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# AGAH - Annual Meeting 2005 - Club Phase 1

## 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

**Strasburg, March 17th, 2005**

**Dr. Reiner Frey**

**Klinische Pharmakologie**

**Bayer HealthCare AG**

**Wuppertal**



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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**

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- **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**

# AGAH - Annual Meeting 2005 - Club Phase 1

- **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**

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# 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)**

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# 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):** **∅ 49 days (range 28 - 90 days)**
**(from submission until approval)**

**Approval time Ethics Committee (25):** **∅ 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.**

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# 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) |

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# 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) |

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# 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):** **∅ 41 days (range 30 - 52 days)**
**(from submission until approval)**

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

**Situation well improved with respect to timelines and formal issues**

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# 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)** |

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# 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) |

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# 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.

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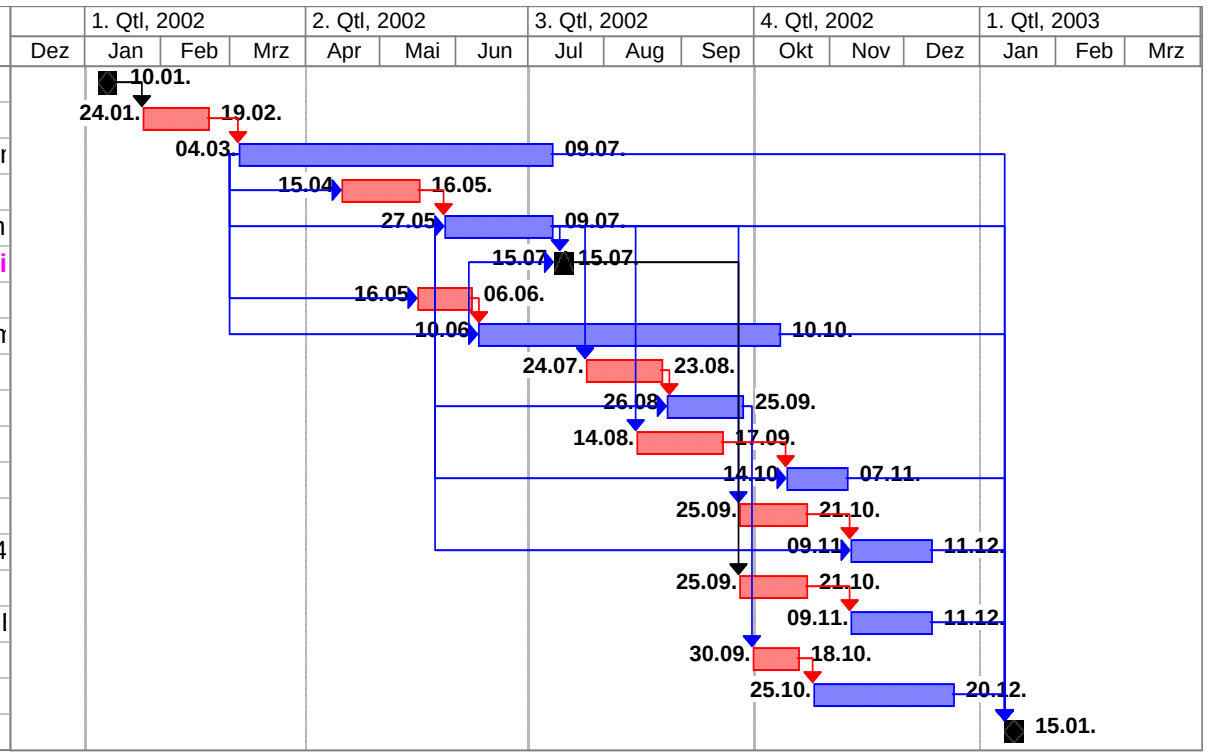
# Phase I Studies in Germany
# Development Plan before August 2004

## Consequences for development times:

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

| Nr. | Task Name |
|---|---|
| 1 | Freigabekonferenz |
| 2 | Studie #1 Ethik |
| 3 | Studie #1, Singel Dose Escalatior |
| 4 | Studie #2 Ethik |
| 5 | Studie # 2 relative Bioverf. & Nah |
| 6 | Entscheidung für neue Formuli |
| 7 | Studie #3 Ethik in UK |
| 8 | Studie #3 Resorptionsort im Darm |
| 9 | Studie #4 Ethik |
| 10 | Studie #4 Mehrfachgabe |
| 11 | Studie #5 Ethik |
| 12 | Studie #5 ph-Abhängigkeit |
| 13 | Studie #6 Ethik |
| 14 | Studie #6 Interaktion Metabol. P4 |
| 15 | Studie #7 Ethik |
| 16 | Studie #7 neue Formulierung rel.I |
| 17 | Studie #8 Ethik |
| 18 | Studie #8 Mehrfachgabe |
| 19 | Entscheidung Start Phase II |



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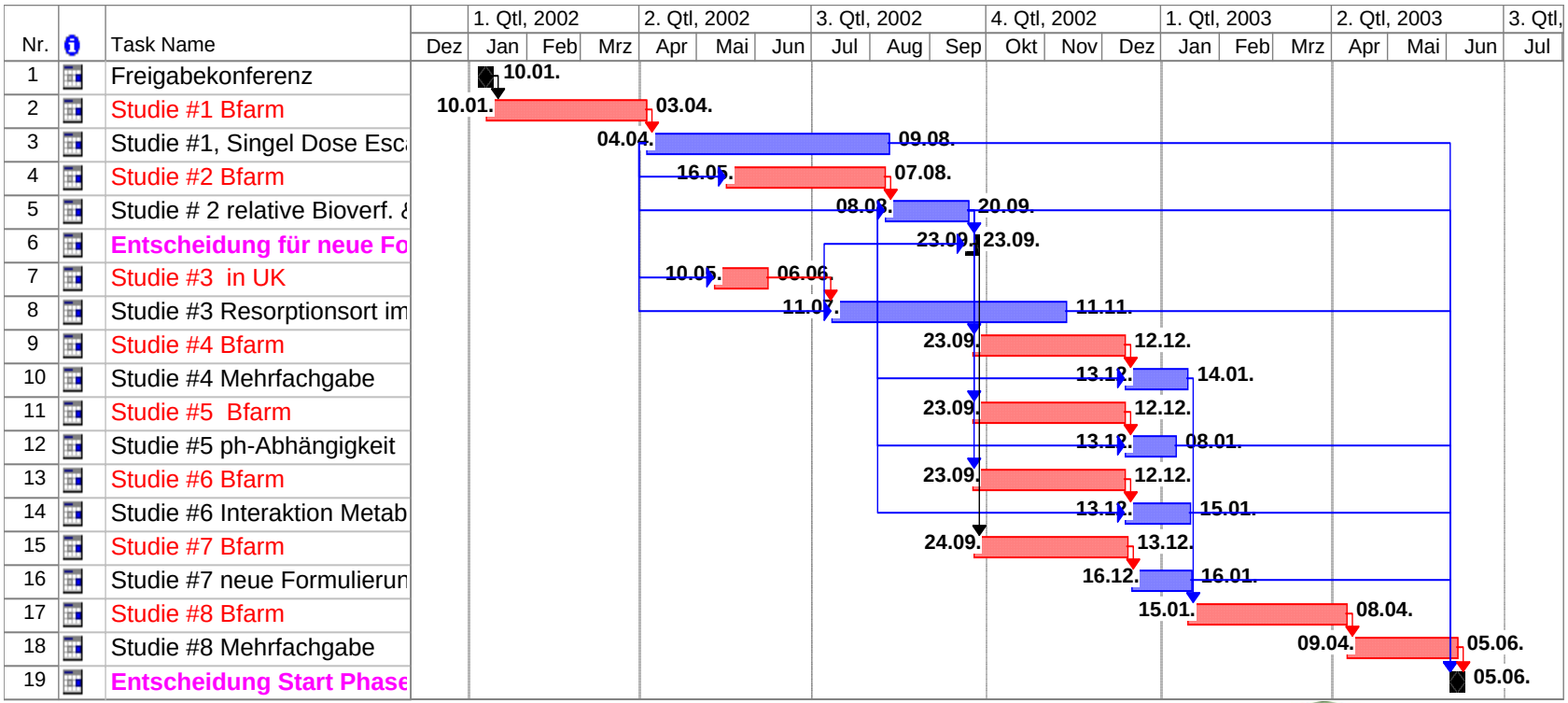
# Phase I Studies in Germany
# Development Plan with Prolonged Approval Times

## Consequences for development times:

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



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# 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** |