FINAL REPORT

I	**The Name of the Institution to be evaluated**	**National Institute for Chemical - Pharmaceutical Research and Development – ICCF**
II	**Evaluation Period**	ICCF: 2007- 2011 Visit: April 19-20, 2012
III	**Members of the Team**	
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I. CONCLUSIONS AND RECOMMENDATIONS

Our team has evaluated the National Institute for Chemical - Pharmaceutical Research and Development – ICCF. The self-evaluation documents were made available through web based access about 2 weeks before the site visit, which took place in Bucharest on April 19-20 (2012).

During the visit, the panel received oral presentations from all the team leaders and was able to have detailed discussions with the management group, to meet PhD students and to inspect the research facilities. The site visits, including the discussions, were very useful since they provided an important additional view of the human and infrastructure resources of the institute.

Besides the positive impressions the team also noted a number of problematic issues, which pose barriers for achieving a level of internationally competitive science in the institute. The evaluation committee is aware of the origin of difficulties and the tremendous effort of the ICCF management to overcome those problems. As we see during the past two decades potential users of the R&D activity of ICCF almost disappeared. Some local pharmaceutical producers tend to buy foreign licenses. Others are not interested in innovation. A third group would be interested but cannot afford it financially. Parallel with that **from 2007 to 2011 the total RD income of ICCF was reduced to 65%**. Especially **the withdrawal of resources already covered by contracts hit the institute**. Under those conditions the ICCF leadership has attempted to adapt to the shrinking resources. The institute **reduced** the other cost including **utility cost to 37%**. They **preserved the core personnel**. After careful selection they have **begun modernizing** the **key facilities** (laboratories 2, 7, 8). They also **implemented new R&D activities** (development of herbal-based drugs). Although the perspectives in some directions are encouraging, yet the present outcome of the institute is low by international standards. Further development would be necessary, **with needed administrative and financial support from the supervising authorities.** The cardinal issue would be of recruiting young, energetic and ambitious people with good publication record and experience in strategically important new directions.

Noted issues are listed in detail below and further elaborated in section IV „Specific measures, targets and recommendations to be met in a time of 3 years".

1.) Reconsider the R&D directions of the institute. Keep exclusively directions which comply with the core mission of the institute and which will have a high chance to lead to marketable drugs/technologies. Discontinue research directions which aim to produce potential drugs which do not have a real chance to enter the clinical trials. Introduce new directions and update the existing ones in order to become modern approaches in drug discovery.
2.) Recruit at least two highly qualified young researchers (at least at postdoctoral level, working in prestigious universities/ research institutes from abroad) with excellent publications having expertise in: functional genomics/ bioinformatics and computer-aided drug design/ molecular biology/ or protein chemistry. Encourage these researchers to apply for reintegration/young team/postdoctoral/Ideas grants at national or EC research funding authorities.
3.) Set-up a "Functional Genomics" (let's denote it Team E_0) group having as mission to perform fundamental research and generate new ideas for innovative drugs. Nominate as group leader one of the young researchers hired according to the previous step and give him/her the freedom to choose the members of this team and decide the specific goals of this team in the framework of functional genomics. Apply for new grants for infrastructure and use the ongoing projects to provide suitable equipment to this team.
4.) Consider to merge Teams E_6 and E_2 as well as Teams E_4 and E_5.
5.) Encourage and create all conditions for continuous interdepartmental collaboration and exchange of ideas and information between Team E_0 and all other teams but particularly

Teams E_1 and E_3. Products suggested for testing as potential drugs by E_1 and E_3 should pass the checking of Team E_0 and then of Team E_1. Synthesis of potential drugs passing these tests will be synthesized or purified by Team (E_4 + E_5) (at laboratory or pilot-scale) and checked for purity and other physico-chemical characteristics by Team E_7. Then, full range of *in vitro* tests of pre-clinical analysis for resulting products should be performed by Team (E_2 + E_6). Finally, *in vivo* pre-clinical tests - in full agreement with national and EU criteria for drug validation - should be done by Team E_8.

Potential drugs resulting at step 5) should be evaluated whether they deserve to be sent directly to clinical tests on the expenses of the institute or a strategic partnership should be negotiated with an appropriate pharmaceutical company. In the latter situation official collaboration documents should be signed where the terms of *know-how* transfer as well as the revenue of the institute resulting from its intellectual property on the given product(s) should be clearly stated.

II. EVALUATION OF TEAMS

Team E_1 - Microbial biotechnology

This is one of the largest group of the institute having 10 researchers and 3 PhD students. The team has two main research directions:

- Development of biosynthesis processes, and
- Design & development of unconventional processes for sustainable development.

The scientific output of the group is at the average level of the instiute having 0.9 articles with non-zero AIS/ researcher; however, the average level of these publications as reflected by the cumulated AIS per article is below the institute average (0.35 for this team compared to 0.47 for the institute). Remarkably, this team has 6 out of 19 patents granted to the whole institute; this fact clearly reflects the orientation of this group to applied research.

The main achievements are:

- New biopolymers: e.g. curdlan, pseudozan, poly-(3-hydroxyalkanoate),
- Food bio-supplements (nutraceuticals) of microbial origin,
- Microbial products for sustainable agriculture, and
- Biotechnologies for renewable energy sources from agricultural wastes (biogas from cereal straws).

Some of the new biopolymers obtained and purified by this team has potential and promissing medical applications in:

- Treatment of infected wounds,
- Controlled drug release,
- Immunomodulation, and
- Adjuvants for vaccines.

However, it is not clear what are the particular features of these biopolymer which would make them to be preferred for other existing biomaterials broadly used for the mentioned medical applications.

Some of the research directions of this team are obsolete or do not belong to the main mission of this institute: chemical pharmaceutical R&D (in agreement with the name of the institute). For example:

- Crosslinked biopolymers suggested to be applied for immobilization/separation/purification of enzymes: there are numerous other polymers successfully used for decades to this purpose; this research direction should be discontinued,
- Microbial products for sustainable agriculture: this reserach direction together with its results should be transfered to a research institute dedicated to agricultural biotechnologies,
- Biotechnologies for renewable energy sources (biogas from cereal wastes): similarly, this is a field of activity for a research institute specialized in biotechnologies, where this research direction should be transferred, and
- Food bio-supplements (nutraceuticals)
  According to Merriam-Webster, nutraceuticals are defined as „a foodstuff (as a fortified food or dietary supplement) that provides health benefits in addition to its basic nutritional value". The existing regulations in EU states have some disparities regarding nutraceuticals and consider them either food supplements, registered medicines or prescription-only medicines. On the other hand all regulations agree that unless they are considered medicines, nutraceuticals (and also food supplements) cannot have medical claims but only health claims. Thus, Directive 2000/13/EC states that the labeling of food supplements must not contain any

statement attributing to the product properties of preventing, treating or curing a human disease. In conclusion, any medical claims for a nutraceuticals would be equivalent to consider it a medicinal product and is required to comply with the regulatory requirements for medicinal products in respect of safety, efficacy and quality testing and marketing authorization procedures. Consequently, any medical claims given to a nutraceuticals/ food supplement should be substantiated by rigorous safety and efficacy studies. Moreover, there is concerted action supported by the European Commission on "Process for the Assessment of Scientific Support for Claims" (PASSCLAIM) which suggested that health claims should be also based on sound scientific evidence, using appropriate validated biomarkers (Eur J Nutr (2005) [Suppl 1] 44 : I/1–I/2).

It is not clear if the research products of this team termed "nutraceuticals" have the claimed characteristics ("tumor preventing agents", "hypoglycemic adjuvants") substantiated by comprehensive and rigorous scientific studies. Simple concoctions of different ingredients like vitamins, minerals and plant extracts (with more or less evident medical efficacies) without a clear, scientifically sound evidence concerning the probability of a novel and/or improved overall medical efficiency cannot be considered to be the objective of a research study financed from public resources.

Focusing the scientific activity of this team on the novel biopolymers they are producing which seem to have interesting medical applications, introducing modern experimental techniques (like tools of molecular biology, proteomics, recombinant DNA technology, etc) would significantly increase the level of scientific output. Results should be published in journals with high AIS but first of all should be protected by international patents, given the orientation of this group to applied research. Production of biopolymers may be transfered to a new, spin-off company, that takes the responsibility for quality control and marketing also. A good business model/contract between the spin-off company and the Institute has to be worked out, defining responsibilities and the share of surplus. E.g. for the know-how the income has to be shared with the institute. Paying a lump sum at the beginning is not realistic when the company itself is in need of starting funds.

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Team E_2 - Biopharmacology

Team E_2 has a focused activity oriented to *in vitro* testing of safety and efficacy of compounds/materials with potential applicability in pharmaceutics and/or medicine. This group has 6.75 full time equivalent researchers and 2 PhD students. Between 2007-2011 this team has run 15 research projects and has been involved in many national and international collaborations. Remarkably, the group is running 2 international projects: one within FP7 and one within POS-CCE. As far as he scientific results are concerned, the main achievements are testing methods for:

- Antidiabetic activity using multiple test systems,
- Antihypertensive activity based on ACE2 assay,
- Cell culture model for assessment of anti-atherosclerotic effects on HUVEC cells,
- Refined model of evaluation of cytokine mediated cytotoxic responses, and
- Refined model for the evaluation of cytotoxicity.

The team claims to publish 8 papers in non-zero AIS journals cumulating a total AIS = 11.24. Thus, the scientific output of the team would be above the average of the institute as reflected by the number of articles and by the mean value AIS, both per article: 1.18 articles in non-zero journals/researcher and 1.4 AIS /published article. However, the 8 papers listed (A22, A23, A39, A40, A41, A44, A55, A56) are not based on experimental tests done by the members of Team E_2. Two other papers, A45 and A63 in the list, reflect truly the concerted effort of Team E_2 members in collaboration with Teams E_3 and E_7, and represent the true mission of the Biopharmacology Laboratory.

Note to ICCF and ANCS: In the statistics on the achievements of the teams every single paper was attributed to a single, separate team, giving the impression that there was absolutely no collaboration between the teams. Which is, luckily, not true.

The team has a recently renovated laboratory and posseses appropriate, modern infrastructure.

As far as the reported scientific achievements are concerned (as listed above) it should be emphasized here too that medical claims for the tested products can be validated only by rigurous, scientifically sound studies – as mentioned at observations for Team 1 activity. *In vitro* tests are important but not sufficient to claim, for instance, antidiabetic or antihypertensive activities. *In vitro* tests should rather serve as hypothesis generators and indicators of possible mechanisms of action of the tested product and must be complemented by *in vivo* and clinical tests.

It can be recommended this team to introduce in its research studies the modern techniques like those of molecular biology and functional genomics including gene silencing or overexpression (see also comments at Team E_8). In this way it will be possible to perform research studies concerning the molecular mechanisms of action, signaling pathways for the tested compounds. In addition, it can be recommended to increase the number of original papers published in journals with high AIS (at present, the team's list of publications, as mentioned above, has many review articles, some of them being just short evaluations of single original paper).

Team E_3 - Plant biotechnology

This is a relatively large group of mainly young, enthusiastic members. There are 9.25 full time equivalent researchers and 1 PhD student in this team. The team has modern infrastructure, appropriate for the studies performed at present.

The activity of this group is oriented, according to the team's presentation material, to three main directions:

- Drug-design activity, involving a.) the isolation of the various selective vegetal extracts enriched in the phytocompund(s) of interest; b.) analytical screening of the vegetal extracts thus obtained and selection of those which have the most appropriate composition for the target characteristics,
- Preparation of the final bioactive product; the end-product is transferred to pilot-scale tests or the beneficiary SME's, and
- Setting directions and recommendations for sustainable development (particularly for production of medicinal and aromatic plants).

An eye-drops solution based on desert truffles has been developed and it follows the market authorization procedure. An international patent application was already submitted and a clinical trial performed by a Swiss company is in progress.

As a result of the team's activity, 13 technologies were set up leading to 14 herbal-based products. This group was involved in 13 national and 3 international projects and established numerous collaborations with national or international partners. The R&D outcome of this team was the following: 6 national patents granted (3 patents have been applied) and 8 articles published in non-zero AIS journals, that is 0,3 AIS/ article and 0.86 articles in non-zero AIS journals/researcher. Although these values are below the average values for the whole institute, the patents granted to this lab as well as the relatively high number of products transferred to SMEs are good points, proving the orientation of the team to development activities.

There are a couple of problems with the research activity of this group which should be considered and solved accordingly:

1.) The third direction of activity "Setting directions and recommendations for sustainable development" is a policy study and according to Frascati manual it is not a R&D activity. Therefore, this type of activities should be transferred to companies/institutions dedicated to consulting activities,
2.) R&D objectives like "ecological insecticides" or "environment-friendly herbal inhibitors designed to combat both corrosion and deposition of crust of thermal plants" should not be the research objectives of ICCF given that its mission is chemical-pharmaceutical R&D, and
3.) The activity of this group concerning "Herbal products development" is particularly interesting and may lead in future to new drugs and new scientific knowledge. However, at present, the activity of this group in this field is restricted only to development activities. Mainly, there are no research activities performed by this team. Given the good human resources and the infrastructure of this group the present activity in this direction is insufficient. The typical studies of the team are limited to analytical screening of various plant extracts (including pharmacotoxicological screening) and setup of the final combination of plant extracts. These steps are definitely essential for any research study devoted to work out a novel herbal drug but these steps are only the initial ones and they are by far not sufficient for launching a new drug which can be later on registered and marketed. The recent EU Directive on "Traditional Herbal Medicinal Products" (THMPD) which came into force in April 2011, is rather permissive in

giving license to herbal products which have been used at least 30 years (including 15 years in Europe). However, herbal product will be considered as a medicinal product only when properties for treating or preventing disease in human beings are claimed or where it has a pharmacological, immunological or metabolic action. Thus, the plant extracts developed and intended for marketing and which claim to possess medical efficiency must provide clear scientific evidence for the claimed medical efficiency. The present trend in the research dedicated to herbal drugs is to take advantage of the huge medical experience behind traditional medicine but using the modern tools of life sciences. There are difficulties in this respect due to the quite general principles of traditional medicine to use multiple active ingredients directed to multiple physiological targets (as opposed to the quasi-general principle of modern medicine "single ingredient directed to single target"). Despite difficulties, new tools, new approaches are emerging to fit the new type of research studies dealing with traditional herbal drugs. For instance, systems biology is broadly accepted to represent a potential bridge between traditional medicine and Western scientific methodology. There are quite many successful approaches in this respect (it is recommended as a preliminary information source the "Outlook on Traditional Asian Medicine" which was published in volume 480 of Nature in 22 December 2011): artemisin, the antimalarial component of *Artemisia annua*, a herb used for hundreds of years in traditional Chinese medicine – due to the research studies performed by phytochemist Youyou Tu and others – became the leading treatment for malaria. Similarly, the research work of Tingdong Zhang helped registration of arsenic trioxide – originating also from traditional medicine – for use in leukemia. There are also numerous recent examples of papers published in prestigious journals, where research studies on remedies of traditional medicine are studied using modern tools and scientific endeavor, e.g. Proc Natl Acad Sci U S A. 105(12): 4826–4831(2008); J. Clin. Oncol. *28,* 744-752 (2010); PLoS Genet. 8(4):e1002657 (2012). It is also worthwhile to note that there are research centers in EU devoted to find (scientific) bridges between traditional and Western medicine, like the Sino-Dutch Centre for Preventive and Personalized Medicine (see www.sinodutchcentre.nl/index.php?parentContentID=&contentID=2CBE9922-A97B-407D-8CB3-BAB2AE9E9055).

It is recommended this group to reconsider its activity in the design of herbal drugs and reorient its research activity in terms of the observations mentioned above.

Production of plant extracts could be transferred to a spin-off company created within the institute.

Team E_4 - Synthesis of natural active substances and derivatives

This team is composed of 5.375 full time equivalent researchers. The main research directions are:

- Total synthesis of prostaglandins and prostamide derivatives,
- Synthesis of new nucleotide analogs (potential antitumor/antiviral drugs),
- Stereocontrolled synthesis of structural analogs of steroid hormones, and
- Synthesis of fatty acid esters and corresponding ethanolamides (as potential therapeutic agents).

As a result of their activity they succeeded to set up the synthesis for several prostaglandin and prostamid derivatives used as last generation antiglaucoma drugs. The beneficiary of their research and of the synthetized drugs was the Italian company "Industriale Chimica SRL". This company paid for the drugs and intermediates produced by this team. In addition, this collaboration led to an international patent – in fact the only one of the institute.

Steroid derivatives obtained by this group were applied (and apparently are in use) for production of luteolytic veterinary drugs.

Apparently, the nucleotide analogs obtained by this team might have antitumor/antiviral activity but they are still tested for their *in vivo* toxicity/efficiency.

The group published 13 articles in non-zero AIS journals cumulating a total AIS=3.13. Thus, the scientific output is 2.42 articles/researcher (almost 2.5 times higher than the average of the institute) and 0.24 AIS/article (two times lower than the institute average).

In other words the group succeeded to publish many articles but in journals with low AIS. The strength of this team resides in its expertise in fine organic synthesis. The members of the group have been able to set up synthesis of compounds with about 50 steps. The group is able to develop complicate chemical synthesis at pilot-scale for requested compounds. This provides an important perspective for the future of the institute: requested chemical compounds, with high potential to become marketed drugs can be synthetized and corresponding technology can be setup by this group.

However, activity and composition of this group needs also to be improved:

- young researchers should be hired,
- laboratories should be renovated,
- modern infrastructure is needed (including an NMR spectrometer), and
- research results should be published in journals with much higher AIS.

This team should merge Team E_5 due to their highly similar research goals. In this way, the joint expertise and joint infrastructures of these teams should have synergistic advantages for both teams as well as for the whole institute.

Team E_5 - Synthesis of innovative drug substances

This group is relatively large having 8.125 full time equivalent researchers and 1 PhD student. There are two main research domains:

- Synthesis of innovative products with potential therapeutic activity, and
- Development of competitive technologies to synthesize generic medicines.

As a result of their activity they succeeded to perform synthesis of an impressive number of new compounds: 213 original structures and 77 known precursors, necessary for synthesis of the original structures. The original compounds were tested pharmacologically towards evidencing:

- Modern antidiabetics from β_3- adrenoreceptor agonist's class (arylethanolamine derivatives),
- Original anti-Alzheimer compounds (adamantane derivatives),
- Heterocyclic derivatives as potential metal proteinase inhibitors,
- Original thioureides, dibenzothiepines, dibenzooxepines and quinolones with (potential) antimicrobial activity, and
- Complex combinations of transitional metals with oxicam ligands, for anti-inflamatory therapies.

The scientific outcome of this team is high from the point of view of the number of publications in non-zero AIS journals: 23, that is an average of 2.83 per researcher (almost 3 times higher than the institute average). Unfortunately, the average AIS of the journals where these articles were published is low: 0.19 (that is more than twice lower than the institute average). In addition, there are 5 patents granted for this team and no products/technologies emerging from the research of this group.

The idea to develop competitive technologies for generic medicines is highly attractive. Some generic medicines, like anticoagulants, antibiotics, anti-AIDS and especially cancer drugs, although vital in many health problems, are sometimes missing on the Romanian market with potentially disastrous consequences. The identification of these problematic medicines for the Romanian health system and the setup of appropriate technologies for their production could be particularly useful also for the research activity of this group. This institute is almost the only public entity that can provide expertise on this crucial issue, both for guiding public policies and for operational development of the industry. Hence, the strategy and plan of the institute must specify to what extent, and in what respect it can meet this responsibility so that proper decisions can be taken.

The discrepancy between the huge work performed (synthesis of 213 original compounds) by this group and the lack of patents and of new product transferred to SME or other industrial companies can be explained first of all by the little originality in choosing the directions of the team's research directions. Thus, the field of β_3-adrenoreceptor agonist's class (particularly the arylethanolamine derivatives) targeting diabetes has been since long tried (started before 2000) and there are quite many patents issued in this direction. Adamantan derivatives represented by Memantine as drugs for Alzheimer disease were launched by Eli Lilly & Co in 1968 and many new derivatives were tested since then. However, a later explanation of this team makes clear that the studies regarding Memantine are rather intended to set up an suitable technology for production of a Memantine (and possibly its derivatives) as a generic API, given that it is not available in Romania due to its very high cost. Regarding "quinolones as potential antimicrobial agents" – part of research directions of this group - it may be noticed that there is even a book published in 2004 on this subject:

"Quinolone Antimicrobial Agents" (3rd Edition) David C. Hooper; Ethan Rubinstein. American Society of Microbiology Press, Washington, DC 20036, USA. ISBN: 1-55581-231-7.

It is hard to believe that the researchers/companies who launched on the market these (classes of) compounds did not explore a large number of similar derivatives. That is why there is little chance to find new derivatives from the same class of compounds, with much higher therapeutic efficiency. However, supposing the team succeeded to obtain some highly promising compounds, they should be tested adequately, using up-to-date procedures. For instance, evaluation of anti-Alzheimer effect of the newly synthesized adamantan derivatives simply based on the results on rats tested with "Y labyrinth tests" and "modified black and white box test" – are insufficient (see also comments at Team E_8). Any potential drug, after passing the appropriate *in vitro* and *in vivo* tests and the standard protocols of toxicity it must pass the double blind, randomized clinical trials to validate the claimed medical effect. Has any of the potential drugs been obtained by this group followed and passed this sequence of mandatory steps for validation of a drug? Has any chemical compound synthesized in this group in the last 10-20 years been validated as drug and entered on the market? If not, why to find new potential drugs if they will never be tested whether they are real drugs? And why to perform research (paid mainly from public funds) to find novel drugs if the potential candidates will never be tested whether they can be used or not as drugs and consequently will never enter on the market?

It is recommended that in future only those compounds be developed and studied which: a) Have a chance to be therapeutically active, and b) Have a real chance to be tested correctly and completely as potential drugs.

Team E_6 - Pharmaceutical nanotechnology

This is a small team composed of 3.25 full time equivalent reserachers and 1 PhD student. It is a new team, created about 3 years ago with the intention to initiate research in the field of nanotechnologies applied in drug development.

As a main results of its activity this group succeeded to develop some methods for entraping various drugs into liposomes. Specifically, for drospirenone a transdermal delivery system based on nanovesicles was set up. Similarly, for fluoroquinolones – antibiotics with large antimicrobial spectrum – a drug delivery system based on encapsulation into liposomes was established.

The group has not been able to publish any non-zero AIS article and no patents were granted for its results.

The project proposals mentioned in the presentation material of this group does not seem to be original and do not have a real chance to be applied. For the first one, related to the use of magnetic nanostructures as drug carriers for a new thrombolytic therapy, it should be emphasized that there are already published articles in this respect as for example: "Magnetically targeted thrombolysis with recombinant tissue plasminogen activator to polyacrylic acid-coated nanoparticles" published 2009 in Biomaterials 30 (19): 3343-3351.

Regarding the second project proposal "Phytotherapeutic product used in some stages of antitumoral treatment obtained by nanotechnology" please read the observation made about phytotherapeutical drugs at Team E_3.

Although the field of pharmaceutical nanotechnology is a highly promising one, this group does not provide trustful elements to be supported in the future. The team might join another group, for instance Team E_1 or Team E_2, where its expertise in new drug delivery systems can be very useful.

Team E_7 - Analytical research

This team has 6.5 full time equivalent researchers and 1 PhD student. It is specialized in the development of analytical methods particularly those requested by pharmaceutical R&D. The laboratories of this team are very well equipped having modern specific instruments like:

- Organic elemental analyzer,
- UV-VIS and FTIR spectrometers,
- Atomic absorption spectrometers,
- Inductively coupled plasma-MS,
- Several HPLCs with UV, fluorescence, refraction index, diode array or light-scattering MS detectors, and
- Ultra performance liquid chromatograph coupled to MS (UPLC-MS)
- HPLC-MS-MS.

This group of highly qualified and experienced specialists succeeded to set up as much as 400 analytical methods for a large variety of compounds: pharmaceutically active substances, inorganic impurities in pharmaceuticals, bioactive compounds from plant extracts, synthetic organic substances with potential medical effect.

It is worth underlining that Team E_7 reached the EU requirement for complete characterization of pharmaceutical products and drugs, being certified as a GLP unit and as reference analytical laboratory (unique in Romania).

The publication output of this group is represented by 6 papers published in non-zero AIS journals, that is 0.92 articles/researcher and 0.56 AIS/ article, ranking this group slightly above the average of the institute concerning the AIS/article. The level of the scientific publications (from the point of view of the AIS of the journals where they are published) can be improved. Given that the members of this team have many publications as co-authors in publications where other teams' work is the main topic, it is expected that increasing the overall quality of the institute publications will also lead to a higher quality of this group's articles.

Altogether this team is essential for the activity of the institute and meets all requisites (modern infrastructure, highly qualified personnel, certified GLP work environment) for a modern analytical laboratory assisting the activity of a chemical-pharmaceutical R&D institute.

A reasonable rebuttal of this team is that the 3-years national research projects are not sufficient for the pharmacological and safety tests of potential drugs. Therefore, exceptional 5 to 7 years research projects might be introduced by the national funding authorities for this type of long-term research activities.

Team E_8 - Pharmacological Research

There are 5.5 full time equivalent researchers in this team and 2 PhD students. The main activity of this team consists in:

- Non-clinical toxicological and pharmacological studies,
- Microbiological evaluations,
- *In vivo* pharmacological methods for efficiency, side effects of various compounds (synthetic compounds and natural extracts), and
- Pharmacotoxicological evaluations for biologically active compounds (synthetic compounds and natural extracts).

The team has a renovated working spaces and is about to apply for accreditation as GLP for the microbiology laboratory. According to its presentation material this group developed *in vivo* and/or *ex vivo* methods for pharmacological evaluations and performed pharmacological evaluations of normal an pathological immunological status, of anti-inflammatory effect, anti-Alzheimer potential, anti-diabetic effect, anti-histaminic effect, spasmolytic activity, etc. in order to test the synthetic substances and natural extracts produced in the institute and suggested to have potential therapeutic activities.

The scientific output of the group consists of 1 ISI paper but unfortunately none in non-zero AIS journals. However, the team members are co-authors of 6 granted patents.

Remarkably, this group makes efforts to comply its non-clinical research with international standards. Given the particular importance of this team's field of activity, the extension and overall support of this team is recommended. One specific recommendation would be to extend this team's activity and facilities so that it can use transgenic mice in experiments.

Indeed, this group should play an essential role (together with team E_2) in performing the pre-clinical tests for the synthetic and natural compounds obtained within the institute and having potential therapeutic efficiencies. Unfortunately, it seems that the institute performs only at a limited extent the steps requested for pre-clinical tests of potential drugs and none of these drug candidates have been so far tested clinically towards registration and marketing.

In fact, the *in vivo* phase of preclinical tests should be minimized due to the ethic principles of saving animals. Moreover, validity of animal models as human predictors is controversial and is frequently criticized. However, there is a multitude of ways which can be used towards screening and selection of potential drug candidates. The paragraph below summarizes potential directions requested in modern drug design and screening, that are recommended not only to Team 8 but to other Teams of the Institute, including capacities suggested in this evaluation but not available at present.

One of the very initial steps of evaluating a potential drug should be the target identification and validation. The traditional approach was to consider as target a disease or a pathological condition like diabetes, Alzheimer disease, chronic fatigue syndrome, or AIDS. Nowadays, due the huge progress of knowledge at molecular level, it became obligatory to identify for a drug candidate specific molecular targets as for example receptors, enzymes, elements which control gene expression, ion channels, carrier proteins, deficient signaling pathways, specific metabolic pathways, etc. Computer-aided drug-design can be particularly important at this step and could eliminate numerous drug candidates from further studies. Tools of bioinformatics and *in silico* predictions might be also very useful in suggesting novel chemical compounds which might be studied as possible candidates for a given molecular target. On the other hand, components of active fractions separated from plant extracts - which have been suggested by traditional medicine as remedies for a disease - might suggest potential

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ligands for known molecular targets of that disease. As soon as bioinformatics studies suggested a list of potential ligands/effectors for a given molecular target they should be synthesized and then tested *in vitro* by using, preferentially high throughput, assays to screen large libraries of compounds on the putative target. In this way, compounds which display activity/affinity for the target will be identified while the other non-interacting compounds will be eliminated. Current techniques of molecular and cellular biology (including those of functional genomics) are very important at this step and should be introduced soon in the routine techniques of the institute: immunoprecipitation, pull-down techniques, tandem affinity purification (TAP), yeast two-hybrid system, affinity purification combined with mass spectrometry, loss-of function techniques (RNAi, mutagenesis), gene overexpression. It is also important at this step to emphasize that potential drug candidates must display specificity, potency for the selected target and selectivity over other biological targets. Unfortunately, these aspects were not addressed in the research studies of ICCF. Team E_2 of the institute has the potential to introduce in its activity most of the above mentioned techniques. The same team E_2 - possibly in collaboration with teams E_6 and E_8 - should be able to perform most of biological activity testing. Here too, regulations of national and EU authorities for drug validation should be taken into account. Thus, absorption, distribution, metabolism and excretion (ADME) of potential candidates should be considered and will help to further screen the valuable drug candidates. In this respect, tests like: Caco-2 and MDCK permeability, volume of distribution, plasma protein binding, blood-brain barrier penetration (has that been tested for the potential anti-Alzheimer drug?), P450 inhibition screening and P450 metabolic stability, elimination half-life, e.t.c. should be regularly performed. These tests are either not explicitly mentioned in the presentation materials of the research teams or they are not performed in the institute at present. It is also not clear whether preclinical pharmacological analysis performed within the institute on the candidate drugs covers *in vitro* tissue studies and *in vivo* pharmacokinetic and pharmacodynamics experiments according to current regulations. At this step, testing of the candidate drug efficacy, potency and specificity have a crucial importance. Regarding the toxicity tests it is worth mentioning that specific aspects like genetic toxicology, toxicokinetics, reproductive toxicity and carcinogenicity should be also addressed.

III. JUSTIFICATIONS OF MARKS

C1: The quality of R&D activities and their results **Mark: 2.0**

The institute published 67 articles in non-zero rAIS journals cumulating a total AIS of 31.456. Given that in the institute are 64 researchers, it results that regarding the publications the average values are 0.47 AIS/article and 1.05 articles/researcher (articles published in non-zero AIS journals). In other words, the average publication level of the institute is 0.2 articles/researcher/year which is a low level for a national R&D institute working in a hot field of present research. The low AIS of the journals where the articles were published can be explained by the fact that the great majority of the articles were published in Romanian journals like Revista de Chimie or Revue Roumaine de Chimie. This fact is reflected also by the low number of citations of the institute articles.

As concerning the patents, there were 19 patents granted, out of which just one was an international patent. This number is also very low, especially if we take into account that the mission of the institute should preferentially encourage the applied research.

Altogether, it can be concluded that, despite the high human and logistic potential, the present capacity of the institute to generate good quality papers and valuable patents (reflecting the quality and the quantity of basic and applied research performed within the institute) is low.

Most of the projects and contracts of the institute come from national sources. However, 5 projects/contracts (out the total number of 93 projects) come from international sources. Notably, one is a EU project that started in 2011. The number of projects/contracts from private sources is 28 (24 national and 4 international). However, the total funds from private sources is still (very) low, some €25,600 in 2011 representing only 2% of the total R&D incomes. The total international funds (public and private) are also low, 6.3% of the total income. The institute has additional sources of income, mainly from non-RD services and small scale production, which represent 13.8% of the total income. The ability of the different teams to attract funds differs.

There is just one international patent granted, having as co-author one of the members of Team E_4 (Dr. Florea Cocu) with no commercialization and no financial benefits. This number is by far insufficient given the clear orientation of the institute to applied research.

There are potentials but no start-ups and spin-offs originating from the R&D activity of the institute. In 2008, a plant technology of an original product, MELACHORD for nervous system diseases therapy, was transferred to a private company. At present, as a consequence of a privately financed research study an original ophthalmologic eye-drops medicine based on dessert truffles was set up and clinical trials are in progress (performed by a Swiss company).

Dissemination of R&D results of teams was performed by communications in national and international conferences/workshops/congresses.

To guarantee an effective data flow and to inform the staff about ongoing activities, the institute use an email system, meetings and the institute homepage (http://cfarm.ncpri.ro/). The External communications and information sharing is low and should be improved. The national dissemination activity at RD-ICCF has been performed by publications in Romanian journals and magazines, books, documentaries, and web pages. The international dissemination activity at RD-ICCF has been performed by conference poster presentations but the international dissemination activity is very weak and should be improved.

Short summary: Quality and quantity of scientific research publications are both low. Good research capacities in some teams. Several experts among the scientific leaders. However, heterogeneity among the different teams.

C2: Human resources quality **Mark: 3.0**

The institute has 131 employees, from which 89 are engaged in a research activity, divided into 8 teams. There is heterogeneity in the performance level. There is one team (Team E_7) which excels both in human resources and modern infrastructure while in some other teams the quality of R&D activity is lower.

The average age of personnel is quite high, 48 years. There are no examples of brain gain within the institute staff. The age structure of the institute is not good; the ratio between junior and senior staff is very low. There are many senior scientists and only a few younger scientists. In some of the teams there are PhD studentsworking towards obtaining a PhD degree. The number of postdoctoral students is very low, in fact only 1. There are no foreign professionals in the institute.

According to the data provided to the evaluators there are 89 individuals involved in R&D activities and 32 in administrative activities, that is 68% in R&D and 32% in administration. This 2:1 ratio between R&D staff and administrative staff is quite high. Possibly, it reflects the large size of the institute relative to the low number of R&D personnel and the old-fashioned facilities (e.g. heating system) of the building which needs too many auxiliary personnel.

Short summary: More senior and less junior scientists. Several senior experts among the scientists. Diverse background among the scientists (positive). However, no international/foreign scientists. Low number of PhDstudents and PostDocs. Large quality differences among the teams.

C3: Quality infrastructure and its rate of exploitation **Mark: 3.0**

There are numerous modern devices in the institute. Team E_7 is particularly well equipped with performing infrastructure. There is a modern pilot plant built and equipped as a multifunctional entity mostly intended for Team E4 (exhaustion walk-in fume cupboards and filter and fume cupboards, reaction vessels, HPLC/flash preparative chromatography, classified spaces GMP complying etc) but at present used for the studies concerning the original ophthalmologic eye-drops medicine based on dessert truffles. Team E8 has a renovated and equipped spaces complying with GLP standards. Both Teams E_4 and E_5 would need an NMR machine necessary for characterization of the organic compounds which they synthesize. In addition, new infrastructure is necessary if techniques of functional genomics, molecular biology and protein chemistry are to be introduced (as recommended).

Most of infrastructure is exploited more than 75% according to the research staff of the institute. However, there are performing devices like the flow cytometer which has only 25-50% exploitation rate.

Short summary: Very good quality in some teams, not modern in others (e.g. chemical labs). Excellent modern equipment of the Analytical research Team E_7. Old, not modern buildings.

C4: Management efficiency and quality of the research environemnt **Mark: 3.0**

There are several highly qualified researchers in the institute. Motivation and enthusiasm of many (particularly young researchers, PhD students) is a strong asset of the research staff. However, some staff members apparently are not aware of the present trends in R&D in drug discovery and the tremendous technical progress in this field. The Institute does not perform regular individual or team evaluations. The Institute's management team is using, in general, non-financial rewards.

ICCF operates under the direct coordination of the National Authority for Scientific Research (NASR) within the Ministry of Education, Research, Youth and Sport. Among the 7 members of the Administration Council there are also representatives from the Ministry of Economy, Ministry of Labor and Ministry of Environment. Administrative procedure is issued by the institution and is determined by government level rules. There have been large efforts of the Direction Committee including the General Director, Scientific Director and Economical Director to ensure the administrative efficiency of the institute. Dramatic decrease of national R&D funds starting with 2009 represented a severe challenge which the institute has faced successfully. On time pay of salaries was a sign of an appropriate strategy of the Direction Committee in this respect. Some delays in reimbursement of the collaborators are shortcomings which are accountable under the existing financial circumstances but should be overcome in the future.

Members of R&D staff were asked about their satisfaction. They did not mention any specific reason for dissatisfaction but they did not explicitly mention their satisfaction for the quality of the research environment. No internal questionnaires-system is used to evaluate satisfaction of R&D employees. The organization should perform regular R&D staff satisfaction surveys and then take action based on the feedback.

There were no objections from the staff regarding the administrative efficiency of the institute.

According to the members of the research staff there is transparency of the decision of the leadership.

As far as the scientific work is concerned the researchers and also the PhD students have the freedom to contribute to choosing the right decisions in their research subjects. Apparently, the staff is often consulted regarding the decisions to be made at the level of the institute.

There are no issues regarding the professional ethics and good conduct. A Code of Ethics is enclosed to the internal regulation of the institute in agreement with EC Recommendation 576/2005 on the European Charter for Researchers and a Code of Conduct for the Recruitment of Researchers. Also, there is a Commission of Ethics set up by the scientific council.

The administrative staff is available for the great majority of administrative problems encountered within the institute. Administration of the R&D contracts involves numerous time-consuming, bureaucratic actions which are performed by the research staff although they might be, at least in part, taken over by the Administrative staff. However, the research staff seems not to be concerned about the administrative burden of their contracts.

The Analytical Research Team E_7 succeeded to obtain the GLP Authorization and Pharmacological Research Team E_8 started the forms to obtain GLP accreditation from the National authorities. Other teams, particularly those where GLP accreditation is a prerequisite for performing certified stages of pre-clinical analysis, should also apply for GLP accreditation.

Short summary: OK management, well informed team-leaders and researchers. Motivated team-members. Solidarity among the employees. However, few young scientists among the leaders. Very little out-reach.

C5: Quality and credibility of the institutional development plan **Mark: 3.0**

The SWOT analysis in the Development Plan is realistic and is a good starting point for establishing the development directions of the institute. The chapter dedicated to Scientific research directions, mentions the three principles which are intended to be respected. However, only the first one deserves in fact the profile of the institute: "to follow the actual trends in the fields of activity having in view those topics in which the institute has got a long term expertise and their qualitative improvement". The other two principles are concerned with technologies for renewable resources and "non-pharm bio-products: biopesticides, biofertilizers" which in fact do not belong to the core mission of the institute; therefore, they should be cancelled and ongoing projects in these directions should be discontinued. The institute should focus on its main mission: chemical-pharmaceutical R&D activities. The research directions mentioned under the sub-chapter "Microbial Biotechnologies" are phrased in very general terms, suggesting mainly outdated, old-fashioned research goals like "isolation of new bioproducts", their testing for "antiviral, anti-tumoral" effects. Mutagenesis experiments are planned to be performed by "physical treatments – irradiation" without mentioning site-directed mutagenesis, as a more efficient tool of molecular biology in appropriate situations.

There is an excellent scheme on page 8 of the Development Plan for the planned activities in the field of Extractive Biotechnologies (including those for discovery of drugs from plants). Similarly, scheme on page 9 for developing innovative synthetic drugs is very realistic and in agreement with the modern trends. These two schemes demonstrate that the leadership of the institute is fully aware of the present R&D directions in these fields which, clearly, should be followed by the institute as well. A question can be raised in this direction: why these schemes have not been applied so far in the institute?

Plans for technological development as described under sub-chapter for "Improved technologies of generics" are very much welcome and it is strongly recommended to be applied soon, given the market needs in this respect (see observation for Team E_5).

The research projects planned for the first 4 years under "Pharmacological technologies" (page 10) are not original. For example, as concerning the research study to obtain magnetic biopolymers coated with anti-thrombolytic agents, at least one article was already published in this respect (Biopolymers 30, 5125-5130 (2009)). Notably, under "Pharmacological research" it is stated that "the aim is to perform the pre-clinical characterization of the new pharmaceutical and similar products". This aim is strongly supported by the evaluators.

There are several ways mentioned in the Development Plan which would lead to new directions in R&D activities of the institute: compliance to the national and/or EU R&D strategies, attention paid to priorities of non-EU countries, taking over the ideas of the education/ research/ industrial partners of the institute. In addition, it is mentioned that new ideas might be stimulated by bottom up or top down mechanisms. Unfortunately, there is no mention about an essential mechanism which should be introduced in the strategy of the institute: fundamental, application-oriented research studies to be performed within the institute. This approach would represent an essential source of original ideas for the institute R&D activity. Particularly, this approach should be oriented to evidence new targets for known diseases and to identify new modulators (synthetic or natural) of the known molecular targets of various diseases.

A list of promising tools to recruit young graduated people in the institute is given. These tools are important in order to enrich the R&D staff of the institute with young, motivated individuals. There is another source of highly qualified young researchers which should be also used by this institute: Romanian young researchers from the diaspora, preferentially at postdoctoral level, who are working in prestigious research units. They can be attracted by good working conditions, decent salaries, freedom to choose the members of their teams and to decide their specific research objectives (within the mission of the institute). A clear strategy is needed. Although it is not the mission of the evaluators, here is a chance to mention that attracting the required personnel from abroad is aided in several countries also by governmental sources.

The plans in this respect are reasonable. A little bit more emphasis on how to attract for collaboration highly performing research institutes and/or innovative pharmaceutical companies would have been useful. In addition, a strategy to develop European collaborations and common projects should be established.

Organization of scientific meetings within the institute is a good way of increasing the visibility of the institute. However, it is important who is participating in these events, what are the scientific prestige of the invited lecturers, what is the R&D offer of the institute in these scientific events and how relevant and new it is for the present trends in e.g. drug development.

There are still no signs of critical mass in the key R&D directions of the institute and it is not clear how its appearance is intended to be stimulated.

Short summary: Good Development plan. Clear and realistic. Aware of the major problems. Good SWOT analysis. Less clear on HOW to implement.

IV. SPECIFIC MEASURES, TARGETS AND RECOMMENDATIONS TO BE MET IN A TIME OF 3 YEARS

The quality of R&D activities and their results

More original approach in selecting the research subjects of the R&D activities. Introduce modern tools of drug design and drug validation. Use intensively tools of bioinformatics, computer-aided drug design, *in silico* simulations/predictions. Introduce modern techniques of molecular biology and functional genomics in experimental work of the teams. More protein chemistry and its techniques would be also welcome in the context of recommended new research orientation. Create conditions for performing pre-clinical tests (according to EU criteria) of potential drugs within the institute. In this way the quality of the papers emerging from the institute should increase considerably as well as the potential of international patents granted to the institute. Establish European collaborations. More transfer of technology from the research laboratory to start-up and spin-off company/companies.

Human resources quality

Hire successful and highly qualified young researchers, preferentially selected from Romanian scientists (at postdoctoral level) working in prestigious research units from abroad. Their reintegration should be encouraged by giving them excellent working conditions, decent salaries, freedom to select the members of their teams and decide the research direction they will follow (within the R&D mission of the institute). Increase international collaborations. More PhDstudents and PostDocs.

Quality infrastructure and its rate of exploitation

Apply for institutional projects for infrastructure. Purchase the necessary new equipment in parallel with hiring young researchers properly qualified to exploit the new equipment. Establish a/several core facility/facilities.

Management efficiency and quality of the research environemnt

Acceleration of GLP accreditation for the institute laboratories (where applicable). Invite outstanding specialist actively working in the field of drug discovery (as well as in other fields relevant to the Institute) to deliver seminars or short courses in the institute. Encourage young researchers to attend valuable practical courses abroad in their fields, including those fields which are planned to be initiated within the institute.

Quality and credibility of the institutional development plan

Re-analyze the general and specific R&D directions of the institute. Discontinue old-fashioned research directions and those which do not belong to the chemical-pharmaceutical R&D mission of the institute. Strengthen Microbial biotechnology with internationally experienced younger scientists. Introduce modern techniques of molecular biology, recombinant DNA technology, bioinformatics and computer-aided drug design. Set up a new team for Functional Genomics, dedicated to fundamental research in drug-development, which should apply all these modern tools towards generating new ideas for innovative drug development. Establish a few, larger European collaborations.

V. Proposed certification level: A – (mean 2.8)

Nr. crt.	Name, Surname	Signature
Evaluation TEAM		
1	Wenxin Wang	
2	Peter Lindblad	
3	Stefan Szedlacsek	
4	Anica Dricu	
5	Ferenc Deák	
Observers		
1	Coordinating Authority	
2	CCCDI Representative – Lucian Pintilie	
3	ANCS Representative – Daniela Iacob	

Date: June 6 (2012)

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Date: June 6 (2012) 08/06/2012