Implementing the Directive - from the Swedish Perspective

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Previous system in Sweden

CA
(LVFS 1996:17)
Approval of applications + substantial amendments (within timeframes)
GCP standard
GMP for IMPs
Safety and quality reports
Annual/final reports
Insp.: GCP 1993 - ;GLP;
GMP-insp. >50 y.

EC
Positive opinion on application
+ substantial amendments
Single opinion in MCTs
SAE reports reviewed by
CA
Final reports, on request

New regulations of the EC review of CTs in Sweden:

- Law on Ethical Review of Research in Humans (Jan 1, 2004), applicable to CTs from May 1, 2004
- Ordinance for EC review and for the work of the ECs (Oct 2003)
- Provisions for the work of the ECs (under development)

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EC Organisation
i.e. independent authorities

- 6 regional ECs
- EC members appointed by the government, nominated by university faculties and county council (10 scientists + 5 laypersons; chaired by a judge)
- Regional ECs financed by fees
- 1 central EC
- Central EC members (4 scientists + 2 laypersons; chaired by a judge)

EC Tasks

- Regional ECs: EC of principal investigator or co-ordinating investigator
- Opinion on clinical trials within timeframes:

  approval ± conditions, non-approval or hand-over to the central EC
- Central EC: Referrals, appeals, policy matters, supervision

Changes in the Medicinal Products Act (1992:859), April 2004

- Specified requirements for subject information and consent
- Special protection of minors and incapacitated subjects
- Sponsor obligation to provide IMPs without cost for the patient

Swedish exemptions from sponsor obligation to provide IMPs without cost in CTs:

- *performed without participation of the pharmaceutical industry*
- *in Orphan Drugs for which the granting of marketing authorisation has been linked to conditions for follow-up trials*
- *of special importance to public health*

Little need for CA changes in Sweden

- Previous Swedish regulations very similar to the new Directive requirements
- CA authorisation (explicit)
- Inspections in place
- Routines for phase I approval

Application to and contacts with Medical Products Agency May 1, 2004

LVFS 2003:6 (The Medical Products Agency's provisions and guidelines on clinical trials of medicinal products for human use)

June 26, 2003

www.mpa.se

LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

approvals • authorisation • clinical trials • communication • competence • cosmetics • dialogue • directives • efficacy • environment • evaluation • guidelines • harmonisation • health economics • herbals • homeopathics • information • inspection • laboratory analysis • market surveillance • medicinal products • narcotics • public health • quality • registration • regulations • reliability • risk/benefit • safety • scientific • standardisation • transparency • vigilance

Changes in Sweden
May 1, 2004

- Applicant to CA = Sponsor
- Electronic + paper application form
- One application in MCT
- Timeline for handling amendments
- No annual report
- Final report within 12 m. after end of CT

Implementation of Directive 2001/20/EC at the MPA

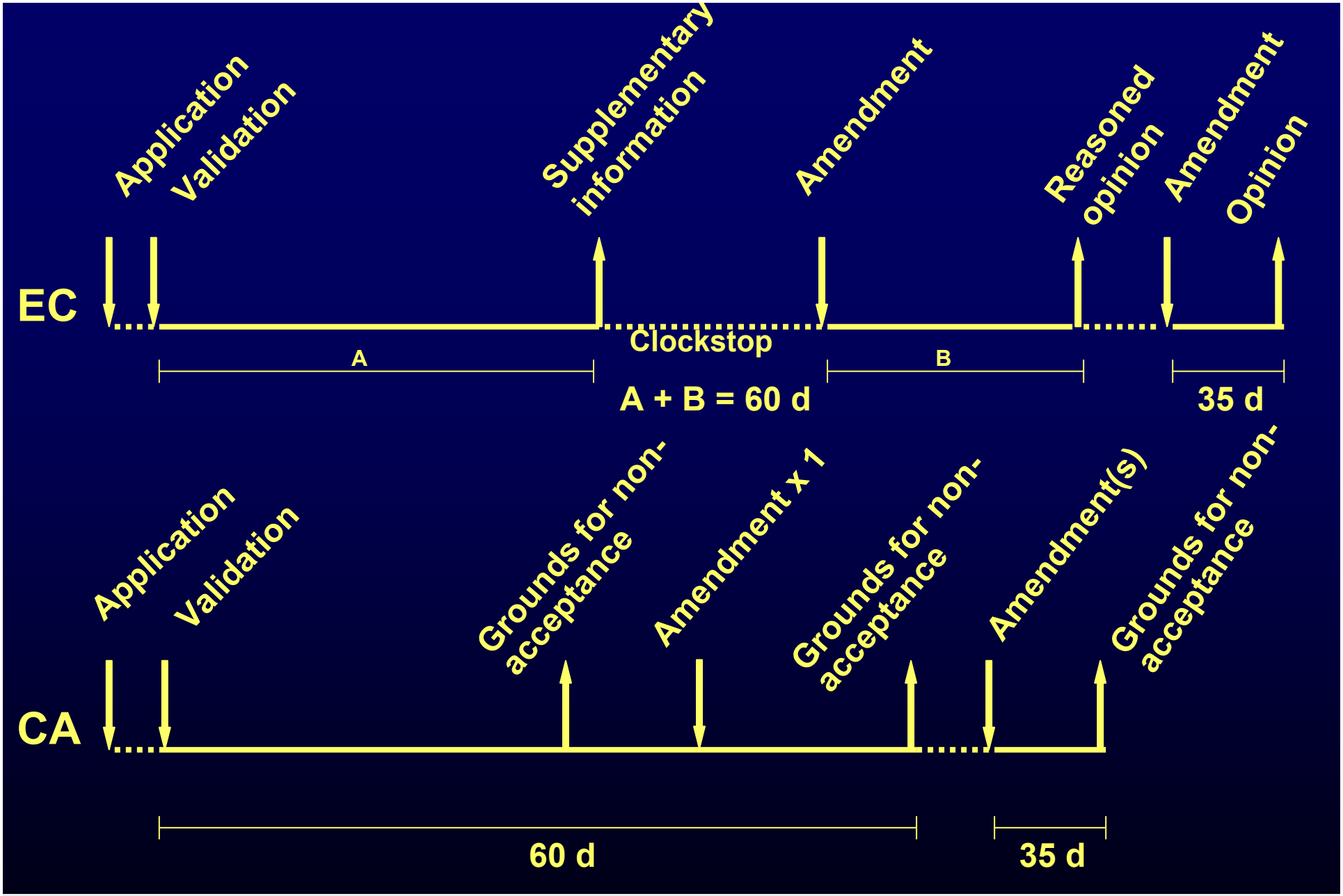
- The procedure
  - new regulations
  - new instructions
- Information
  - new updated MPA website
  - information meetings
  - telephone support to sponsors/CROs

New IT system - Documentum

- Document management (version control)
- Workflow with automated tasks
- Case management; track-keeping of deadlines
- Reporting function
- Audit trail

MPA review of CT applications

- Administrative check - 3-5 days
- Application not valid - supplementary documentation requested within 30 d.
- Application valid - clock starts - primary evaluation (usually) within 30 d.
- Need for additional information - amendment once, requested within 10 d. (as a rule)
- Trial can start unless grounds for non-acceptance have been given within 60 days by the MPA



Safety reporting to the MPA and the ECs in Sweden

- To the MPA:
- According to the Dir. 2001/20/EC and as explained in the Commission guidelines
- To the EC:
- Probably (not yet decided) according to the previous system, i.e. the reports are evaluated by the MPA and in case action is needed, the EC is informed

Challenges/Problems

- IMP without cost - ”solved” in Sweden
- Clinical trials in acutely incapacitated /comatous patients - issue not yet solved in Sweden
- Information exchange with ECs - procedure ongoing
- Efficiency/demands - on investigator/sponsor, CAs, health care system, political system -

a challenge to all parties

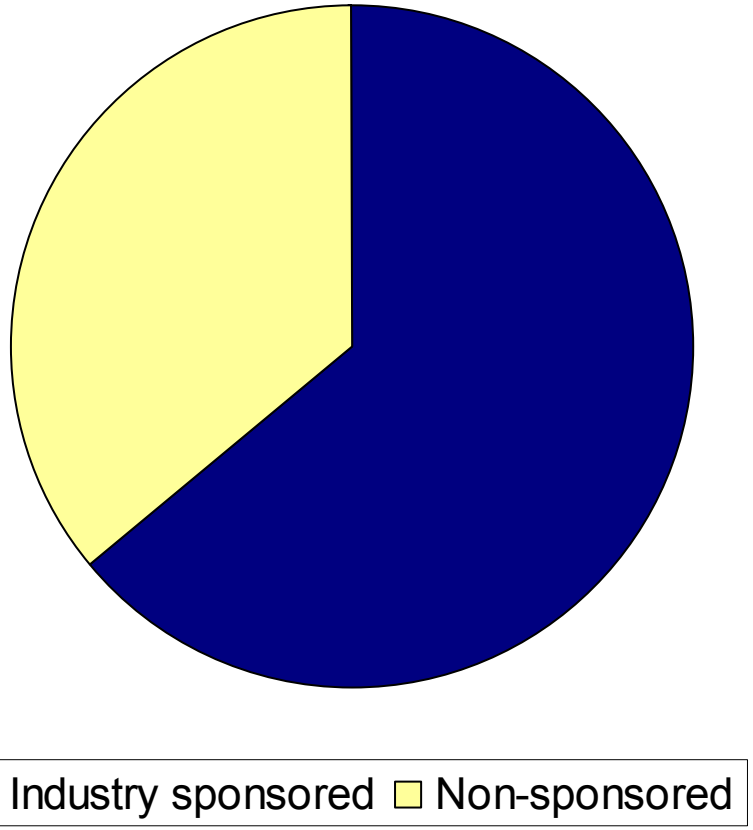
Exchange of information between EC and CA

- Conditional approvals/request for changes
- Rejection of single site(s) in MCT
- Addition of site(s)/ change of principal investigator.
- Grounds for non-acceptance of amendment
- Safety or quality concerns reported
- GCP inspections

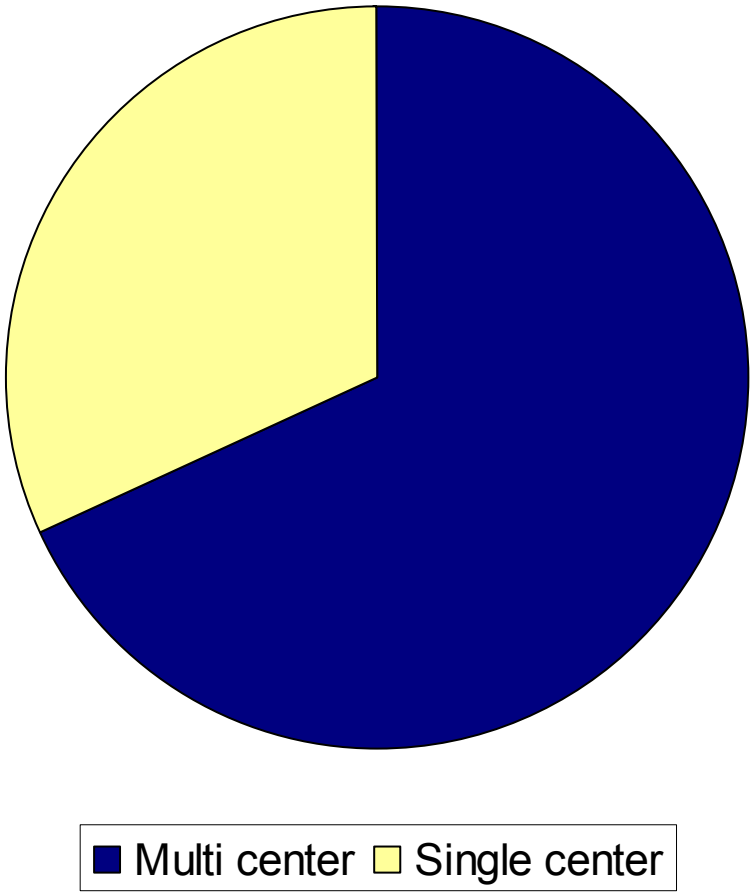
Non-commercial trials in Sweden

- Providing IMP without cost - Swedish law allows exemptions
- IMP can be provided by a pharmaceutical company - not linked to sponsor obligations
- Monitoring: cooperation and exchange of monitoring arrangements among research nurses
- GCP, GMP standards required since several years

Industry sponsored/Non-sponsored Clinical Trials in Sweden 2003



Multi center/Single center Clinical Trials in Sweden 2003



Applicants' contributions

- Well prepared applications
- Be present for contacts from the CA during application validation and handling

MPA contributions
in the CT application procedure

- Offer early contact/advice to sponsor
- Keep 30 days primary evaluation time
- Always written answers/authorisation
- Provide clear grounds for non-acceptance
- Continuos update of the MPA website

www.mpa.se

MPA contributions/activities

- Actively participate in education/information of all concerned parties
- Create fora for scientific discussion with ECs
- Attract more phase I-II trials to Sweden ”umbrella” system
- Attract more trials with ”advanced therapies” to Sweden
- Attract more phase IV - follow-up studies to Sweden - unique possibilities for patient follow-up/analysis of background risks

Multi-step Clinical Trials in Sweden
Phase I/II

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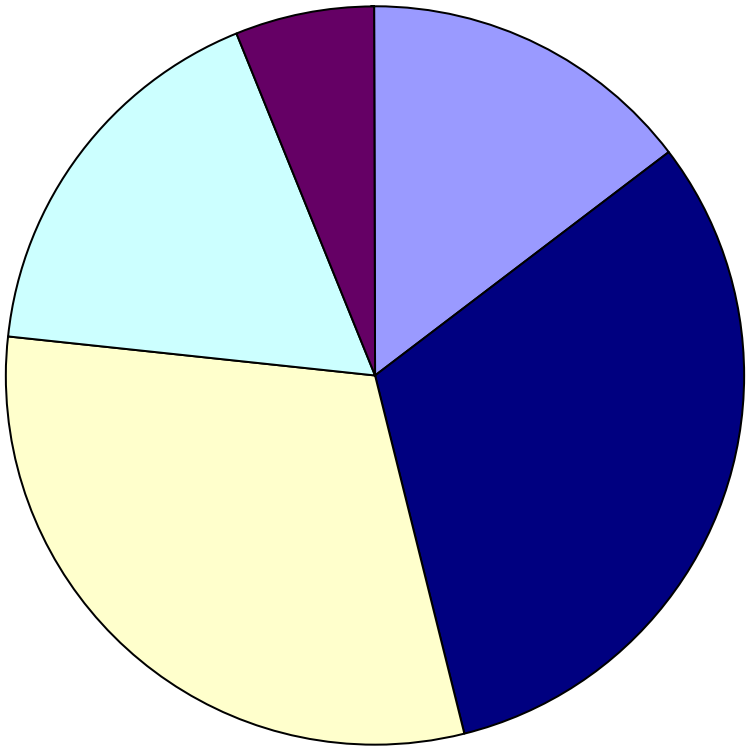
SE Multi-Step CT Applications

- Uses
  - Interdependent designs
    Selection of dose or formulation from a first step
  - Critical safety issues
    Very toxic compounds and/or narrow margins:
    Step-wise dose increments with back-reporting/confirmation
- Provisions
  - SE directive implementation LVFS 2003:6 §10
    Allows for mandatory reporting to MPA at critical steps

Clinical Trials in Sweden 2003



Swedish experiences from the Directive

May 1 - June 11, 2004

- 1st CT application in the EU - from Sweden
- 1st CT approval in the EU - from Sweden
- Overall, 35 CT applications in the EudraCT (June 11, 2004),
- Overall, 19 CT applications to the MPA (June 11, 2004)

Summary/Conclusion
Swedish Experience

The new system provides Challenges/Opportunities for clinical trials in the Community

The new system requires few changes in Sweden