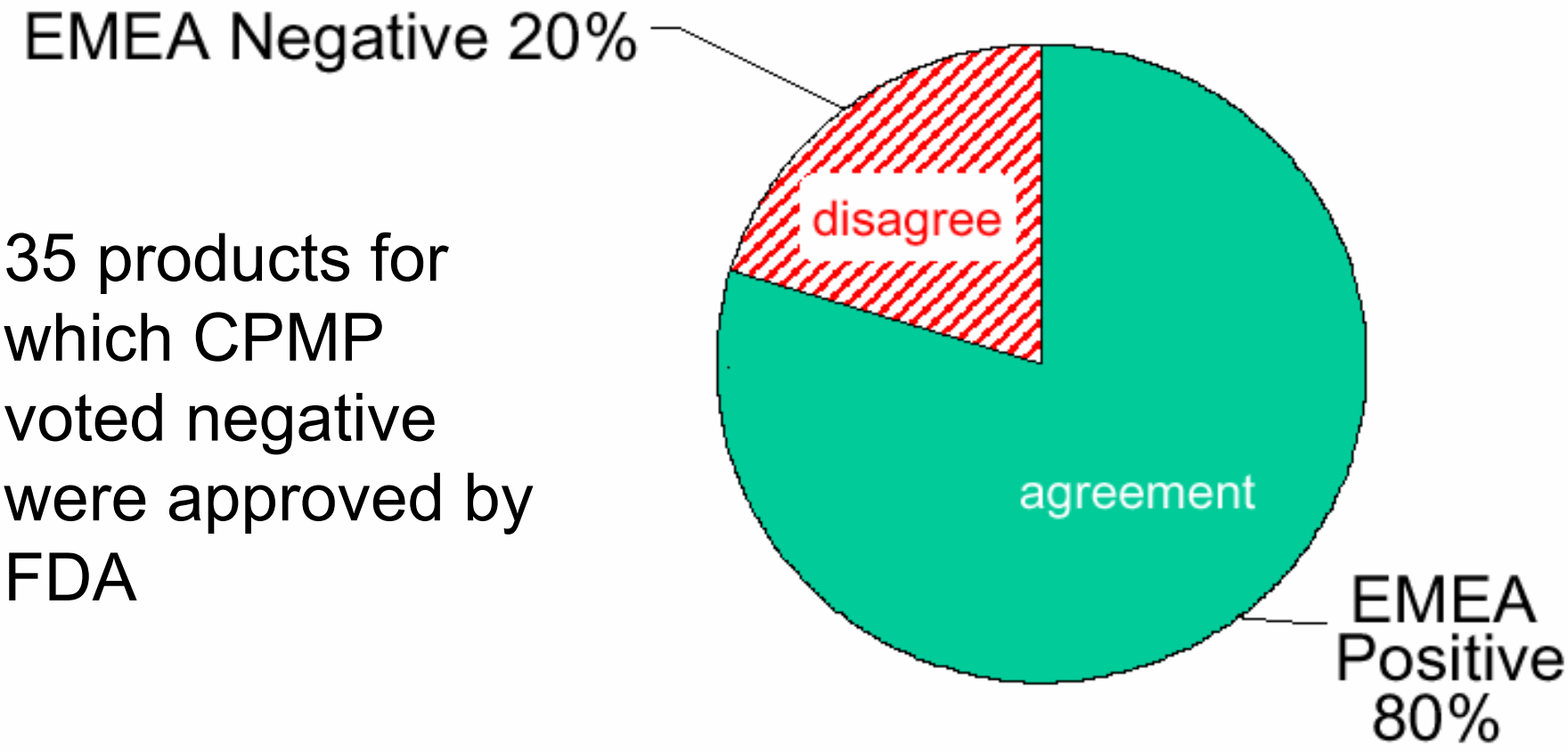
EMEA outcome for **FDA positive** applications (n=139)



35 products for which CPMP voted negative were approved by FDA

[E. Abadie, CMR Workshop Sept. 15/16 2003, Washington]

Industry perspective - Risks of pSA

- Missing transparency
  - procedure so far not formally described
  - industry not allowed to participate
  - there will be no joint outcome document
- Not really joint but parallel, outcome may differ
- Risk for higher hurdles (group dynamics, differences in therapeutic environment)
- Prolongs overall timelines for authority advice

When should Industry use pSA?

- For issues that can be solved on scientific level independent of therapeutic environment
- For conflicting EMEA/FDA advices that are major obstacles to further development
- If access to all markets by full program not speed to market is driver of development
- If CPMP and FDA guidelines deviate considerably
- To harmonise comparator treatment
- To benefit from special expertise of one authority

What Industry would really need

Transparency !

- Inform on preliminary advice to allow for pSA
- Industry participation in meetings

Flexibility !

- If deviations in seperate advice, follow up pSA
- Shorten SA procedure
- Compromises supporting globalisation

Simplify !

- Effective and simple meeting structures for (too many) stakeholders

FDA / EMEA co-operation - Good News

- Possibility for interaction facilitates global development
- EMEA, national EU authorities interested in FDA position

...Not yet so Good News

- Conflict resolution ?
- Sponsor involvement
- Increased FDA/EMEA information share w/o procedures
  - risk of preliminary / incomplete information
- Procedures/Guidelines to be developed for all areas
- FDA not yet asking for CPMP position
- What is the impact on ICH ?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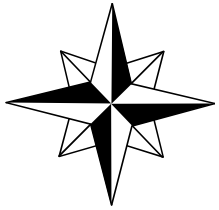
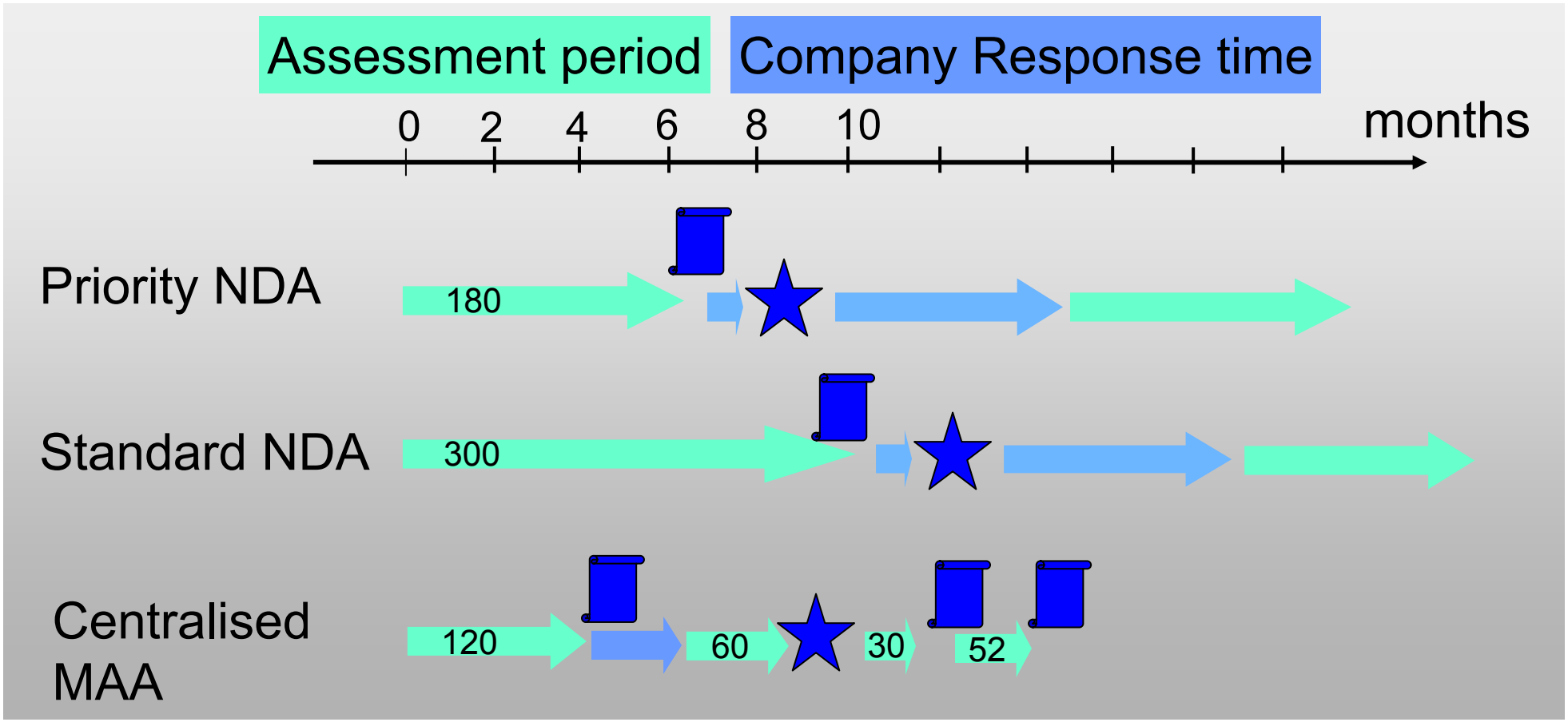
BACK UP



Approval procedure in EU and US



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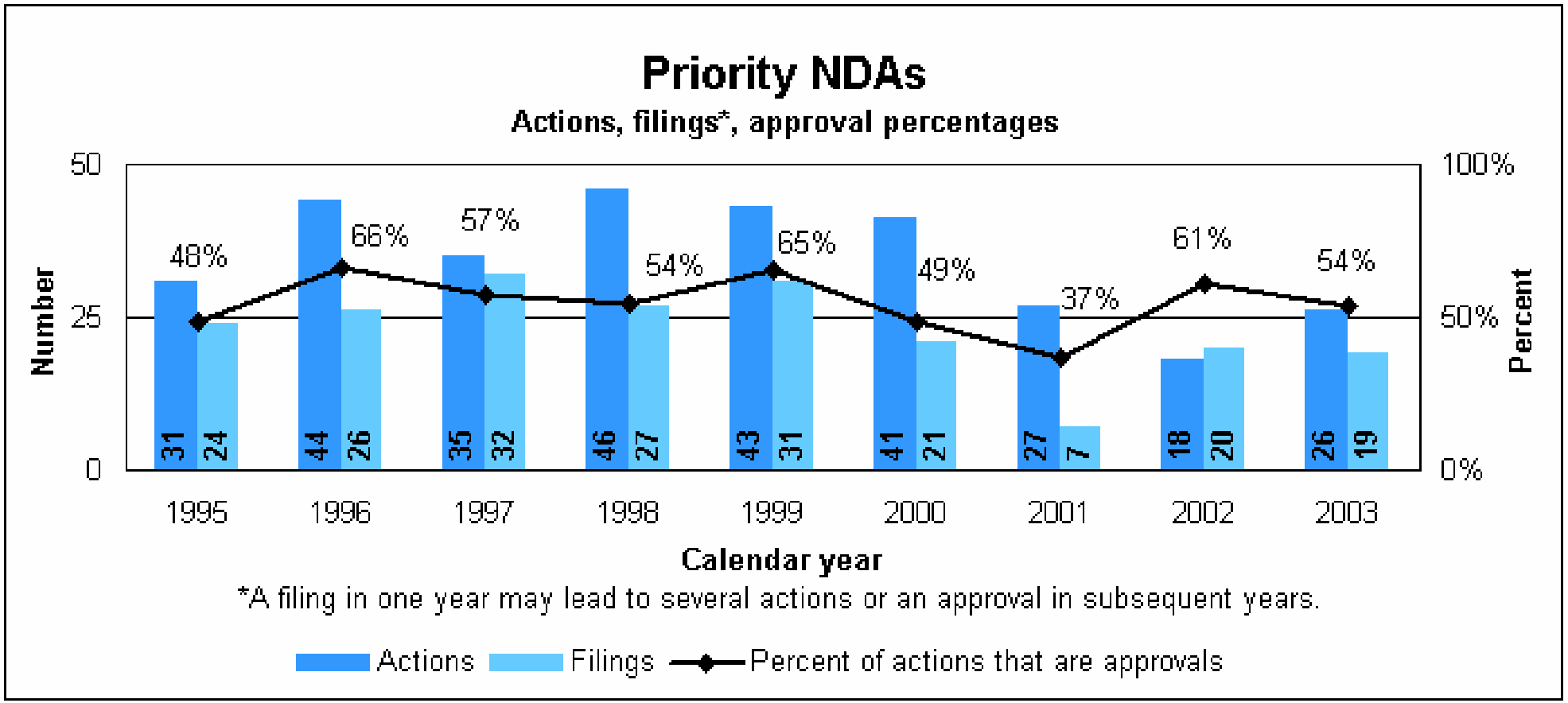
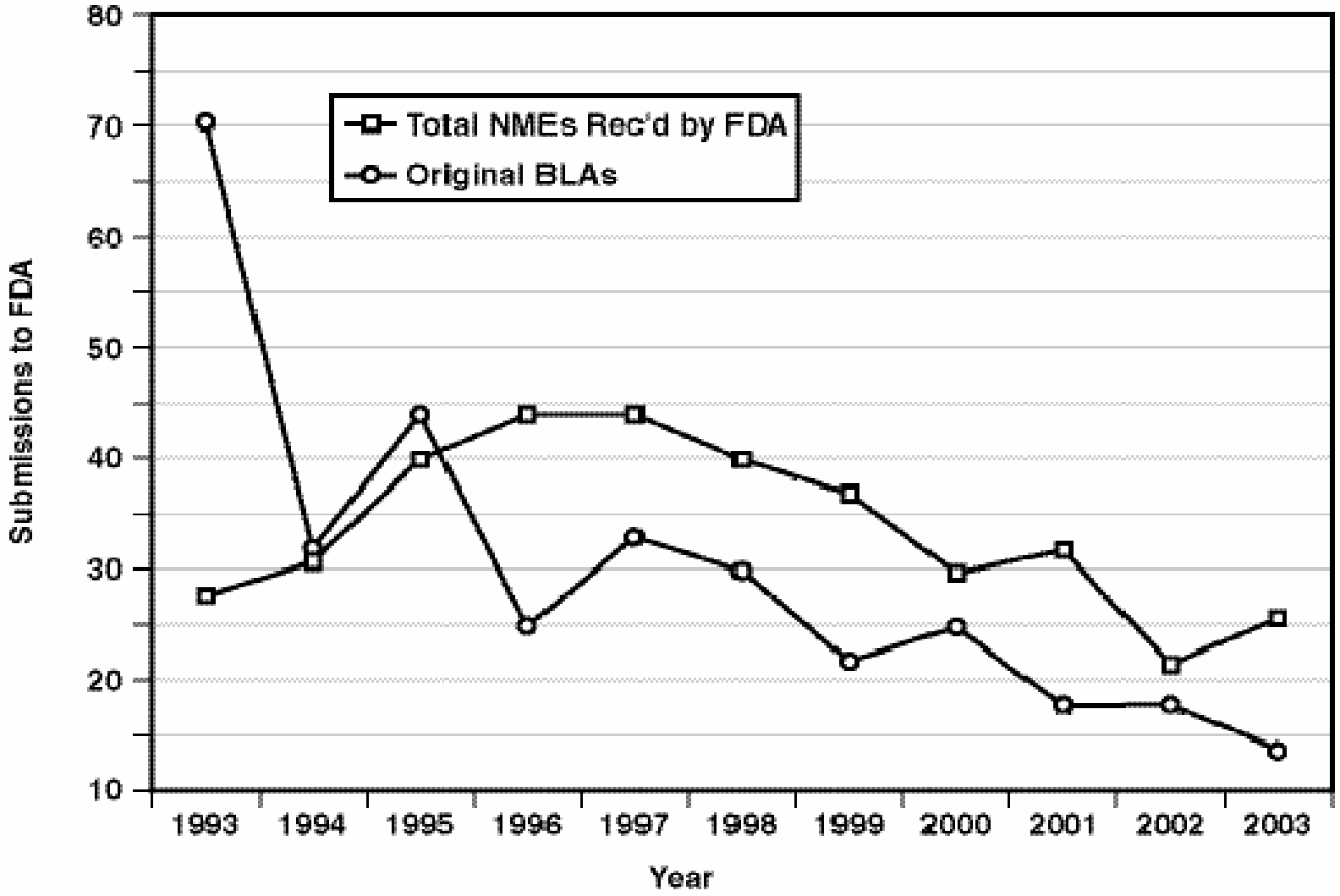

Priority NDAs
Actions, filings*, approval percentages
Number
Percent
50
25
0
100%
50%
0%
48%
66%
57%
54%
65%
49%
37%
61%
54%
31
24
44
26
35
32
46
27
43
31
41
21
27
7
18
20
26
19
1995
1996
1997
1998
1999
2000
2001
2002
2003
Calendar year
*A filing in one year may lead to several actions or an approval in subsequent years.
Actions
Filings
Percent of actions that are approvals

Figure 2: 10-Year Trends in Major Drug and Biological Product Submissions to FDA

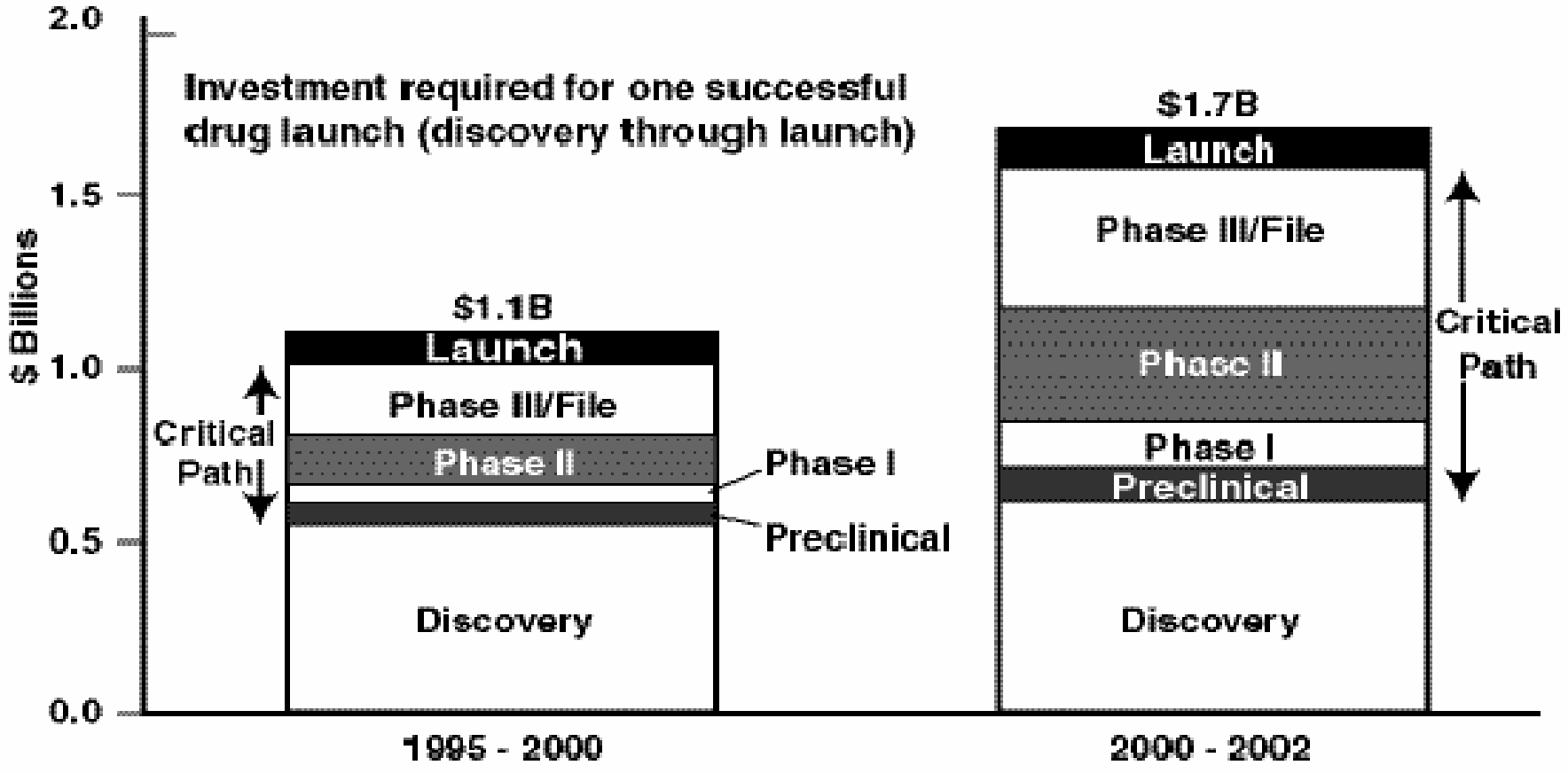


Innovation or Stagnation, FDA March 2004

Parallel Scientific Advice - Timelines

- Meeting co-ordination major challenge for project managers, inform well in advance
- Parallel approach needs exact timing
- Feedback in writing is no option in this case
- Delay by 2 m expected compared to conventional procedure

Figure 3: Investment Escalation per Successful Compound



Innovation or Stagnation, FDA March 2004

SOURCE: Windhover's In Vivo: The Business & Medicine Report, Bain drug economics model, 2003

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Can consensus be reached?

35 products for which CPMP voted negative were approved by FDA

20 of them FDA approved even without Advisory Comittee meeting

Submissions were not more than 2 years apart from each other

[E. Abadie, CMR Workshop Sept. 15/16 2003, Washington]

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