

Early Drug Development — Scientific and Regulatory Challenges

Session II: Implications of the new EU-directive on clinical trials

**Experience report from the first year of working
within the new regulatory environment:
Germany**

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- **The EU-Directive 2001/20/EC and the corresponding**
- **Guidance Documents e.g.**
 - Detailed guidance on the request for authorisation to the competent authority
 - Detailed guidance on the application for an Ethics Committee opinion
 - Detailed guidance on the European clinical trials database
 - Detailed guidance on the presentation of adverse reaction reports
 - Detailed guidance on the European database of SUSARS
- **has been transferred to the German drug law and related regulations and are effective since August 6th, 2004**

- **The German Drug Law: “12. AMG Novelle”**
 - § 4 Definitions
 - §§ 40 - 42a general regulations
- **Rechtsverordnung: “GCP Verordnung” based on § 42a**
 - Detailed rules
- **“3. Bekanntmachung zur klinischen Prüfung” draft**
 - Detailed rules from the CA for request for authorisation

- **The report on the experience with the German Drug Law: “12. AMG Novelle” is based on a survey of timelines from 12 CROs and companies and 48 studies and divided in**
- **Learning phase from August to November 2004 and**
- **Consolidation phase from December 2004 till March 2005**

Phase I Studies in Germany Situation until August 2004

- Only one advisory meeting by the EC responsible for the principal investigator was required
- Planning security
- Average approval period EC: 23 days
- Start of study in general: 28 days after submission
- Completion of documents could be well planned
- Reservation of „Time Slot“ in the CRO: 2 - 3 months before start of study
- Approval period for amendments: 3 - 4 days

(Data are related to EC Düsseldorf)

Phase I Studies in Germany

Situation from August to November 2004

Summary on the basis of 26 resp. 25 Phase I studies:

Approval time BfArM (26): \emptyset 49 days (range 28 - 90 days)
(from submission until approval)

Approval time Ethics Committee (25): \emptyset 31 days (range 13 - 56 days)
(from submission until positive
assessment)

The majority of queries/deficiencies was related to formal issues and not foreseeable. Therefore planning was not possible.

Phase I Studies in Germany

Summary August 2004 to November 2004

Detailed BfArM data on the basis of 26 studies:

Study approvals without queries:	6 of 26 studies
Queries due to formal issues:	20 of 26 studies
Queries after:	∅ 11 days (0 - 25)
Response to notification of formal issues :	∅ 5 days (1 - 11)
Deficiency letter regarding contents:	11 of 26 studies
Time between first submission and deficiency letter:	∅ 44 days (16 - 67)
Time between response to notification of formal issues and deficiency letter: (legal period: 30 days)	∅ 29 days (13 - 32)

Phase I Studies in Germany

Summary August 2004 to November 2004

Detailed EC data on the basis of 25 studies:

Study approvals without queries:	6 of 25 studies
Queries due to formal issues:	16 of 25 studies
Queries after:	∅ 10 days (3 - 33)
Response to notification formal issues :	∅ 6 days (1 - 14)
Deficiency letter regarding contents:	6 of 25 studies
Time between first submission and deficiency letter:	∅ 25 days (21 - 29)
Time between response to notification of formal issues and deficiency letter: (legal period: 30 days)	∅ 15 days (7 - 23)

Phase I Studies in Germany Situation from December 2004 until March 2005

Summary on the basis of 22 resp. 16 Phase I studies:

Approval time BfArM (22): \emptyset 41 days (range 30 - 52 days)
(from submission until approval)

Approval time Ethics Committee (16): \emptyset 36 days (range 14 – 61 days)
(from submission until positive
assessment)

Situation well improved with respect to timelines and formal issues

Phase I Studies in Germany

Situation from December 2004 until March 2005

Detailed BfArM data on the basis of 22 studies:

Study approvals without queries:	4 of 22 studies
Queries due to formal issues:	17 of 22 studies
Queries after:	∅ 10 days (5 - 14)
Response to notification of formal issues :	∅ 6 days (1 - 13)
Deficiency letter regarding contents:	1 of 22 studies
Time between first submission and approval:	∅ 41 days (30 - 52)
Time between response to notification of formal issues and approval: (legal period: 30 days)	∅ 30 days (28 - 33)

Phase I Studies in Germany

Situation from December 2004 until March 2005

Detailed EC data on the basis of 16 studies:

Study approvals without queries:	5 of 16 studies
Queries due to formal issues:	7 of 16 studies
Queries after:	∅ 6 days (5 - 7)
Response to notification of formal issues :	∅ 7 days (1 - 12)
Deficiency letter regarding contents:	8 of 16 studies
Time between first submission and deficiency letter:	∅ 23 days (16 – 35)
Time between response to notification of formal issues and deficiency letter: (legal period: 30 days)	∅ 11 days (2 - 22)

Phase I Studies in Germany Conclusion

- After a learning period of all parties involved, approval times are improved and now in a mean range of 36 days for EC & 41 days for BfArM
- Planning security is improved
- Formal issues/requests without consequences for the contents should have no influence on the timelines.
- The approval period of 14 days for consecutive phase I studies of one project which is foreseen in the law (GCP-Verordnung §§ 8 & 9 Abs.3) should be applied more widely.

Phase I Studies in Germany Example Development Plan

Dependency of the development period for a new product
from the approval times of the competent authority and
Ethical Commission

Example:

Phase I Studies in Germany

Example Development Plan

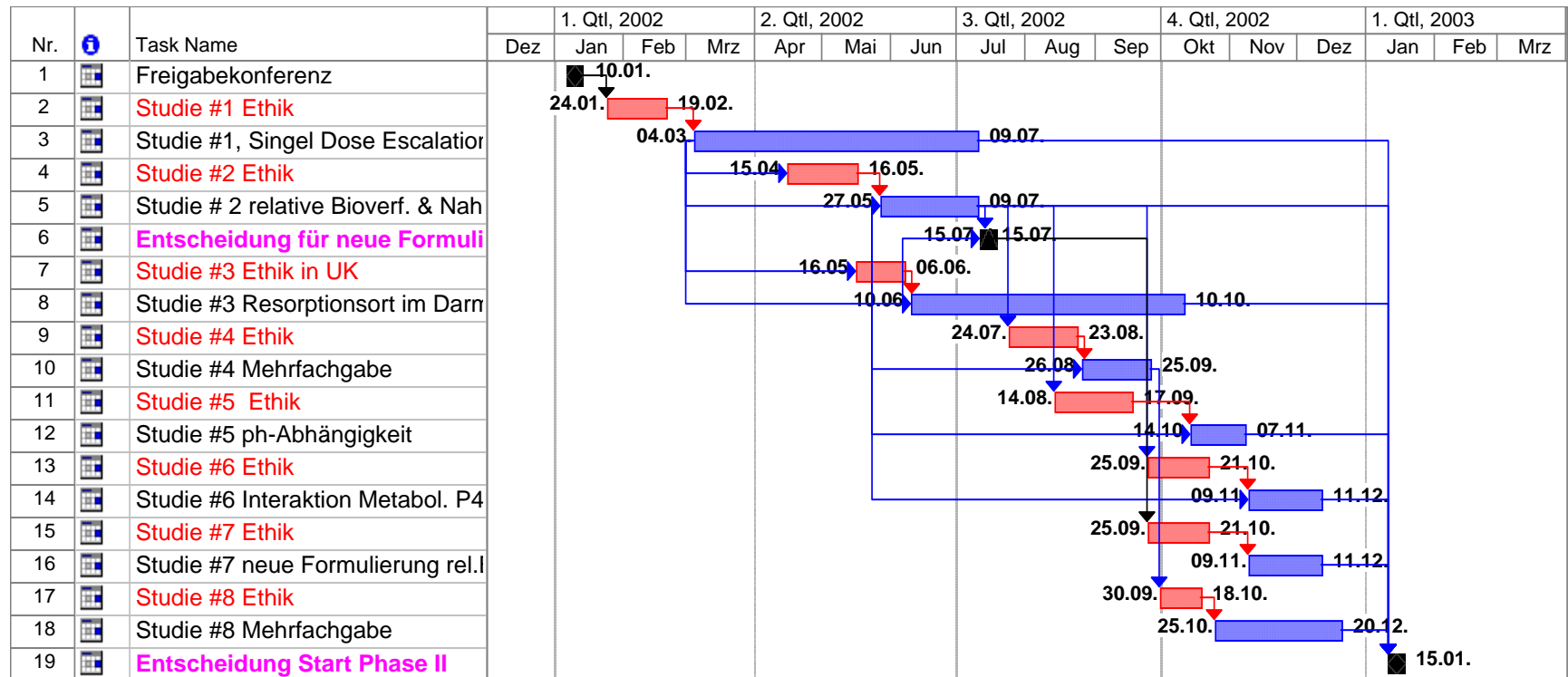
- The following example shows the consequences of a prolonged approval period for the development times of a phase I program.
- Due to the sequential performance of clinical pharmacological studies, an additive effect on the entire development time of a phase I program is generated which is frequently underestimated.
- A decisive factor for the development plan is not the formal approval period determined by law, but the actual period from the first submission until the clinical start of the study and thus until the availability of results.
- The example is based on the actual performance of the study sequence of a project in 2002 with an approval period of about 20 - 30 days between submission and start of study.

Phase I Studies in Germany

Development Plan before August 2004

Consequences for development times:

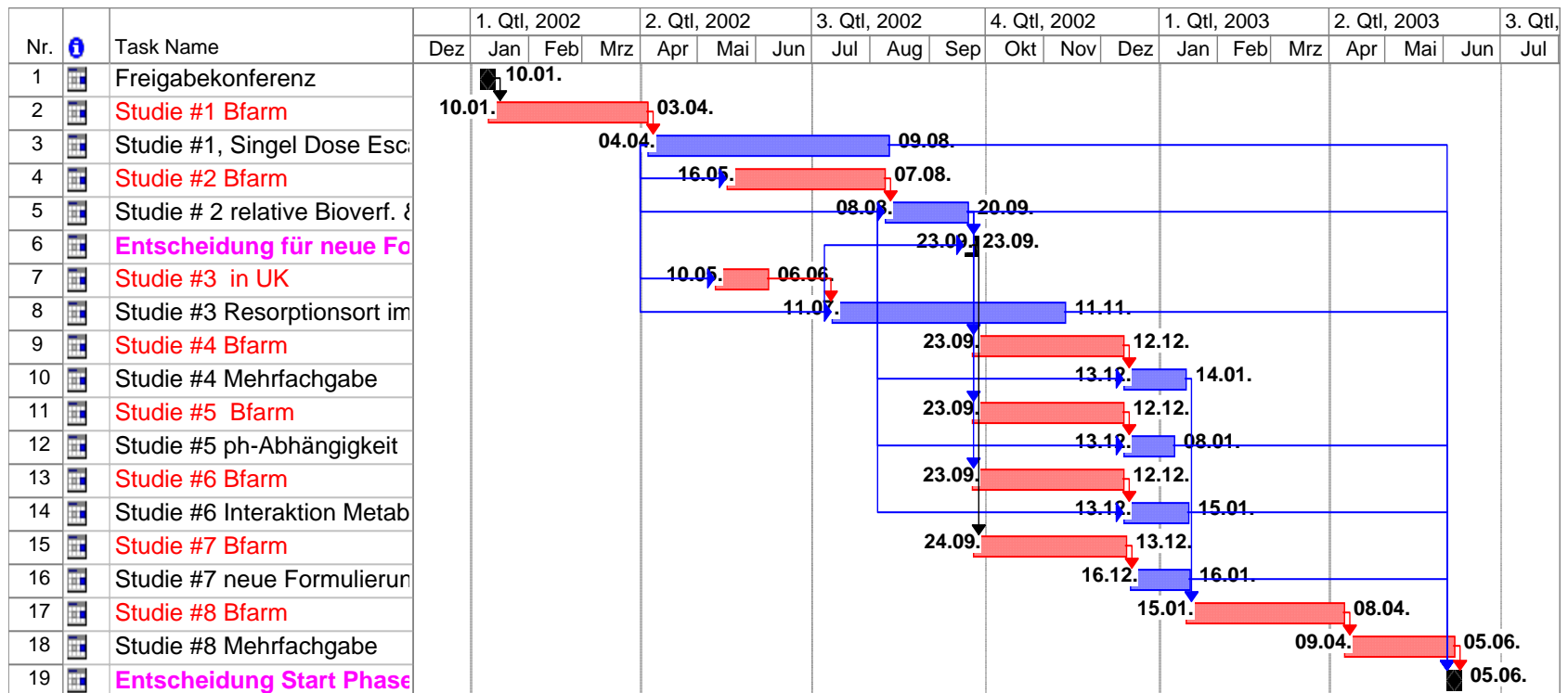
Submission and approval: **20 -30 days**
 Start phase I: **10.1.2001**
 Decision start phase II: **15.1.2002**



Phase I Studies in Germany Development Plan with Prolonged Approval Times

Consequences for development times:

Submission and approval: **60 days**
 Start phase I: **10.1.2005**
 Decision start phase II: **05.6.2006**



Phase I Studies in Germany Development Plan from August 2004

Consequences for development times:

Submission and approval:	23 days	
Start phase I:	10.1.2005	
Decision start phase II:	05.1.2006	
Complete duration until decision:	1 year	-5 days
Submission and approval:	60 days	
Start phase I:	10.1.2005	
Decision start phase II:	05.6.2006	
Complete duration until decision:	1 year	+156 days