Top Institute Pharma

International Scientific Review Committee

Report on the first meeting, April 26 & 27, 2006 in Leiden, the Netherlands

Second version June 1st, 2006 – including comments from ISRC members on first draft

This report has been approved by the members of the International Scientific Review Committee

Report of the first meeting of the International Scientific Review Committee (ISRC) on April 26 and 27, 2006, in Leiden

Summary
The ISRC, in their meeting of April 26 and 27, 2006, concludes that TI Pharma is an important novel approach to strengthen pharmaceutical R&D, as well as Training and Education in the area. On the basis of the 27 projects accepted from the first call for proposals, and in view of the project proposals submitted in the second call, TI Pharma will have a high quality and well-balanced project portfolio, which adequately addresses most aspects of the Priority Medicines report. The committee appreciates the speed and amount of work that has been performed during the start-up phase of the Institute and expressed confidence as to the direction that TI Pharma is moving. The committee reports on a number of observations and formulates recommendations for further consideration.

Introduction
On Wednesday April 26 and Thursday April 27 the ISRC met for the first time with the TI Pharma Executive Board and Management Team. Their task for this first meeting was to review the initial project portfolio which TI Pharma plans to start in 2006.

Members of the ISRC are:

- Prof. dr. E.J. Ruitenberg (chair, Professor of International Public Health, Free University Amsterdam, ex RIVM and Sanquin)
- Prof. dr. A.T. Florence (former Dean of the London School of Pharmacy)
- Prof. dr. P. Krogsgard Larsen (President of the Carlsberg Foundation, Denmark)
- Dr. R. Laing (WHO Geneva, author of the Priority Medicines report)
- Prof. dr. L. Lesko (Food and Drug Administration, USA)
- Prof. dr. R. Metternich (Head of Research, Schering AG, Berlin, unable to attend the first meeting)
- Prof. dr. T.M. Jones, CBE (ex Wellcome Foundation, ex ABPI, unable to attend the first meeting, Prof. Crommelin has met with Prof. Jones separately, approved notes are attached at the end of this report)

Two main questions had to be addressed:

1) Does the program fit with the mission and objectives?
2) Does the program adequately address the objectives set in the Priority Medicines report?

This report summarizes the findings and recommendations of this first meeting. The report starts with preliminary remarks and general observations. The methodology used by the committee is briefly discussed and the sources which the committee used to obtain information on the program are listed. The recommendations are then presented followed by an answer to the two main questions asked. Concluding remarks end the report.

Preliminary remarks

From the pre-information the members of the committee have seen , TI Pharma seems to be an important venture. The Institute is built upon the strengths of the Netherlands in pharmaceutical research e.g. drug delivery and molecular pharmacology & medicinal chemistry.

The fact that the Institute is subsidized by the Ministry of Health rather than Economic Affairs illustrates that public health is on the agenda. It should be realized, however, that basic science does not 1:1 translate into public health benefits: new concept development is inherently linked with project failures.
In general, it should be recognized that TI Pharma is primarily about pharmaceutical science which will benefit, in a broad sense, health and healthcare. However success in the various areas supported by TI Pharma will have clear benefits for health both in the Netherlands and in the World.

Building capacity in science and in education and training should be one focus for the Institute. A consideration to be taken into account would be to build this capacity mainly around post-docs and to a lesser extent around PhD students.

TI Pharma should clearly take advantage of the unique position of the Netherlands: its comprehensive health care system is of high quality and good records are being held. This provides an excellent basis for various projects in the special Theme 6.

Methodology

The committee convened for an evening session and a full day to discuss the current status of TI Pharma and its project portfolio. The agenda for this meeting is attached to this document and illustrates the topics for discussion.

To prepare for the meeting the members of the committee were provided with information by the Top Institute Pharma. This information included:
- An overall presentation detailing the Dutch Top Institute concept as well as some analyses on the proposed portfolio, including links with the Priority Medicines report
- An overview of the 27 accepted projects first call and 65 submitted projects in the second call
- Executive summaries on the content of the 27 accepted projects

Via a protected website the full detailed project proposals of the 27 accepted project could be downloaded as well as the summaries of the 65 submitted projects in the second call. The full Priority Medicines report was also available via the website.

Observations and recommendations

Training and education

An ambitious but achievable training and education program is being formulated, ranging from creating awareness among high school students to top summer schools for TI Pharma professionals.

It is a good idea to build upon, and extend, the existing infrastructure. TI Pharma should ensure proper education and training of scientific directors of the future. They miss some critical skills now, for instance in the field of pharmaco-economics. The future TI Pharma HR staff member should interview scientific directors of industrial partners to identify what PhD's and post-docs miss in their view in terms of training and education. A factor to take into account is that big pharma may have a different view than small companies with <10 FTE, but it should be possible to extract a generic outcome.

The school initiative is a very good idea, this is incredibly important. The success factor here will be to catch the interest of the teachers. On top of the other good ideas presented, a study round tour for TI Pharma scientists may be very worthwhile.

The visiting scientists program works in two ways: ideas flow from visitors to TI Pharma scientists and back, which is very positive. A recommendation would be here to invite Indian and Japanese scientists, in addition to European and Americans. Training and education can also support paying attention to, and even implementation of, the objectives of the Priority Medicines report especially in regard to neglected diseases.

The overall budget for training and education may be too low. As plans become more detailed this should be considered.

Priority Medicines

The management team recognized gaps in the response to the first call with respect to Priority Medicines and indicated the incomplete areas as a priority in the second call. The gaps are

- Theme 6: Special research platform on efficiency analysis is not filled in sufficiently
- Theme 4: 'Infectious diseases' has gaps, specifically in bacterial resistance
- Theme 2: filled in properly except for acute stroke
- Project focused on fixed dose combinations and protein stability are missing

The committee endorses the decision that Theme 2, Cardiovascular diseases, (except for projects dealing with acute stroke) and Theme 3, Neoplastic diseases, were closed in the second call.

The management team was successful in obtaining projects in the areas which are needed to fill the gaps, as is demonstrated by the large number of projects in both Theme 4 and Theme 6. Especially in Theme 4 a number of projects address antibacterial resistance. Specific projects on protein stability and powder mixing for fixed dose combinations were submitted. To this end, the management team used the tool of 'commissioned research'. The ISRC fully endorses this approach and is happy to see a successful result while sticking to the overall rules set for the program. The committee praise the management team for their work in this respect.

Neglected diseases form a separate group. The TI Pharma process of calls may not be the suitable mechanism to stimulate work on these diseases. Organizing a workshop on neglected diseases, however, may be a possible alternative to an open call to get projects in this area, or at least address the issue. The ISRC recommended that such a workshop be held in 2006 bringing together the TI Pharma industrial and academic partners with public private organizations such as DNDI to exchange information on needs and capabilities. This may lead to TI Pharma supporting specific component projects. The committee recommends to keep neglected diseases on the TI Pharma agenda but realizes that TI Pharma cannot solve the problem on its own. The strength of the Dutch in formulation science and chemistry could be used also in this area and awareness should be created.

Quality of proposals per Theme and Discipline

Theme 1 – (Auto-)Immune diseases

The committee supports the notion that the already strong COPD platform can be extended with projects in the second call. A number of projects really are complementary to the existing portfolio. It is good to focus on COPD instead of addressing other diseases such as rheumatoid arthritis

Theme 2 – Cardiovascular diseases

T2-11, novel pro- and anticoagulant drugs, is really a challenging project which is very good to have in the portfolio. Acute stroke can be added as an indication, which is possible with projects in the second call. The second call project on egg proteins is unrealistic in the details provided on timing and costing of the clinical trials component.

Theme 3 – Neoplastic diseases

Here TI Pharma really has the top on board. A good mix of projects, where the two kinase projects should be linked. The clear focus on biomarkers is good. The Theme is justifiably closed in the second call.

Theme 4 – Infectious diseases
The first call had insufficient projects dealing with antimicrobial resistance. This is solved by the large number of submitted projects in the second call. The malaria project is very good and directly addresses the Priority Medicines report.

Theme 5 – CNS diseases
There has been a specific request for projects in this Theme in the second call. This is needed as the current portfolio is not yet balanced. With the large number of projects submitted in the second call the committee is confident that also this Theme will be filled in properly.

A special case is discussed: project T5-3, 'Influence of early life events on development of the central nervous and immune system and vulnerability to disease'. The management team asked the committee to give advice on this project, since there was no agreement amongst referees: there is no doubt regarding the scientific quality of this project but it is missing a clear pharmaceutical focus.
The committee unanimously agreed that this project does not fit in the TI Pharma portfolio.

Theme 6 – Efficiency analysis
This Theme has the special attention of the TI Pharma management team. Building upon their very good infrastructure, the Netherlands really can make a difference here. Projects from the second call provide an excellent base to further build a strong portfolio in this Theme. Beyond safety, effectiveness also can be taken into account. Make sure that there are good external reviewers in this Theme, especially in addressing the issue on pharmaco-economics.

Discipline 1 - Therapeutic Target Finding, Validation and Animal Models
The toll like receptor project is a very promising project on this new receptor family. There is no real need to extend this Discipline with second call projects.

Discipline 2 - Lead Selection, In-Silico and PK/PD Modeling
Clearly, there are some very strong consortia in this Discipline. The PK/PD modeling project is really world class and on at the forefront in this field. The focus on children and disease effects in the elderly is extremely relevant. The choice to address two specific topics, metabolism and morphine, is a good one.

Discipline 3 - Predictive Drug Disposition and Toxicology
TI Pharma needs this Discipline even when quality is an issue. Currently there are no projects accepted but two relevant projects are submitted in the second call. It is possible to address this Discipline within Theme 6. The second call projects are very well suitable for this.

Discipline 4 – Biomarkers and Bio-sensoring
The project on the CSF proteome has a clear link with Theme 5, CNS diseases. It is also a model project with relevance for many different diseases. Biobanks of CSF data are available but validation is an issue. A question to be answered is how to obtain a standard protocol. Although there are only few projects in this Discipline, biomarkers as such are extensively addressed via the Themes.

Discipline 5 - Drug Formulation, Delivery and Targeting
The accepted project is of high quality. Several projects in the Themes address delivery applications. The second call looks promising. Project D5-203 on nanocrystals and Blood Brain Barrier should link with project T5-5 on nanoscience as a tool to improve bioavailability.

Discipline 6 – Pharmaceutical Production Technologies
No projects in the first call but two highly relevant (commissioned) projects in the second call on protein stability and fixed dose combinations. The committee supports these projects.

Overall, the committee concludes that, taking into account the possibilities offered in the second call, there is a well balanced and high quality portfolio. Neglected diseases require specific attention, for example by means of the suggested workshop. The committee realizes that TI Pharma can not solve this problem alone and commends TI Pharma for their efforts to address this area.

Embedding in the Dutch infrastructure

There are ongoing discussions with other initiatives, like the existing one on Genomics and the new ones on Diagnostics (Centre for Translational Molecular Medicine) and Devices (BioMedicalMaterials), to establish coordinating links between the different research programs. The linking of biobanks (parelsnoer, etc) for drug development needs thinking beyond science. New ways to measure the effectiveness of medication should be the focus. There is a clear link with Theme 6 here.

Organization

The ISRC recommends that TI Pharma would focus on post-docs rather than PhD students. The PhD phase is the first training but to make these people really effective a follow up post-doc position is needed to finish the training period. Special courses for post-docs should be set up. A similar Danish initiative (The Drug Research Academy, Danish University of Pharmaceutical Sciences) could be looked at as a good benchmark.

Synergy between projects, Themes, Disciplines, Academic and Industrial groups should constantly be on the agenda. Some examples were presented by the management team where this issue is addressed in a very good way, for example the COPD project.

With respect to evaluation and monitoring, deliverables should be defined at a project level. The currently defined milestones per project are a good start. It is recommended that TI Pharma continues to set up a monitoring and evaluation system to report on program level., which will also serve as an input for the annual report.

Newsletters are a good way to communicate to all stakeholders on the progress of the Institute. TI Pharma should continue issuing these with a frequency of 4 to 6 times per year.

It is recommended that TI Pharma quickly establish the Board of Trustees in order to strengthen their link with society.

What TI Pharma should not focus on

The focus of the 7th framework program of the EU is not clear yet. This will become clearer during the rest of 2006. The committee will address this topic at its next meeting, scheduled for October 2006.

Nutraceuticals as a topic is not by definition “off limits” to TI Pharma, but in projects involving neutraceuticals explicit pharmaceutical aspects must be present.

Main questions

For this first meeting the committee is asked two answer two main questions:

1) Does the program fit with the mission and objectives?
2) Does the program adequately address the objectives set in the Priority Medicines report?

The ISRC is of the opinion that a definitely positive answer can be given to both questions. The basis for these positive answers is explained below.

Fit with objectives

With respect to question 1, each of the five objectives is discussed:

Starting with the first objective, TI Pharma has been able to attract both big and small pharmaceutical companies as well as top academic groups. For the first time multi-party proposals have been received which makes TI Pharma a really innovative initiative. The committee is impressed by the number of small and medium sized companies which participate in the accepted projects of the first call (40% in volume) and even more by the number of small companies which have been reached in the second call. In the past, collaboration was mainly based on bilateral contacts. TI Pharma has offered to jointly enter pre-competitive research which really makes it possible to start new economic activity and support innovation.

With respect to the second objective, the synergy and knowledge transfer between all participants is on its way and it looks promising. It is too early to judge the translation of scientific research into applications but the multi-partnership proposals between academia and industry provide a sound starting point.

The third objective, reduction of 'time & cost to patient' of new medicines is addressed by Theme 6. Especially with the set of project proposals in the second call this Theme can be filled in properly. It is, of course, too early to judge the results as the research hasn't started yet.

The fourth objective, Priority Medicines, is answered separately, see below.

The fifth objective, training and education, is ambitious but achievable. Plans are currently being developed and the approach is a good one, building, amongst others, upon the experience in graduate schools. See also our detailed recommendations with respect to this objective.

Priority Medicines

With respect to the second question: yes, Priority Medicines are adequately addressed. The accepted projects in the first call provided a good start. The submitted projects in the second call, including those commissioned by the management team, really ensure a well balanced portfolio which fits with the Priority Medicines report. Neglected diseases should be paid attention to, for example by the recommended workshop. The committee realizes that TI Pharma may not be the vehicle to solve the neglected diseases issue, but possibly the network can help to create awareness amongst a larger public, e.g. EU, other ministries and charity funds, regarding neglected disease.

Concluding remarks

The committee views TI Pharma as an innovative approach to strengthen pharmaceutical research and development. The committee is impressed by the speed and amount of work which has been done to date. The committee will meet again in the autumn of 2006 and it is happy to continue to advise TI Pharma on a bi-annual basis.

Agenda

International Scientific Review Committee
April 26 & 27, 2006
Location: Holiday Inn hotel, Leiden

April 26:

18:30	Dinner with Management Team and delegation of the TI Pharma Executive Board During dinner Victor Nickolson and Daan Crommelin (MT TI Pharma) will update the ISRC on the current overall status of the Institute

April 27:

8:30	Introduction and goal for today: agree on schedule and approach
9:00	MT to present strategic program of TI Pharma, including Training & Education and strategic research program
10:00	Questions & discussion
10:30	Break
10:45	Discussion on preliminary conclusions based on preparatory information: does the program fit with the mission and objectives?
12:00	Lunch
12:30	Discussion along Themes/Disciplines, Topics and Priority Medicines - Is the focus right? - What are possible gaps? - What are possibilities for further clustering?
14:00	Progress in second call - Is the current call clear enough? - Has the current call brought in good projects to fill the gaps? - Which areas need special attention?
14:30	Break
14:45	What are area's which TI Pharma should not focus on: - as they do not fit with the (Dutch) partners within TI Pharma - since their real potential will only be revealed in a broader EU project (links with the EU 7th framework program and TI Pharma should be commented upon)
15:15	Wrap up, final conclusion and next steps
16:00	Closure

Short report meeting with prof. Trevor Jones, 24 April at Gatwick (DJAC)

We went through most of the presentation:

Issues for consideration:
--- pediatric diseases: are there more possibilities than only the PK-PD project? Second call?
--- neglected diseases: contact DnDi, Brussels, to see whether consortia (beyond the NL) can be formed. Does the EU 7th framework programme offer chances?
--- project managers: selection is quite important. Choose those who can do more than just monitoring projects.
--- education and training: think about inviting top scientists, e.g. Fabio Pammolli, Lucca, for pharmaco-economic scenario's/network development.

Projects first call:
Questions about: T.3.3. Identification of novel kinases involved cancer relevant processes: looks too ambitious and too small.
T.4.1. Antibodies against Klebsiella pneumoniae as an alternative: will antibodies ever offer a substitute for small molecules? Consider pricing issues and limited interest of Big Pharma for this type of work. Who is going to pay for a phase III study of 8000 patients?
T.4.2.: Design of predictive models, drug delivery and live-virus malaria vaccines for the developing world. Question is: is this the proper antigen? Does it make a chance considering the worldwide major efforts (Gates-foundation). Contact the European Malaria Vaccine Initiative re this project.
T.5.5. Nanocience as a tool for improving bioavailability and blood brain barrier penetration of CNS drugs. Prof Jones questions the concept of using stem cells in the brain for drug transport. He offers to consult.
T.6.1. The Mondriaan project: the Dutch health care landscape as a 'population laboratory'. Consider biobank initiative in the UK. 60 million pounds for 500,000 patients between 40 and 65 y, taking blood and tissue samples. NB ethical issues!

We briefly discussed the status of pharmaceutical technology oriented projects as special projects.

The paper-work re CA and reimbursement scheme still has to be taken care of.

Answering the questionnaire:
Q1 high
Q2 medium. If more big player would participate more chances for successful translational activities
Q3 discovery: high; development: medium (but that is inherent to the pre-competitive nature)
Q4 high
Q5 high

THIS REPORT HAS BEEN APPROVED BY PROFESSOR JONES