European Federation for Pharmaceutical Sciences
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Draft Proposal
Accompanying Measure
EU RTD FP6

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An Integrated Project on

RESEARCH ON AND OPTIMISATION OF CLINICAL TRIALS IN EUROPE

Proposals for research topics, methodologies, techniques and other means to the benefit the European citizens for obtaining new safe medicines faster.

The Challenges

- Can society afford the current level of drug development costs?
- Is it ethical to use resources involving patients and health care personnel on trial activities having only marginal importance – internally as well as externally?

Vision

All the many potential deliverables for health care created as the result of the recent genomic and biotechnological research will have to pass the already existing bottleneck: downstream drug development. A reduction or removal of this bottleneck is crucial for full exploitation of these new advances. Thus, the goal of the present project would be to:

- Optimise the drug development process
  – in order to obtain new safe medicines faster
- Give Europe the best drug development system in the world
  – by applying state-of-the-art technologies in the various parts of the drug development process
- Adjust all regulatory procedures from a science based view
  – to minimise bureaucracy and maximise external validity of clinical trials to patients and society

Means

Europe has, within the pharmaceutical sciences, sufficient research bases of excellence, the multidisciplinary skills, the networking and the ability to conceive the suggested solutions through the "New Safe Medicines Faster" initiative, and the funding and European infrastructure of the 6th Framework Programme of the European Union.

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Objectives

I Set "New Safe Medicines Faster" in motion

II Perform research aiming at providing evidence on how to remedy the downstream drug development bottlenecks.

III Optimise the drug development activities of all contributors of the process through better interaction.

IV Implement the new science based principles of the regulations in Europe and to adjust all activities accordingly.

Research hypotheses as basis for the integrated EU research programme

Postulate: Research results and advances in methodologies and technologies being relevant for the drug development processes are considerable and in progress - but their implementation in the drug development process are lacking behind (e.g. micro-dosing, imaging technologies, clinical trial design)

Hypothesis/Implications: A number of these methodologies and technologies can be and should be implemented.

Postulate: A number of the paradigms underlying drug development (and the procedures based thereupon) are outdated. These regulations are to a large extent prohibiting the methodological progress and add to the burden of bureaucracy (e.g. the randomisation principle blocking the use of biomarkers and e.g. quality assurance procedures).

Hypothesis/Implications: The regulatory paradigms can and should be changed.

Some methodology principles of the integrated project

Review studies: 1) Analyse selected systems/regulations with the aim of identifying superfluous activities, and 2) Analyse state-of-the-art technologies with the aim of identifying their relevance for novel application for the drug development process.

Experimental research: Select specific technologies and design experimental studies for the verification and validation of the relevance of the application of novel methodologies and technologies in the drug development process.

Bench marking: Perform global bench marking with current drug regulatory systems to be able to select the best principles and practice.

Publication: Propose a reshaping of both the drug development activities and the regulatory approval processes according the results obtained.

Preconditions

The proposed research programme can in no way be performed by a single "stake-holder" - be it industry, academia, health care providers or authorities. A coordinated effort is needed. Thus, a united multi-excellence effort is a prerequisite for planning and executing the relevant research programme and implement the results.

The efforts needed must be included in a joint programme – otherwise, it will be impossible to perform the research needed.

The future lies in learning trials as the current system is designed to exclude learning (e.g. randomisation can be performed after bio-marker assessing - however, this is not allowed under to current clinical trial paradigm). It is important to create a stream of trials that are conducted outside the industry sponsored trials and involving academia.

Observations supporting the hypotheses pertaining to the project:

Problems:

- The cost for the society for drug development is too high; we are going the wrong way.
- The industry focuses on own products and neglects the generic problems.
- The academic world is too fragmented to address the generic problems in the scale needed.
- Patients' access to new medicines is delayed.
- The drug development process is ineffective due to e.g. poor predictive capacity. The society will not pay for all the failures since a 50% attrition rate still exists when 75% of the money has been used.
- Clinical trials often have poor external validity in contrast to their high internal validity.
- Industries make misinterpretations ("over-interpretations") of the guidelines, e.g. taking them too rigorously.
- Researchers are not sufficiently involved in the regulatory work and this leads to suppression of science-based points of view.
- More evidence-based medicine is needed.

Bottlenecks:

- Intervention studies should be facilitated.
- Databases cannot talk to each other.
- Ethic Committees are locally based and mutual recognition systems do not exist. This means that cultural thinking plays a large role.
- Ethics is not an objective assessment, since moral changes over time.
- Training is equally important to research. More training is needed.

Barriers:

- For clinicians, the major problem of clinical trials is that they "drown in paper". This takes the forces away from the real issues: the best planning and performance of the clinical trial.
- There is limited interest in spending money on the validation of new methodologies of the drug development processes.
- The strength of EMEA is no satisfactory.
- The European Biotechnology Directive on clinical trials has not improved the situation, rather, it has worsened the situation.
- The role of the industry changes rapidly these days which gives problems due to a blurred border between the academic and the industrial world.
- Industries cannot go for "relaxed" trials.
- Today it is often the responsibility of the individual doctor to obtain the necessary training for him/her.
- Experimental results on drug candidates never reaching the market, still have to be disseminated instead of being kept in the drawers of the industries. For this reason public databases are needed.

Preliminary specific research topics
Some of them include:

- Prediction techniques in general, including best application of statistics.
- Microdosing, i.e. regulatory requirements before first dose in man. Test of multiple candidates.
- Clinical trial design, including how to define biomarkers relevant for the clinical endpoints. Randomise according to the biomarker results.
- Creation of public databases.
- Level of confidence and acceptance of *in vitro*/*in silico* tests.
- Definitions of level of confidence that suit the objectives of the investigation.
- Better chemistry for labelling of drug candidates for PET investigation
- Identification and validation of new bio/surrogate markers and end-points.
- Multivariate analysis of clinical test parameters to obtain more reliable end-points faster.
- Near patient diagnostic tests.
- Improved human disease models for obtaining proof of principle of a drug.
- Improved selection /in/exclusion design) and stratification of patients.
- Population pharmacokinetics – use of random sampling in patient trials.
- Population genetics: clinical profiling of polymorphism and application to responder cohorts.
- Pheno- and geno-typing with biochips ”smart cards”).
- Impact of pharmacogenomics on patient selection in clinical trials.
- Improved information system technologies /webs) for data, documents and project management.
- Prediction of long-term drug use in general practice.
- Ethical aspects of the use of geno-typing for patient selection for drug treatment.

Some key messages
Today’s practice: The focus is on doing the things right.
Tomorrow’s practice: The focus is on doing the right things.

A large part of the current quality assurance procedures has high internal validity, but often very low external validity (e.g. due to inevitable procedures and/or misinterpretation of guidelines by the industrial sponsors).

The cost-benefit outcome of many procedures in the drug development process is very low in a number of contexts.

Motto
No job is finished before the paper work has been reduced.

Conclusion
Yes, it can be done! Preconditions being …

- The engagement and supervision of the European Commission
- Heavy funding and exploitation of the new instruments in the 6th Framework Programme
- The back-up from member state governments and EU Parliament