IFAPPWORLD
INTERNATIONAL FEDERATION OF ASSOCIATIONS OF PHARMACEUTICAL PHYSICIANS & PHARMACEUTICAL MEDICINE

CONTENT

PRESIDENT'S LETTER

Anecdotal Report on IFAPP Activities in 2014 and 2015

Dr Gustavo Kesselring, IFAPP President

Dear Colleagues

It was March 2014 in Berlin, Germany, when the new IFAPP Board of Officers (BoO) with me as the new IFAPP President, with Dr Honorio Silva (President elect), Dr Yil-Seob Lee (Past President), and Prof. Dr Gerfried Nell (Treasurer), and Dr Marléne Llopiz (Secretary) has presented IFAPP's Key Objectives for the next term (see table beside) to IFAPP's House of Delegates (HoD).

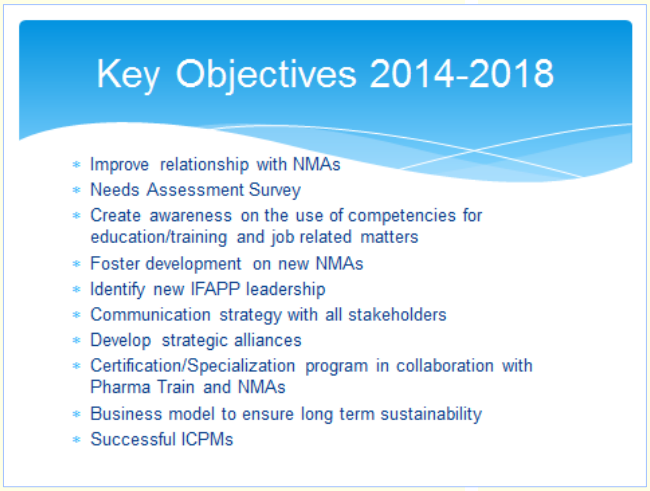
So far much has already been achieved but a great deal remains to be done following the ambitious agenda we have presented. Hereafter I like to draw a picture of what has been achieved so far – following the Key Objectives.

Improve relationship with NMAs

As IFAPP President I have contacted IFAPP's National Member Associations (NMAs) in Argentina, Australia, Germany, Italy, Japan, Korea, Mexico, Peru, Portugal, Singapore, South Africa, Spain, USA (listed in alphabetic order) via regular telephone calls, via telephone conferences, or face to face during conference participations.

In 2014 and 2015 IFAPP is or was involved in several conferences on pharmaceutical medicine (PM) worldwide as listed below, where IFAPP takes or took the opportunities of spreading and anchoring its mission, its aims and objectives.

- 17th International Conference on Pharmaceutical Medicine – ICPM 2014 – together with the 30th Annual Congress of the German Society of Pharmaceutical Medicine (DGPharMed). Berlin, Germany, March 2014.
- World Congress of Basic & Clinical Pharmacology. Cape Town, South Africa, July 2014.
- Argentine Congress on Pharmaceutical Medicine of the Sociedad Argentina de Medicina Farmacéutica (SAMEFA). Buenos Aires, Argentina, December 2014.
- PharmaTrain – IFAPP – SSFA Conference (SSFA – Società di Scienze Farmacologiche Applicate) – Advancing Competent Professionals in Medicines Development. Rome, Italy, June 2015.
- Portuguese Conference on Pharmaceutical Medicine of the Associação dos Médicos Portugueses da Indústria Farmacêutica (AMPIF). Lisbon, Portugal, November 2015.



- Swiss Symposium in Pharmaceutical Medicine (Swiss Association of Pharmaceutical Professionals – SwAPP; Swiss Society of Pharmaceutical Medicine – SGPM/SSPM). Zurich, Switzerland, November 2014 and November 2015.
- Spanish Conference on Pharmaceutical Medicine of the Asociación de Medicina de la Industria Farmaceutica Española (AMIFE). Madrid, Spain, December 2015.

Needs Assessment Survey

In order to better understand the NMA needs scenario worldwide IFAPP's Working Group on Education has launched the Needs Assessment Survey in 2014. The results, which have been presented at the House of Delegate meeting held on May 6th, 2015, prove a clear need in the educational arena of Medical Affairs/Medical Science Liaison (MSL) and of regulatory matters, a need for certification programs besides sharing news and best practices from NMAs. The modernization of the IFAPP website is an issue too.

Create awareness on the use of competencies for education/training and job related matters

During 2014-2015 the Working Group on Education together with several IFAPP individual collaborators have published four articles on education, training and competencies in drug development sciences and pharmaceutical medicine: two publications in the journal Clinical Researcher, one in Frontiers in Pharmacology and another one in the journal of Pharmaceutical Medicine.

Foster development on new NMAs

IFAPP has sponsored a symposium at the 17th World Congress of Basic & Clinical Pharmacology in Cape Town, South Africa, in July 2014. This has reinvigorated the local experts to seek a revival of the South African Society of Pharmaceutical Medicine – but it is still in the early phase.

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>>> >>> I myself and Dr Honorio Silva have been in close contact with our colleagues in Singapore. A 1st Pharmaceutical Medicine Symposium, hosted by the Association of Pharmaceutical Medicine Singapore (APMS) in late October 2015, was a great success with nearly 100 participants. IFAPP WORLD will present a meeting report soon.

The Swedish Society of Physicians working in the Life Sciences Industry (Sveriges Industriläkarförening – SLF) has shown interest in joining IFAPP. The SLF is kindly invited by IFAPP and will come to a decision in 2016.

During the 27th Annual EuroMeeting of the Drug Information Association (DIA) in Paris, France, in April 2015 I have tried to meet the representatives of the French Society of Pharmaceutical Medicine (l'Association des Médecins de l'Industrie Pharmaceutique – AMIPS) for discussing a reconnection with IFAPP. Unfortunately a meeting was impossible due to conflicting agendas.

Communication strategy with all stakeholders

IFAPP's Communication Working Group has worked hard to provide the following achievements:

IFAPP WORLD is now a regular communication tool for all NMAs. However, the distribution needs to get improved by the NMAs to get each issue delivered to their individual members.

IFAPP's LinkedIn group has started as a valuable tool, which very quickly has demonstrated the power to improve communication and interaction with individuals interested in pharmaceutical medicine besides the regular communication with NMAs. To register is simple and free. Just visit IFAPP's website at www.ifapp.org and scroll down to the bottom, click the "in" button, and follow the instructions. Please start right now!

IFAPP's website is planned to get modernized and reformatted in 2016.

Develop strategic alliances

A strategic alliance between IFAPP, PharmaTrain, and the Rutgers University, State University of New Jersey, USA, has been signed to develop the IFAPP Rutgers PharmaTrain Certification Program in Medical Affairs and Drug Development Sciences.

Another strategic alliance with the World Medical Association (WMA) is under evaluation by the WMA and the Faculty of Pharmaceutical Medicine in the United Kingdom (UK). A decision is announced for 2016.

Certification/Specialization program in collaboration with PharmaTrain and NMAs

In 2014 I have approached Chief Medical Officers (CMOs) from Merck and Bayer, and the Heads of Global Medical Affairs from Pfizer and Sanofi to get financial support to develop the IFAPP Rutgers PharmaTrain Certification Program in Medical Affairs and Drug Development Sciences. All these companies have already committed to give financial support and it will be launched during the 18th International Conference on Pharmaceutical Medicine – ICPM 2016 – in April 2016 in São Paulo, Brasil.

Business model to ensure long-term sustainability

Being IFAPP the "house" of pharmaceutical medicine matters worldwide with education in pharmaceutical medicine as an IFAPP core activity I myself as the IFAPP President together with IFAPP's Working Group on Education and PharmaTrain have developed the IFAPP Rutgers PharmaTrain Certification Program in Medical Affairs and Drug Development Sciences as an educational initiative with a consistent business plan that will generate revenues for IFAPP and for all NMAs that would like to implement the program at a national level. This initiative will provide IFAPP a long-term sustainability.

Modernization of IFAPP's Constitution

IFAPP's Board of Officers has recognized that IFAPP's constitution needs to be changed in order to open the door for individual members who like to collaborate with IFAPP, while at the same time IFAPP should remain a federation of NMAs and ruled by the House of Delegates. A revision process is already in place and should be finalized by the end of 2015.

Last but not least

IFAPP's 18th International Conference on Pharmaceutical Medicine – ICPM 2016 – 18th and 19th April 2016 in São Paulo, Brazil, is approaching. The Scientific Committee will provide a world-class conference with topics and matters related to pharmaceutical medicine. By the end of 2015 a full program will be available at www.icpm2016.com. Come to São Paulo and join us at ICPM 2016 – I expect to meet you and the entire pharmaceutical medicine community.

With kind regards
Dr Gustavo Kesselring
IFAPP President

ETHICAL QUANDARY

Placebo-Controlled Clinical Trials in Low-Resource Settings – How Much Standard of Care is Necessary?

The main ethical issues of clinical trials in developing and emerging countries are (1) the quality of informed consent, (2) post-trial access to appropriate treatment, and last but not least (3) the standard of care that should be used in research. According to the World Medical Association's (WMA) Declaration of Helsinki a new intervention must be tested against the best proven intervention(s), and the use of placebo or no intervention is acceptable only in very exceptional circumstances. The following published case provides an example that the question whether a placebo-controlled trial design is ethically justifiable sometimes cannot easily be answered.

The Case

In 2013 the Journal of Clinical Oncology (JCO) published the results of a randomized metastatic HER2-positive breast cancer trial [1]. In the trial 444 patients from Brazil, China, Pakistan, Peru, Russia, Thailand, and Ukraine were recruited between January 2006 and December 2009. Of these, 222 patients were randomly assigned to receive lapatinib plus paclitaxel and 222 to placebo plus paclitaxel.

Roughly 8 years before this trial started, trastuzumab – a similar drug to lapatinib – was approved by the US-American Food and Drug Administration (FDA) for the treatment of metastatic HER2-positive breast cancer; in 2001, i.e., nearly 5 years before start of the lapatinib trial, the superiority of trastuzumab over no HER2 treatment was shown when added to chemotherapy [2].

These facts induced a Brazilian oncologist to write an angry letter to the editor of the JCO just a few weeks after the lapatinib trial was published in this journal [3]. He stated: "This raises ethical considerations about the use of a placebo control arm in a clinical setting with a clear standard of care. The fact that trastuzumab was not reimbursed in the participating countries at the time of initiating the study by no means justifies the choice of placebo >>>

>>> as a control arm". The corresponding author of the lapatinib trial replied [4] in the following way: "... Unfortunately, anti-human epidermal growth factor receptor 2 [HER2] drugs were not universally available at that time in developing countries ... Investigators had the option to unblind the patient's treatment, and those on placebo plus paclitaxel could continue on open-label lapatinib monotherapy."

Additional Notes

Two aspects are worthwhile to be noted: all patients in the lapatinib trial were given access to HER2 targeted therapy as part of the trial, either at randomization or progression; and in the participating countries paclitaxel monotherapy was widely used for first-line treatment and thus considered a suitable treatment option and appropriate control arm by both principal investigators and local ethics committees.

Furthermore, the trial was supported by the financial sponsor with regulatory intent, i.e., to make the drug available to patients in countries where trastuzumab was not readily available. In fact, the financial sponsor, i.e., the lapatinib license holder, could file marketing authorizations in four of the countries.

Several ethicists suppose that it is ethically permissible, in some circumstances, to provide research participants less than the worldwide best care [5]; and that it needs to be decided whether trials should compare novel interventions to the developed-world standard of care, or if it is acceptable, or even preferable, to evaluate them against locally available treatments [6].

What is Your Opinion?

Do you believe that an ethical double standard for clinical research in low-resource settings is impossible to be justified – or do you believe that there is no ethical obligation for this? Your response on this is appreciated.

Dr Peter Kleist
Cantonal Ethics Committee Zurich, Switzerland

Please send your response and opinion to the IFAPP WORLD editor (boebue@boebue.de). With your permission, we might publish it in full or in part and – upon your request – without disclosing your name.

References

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[3] Ades F; J Clin Oncol 2013; 31:4271.
[4] Guan Z; J Clin Oncol 2013; 31:4272.
[5] Lie RK et al.; J Med Ethics 2004; 30:190-3.
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JAPAN: Benefits from Multi-regional Clinical Trials for New Medicines
Perspectives on Drug Development in Japan and Asia (Part II)

| This is the second and last part of an expert's article, which reviews the drug development situation in the Asian region mostly from Japan's point of view, and looks into the changing paradigm in pharmaceutical R&D in the Asian region. |

2.2. Gastric Cancer Studies • The high incidence of gastric cancer in the Asian population is well known. There have been a number of MRCTs involving Asian gastric cancer patients, providing unique aspects of ethnic factors in drug development. In this section, the results of three MRCTs involving Asian countries, TOGA [4], AVAGAST [5], and TyTAN [6] are reviewed to explore the impact of ethnic factors on the results.

TOGA [4] and AVAGAST [5] are global clinical trials involving US, European and Asian countries, investigating the effect of trastuzumab and bevacizumab, respectively, in combination with conventional chemotherapy as compared with that of chemotherapy alone with overall survival (OS) as the primary endpoint.

TyTAN [6] is a clinical trial involving only Asian countries with a similar design to TOGA and AVAGAST, investigating the effect of lapatinib in combination with conventional chemotherapy (paclitaxel).

In summary, OS as the primary endpoint was positive in TOGA, whereas in both AVAGAST and TyTAN, the primary endpoint OS did not reach statistical significance. In subgroup analysis, all three trials indicated the better efficacy in higher degree of HER2-positive patients (IHC3+) as compared with lower degree HER2-positive patients (IHC0/1+ and 2+). Based on the results, it is indicated that gastric cancer patients with higher degree of HER2-positive will have more benefit from these drugs.

In a subgroup analysis by region, TOGA and AVAGAST suggested a lower efficacy in the Asian region compared to European and American regions. In AVAGAST, the longer survival rate in the Asian population was observed in standard chemotherapy group as compared with the European and the American populations.

TyTAN is an Asian clinical trial and provides further insight through more detailed analysis by subpopulation. Again, in TyTAN, OS and PFS improvement was not statically significant with lapatinib plus paclitaxel versus paclitaxel alone in the intent-to-treat population. Subgroup analysis by country indicated that in the Chinese population paclitaxel plus lapatinib significantly improved OS as compared to paclitaxel alone, whereas in the Japanese population no improvement in OS was indicated. It also is of interest that the median OS with paclitaxel alone was considerably longer in the Japanese population (14.6 months), and OS was even higher than that of the Chinese population treated with paclitaxel plus lapatinib (9.7 months). This may suggest that it is very difficult to demonstrate the additional drug effects in the Japanese population with OS as the endpoint.

Based on this observation, even though the Asian populations are ethnically similar, there seem to be regional differences in the treatment effects of gastric cancers. Because medical care environment is known to be different between China and Japan, it is possible to speculate that the medical environment including the access to the standard care or the use of conco- >>>

The first part of this article – published in IFAPP-WORLD-2015-5-October, page 2-4, available at www.ifapp.org – was structured along the following topics (sub-headings):

Current State of Global Simultaneous Drug Development in Japan
Benefits from Global Simultaneous Development
Elimination of a "Drug Lag" in Asia
New Scientific Insights
1. Outcome Data
2. Ethnic Factors
2.1. Iressa Pan Asian Study (IPASS)

Amemdment regarding IFAPP WORLD's October 2015 article
"The Specialist in Medicines Development (SMD) Program – a Pilot in Japan": The author is Dr Kyoko Imamura; we said she is President of the Japanese Association of PM (JAPhMed). In fact she was Past President at that time already, followed by Dr Kazuya Iwamoto, the elected new JAPhMed President. We apologize for this error.

Notes from the Editor

>>> mitant treatment may have an impact on the clinical trial results.

There has been no clear evidence to indicate that any of these factors actually impacted the trial results, and the interpretation of these data needs to be done with caution because of the small sample size in subgroup analysis. However, it is evident that these factors need to be taken into considerations when we consider the strategy of drug development to demonstrate the real benefit to the patients.

Company	Closed Trial Sites	New Trial Sites
Pfizer	Nagoya, Japan	Shanghai, China
Merck	Tsukuba, Japan	---
GlaxoSmithKline	Tsukuba, Japan	Singapore Shanghai, China
Bayer	Kobe, Japan	---
Novartis	Tsukuba, Japan	Singapore Shanghai, China
Roche	---	Shanghai, China
AstraZeneca	---	India Shanghai, China

Table 3: Research Facilities Moving out of Japan

Evolution of Drug Development in Asia

The initial intention of drug development strategies using clinical trials involving Asian countries was to facilitate the development of so-called catch up drugs in Japan by taking advantage of the efficiency in clinical trial operations in Asian countries, especially South Korea.

The purpose of Asian clinical trials has then changed into the more scientific intention to facilitate drug development in the field of high incidence diseases in Asian countries such as gastric cancer as already discussed in the previous section or viral hepatitis.

Recently, there seems to be a more strategic intention to take advantage of the full value of the Asian region for drug development. One approach is to initiate clinical trials in Asian countries and then the drug development strategy is considered for the drug development in other parts of the world, especially again in therapeutic area of high incidence in Asian countries.

Changing Dynamics in Asian Pharmaceutical R&D

As shown in the **Table 3**, all the research facilities in US and European based companies in Japan have moved to other Asian markets like Shanghai or Singapore. As a natural consequence, the R&D investment to Japan has been significantly reduced, while R&D investment in China keeps increasing. This likely reflects a global pharmaceutical industry point of view and the high expectation for China to be a fast growing market.

Despite the difficult situation, Japan is consistently delivering the improvement in drug development. Global simultaneous development has become the standard approach for drug development in most major pharmaceutical companies located in Japan, resulting in the elimination of drug lags. Asian collaboration in the form of Asian clinical trials seems to be an established way for efficient drug development in the region, contributing to global drug development. Based on these progresses combined with the consistent and significant improvement in the regulatory situation, it seems that Japan started to regain attention as an important country for drug development.

Conclusions

Global development including Asian countries has resulted in the elimination of drug lags, and new scientific insights regarding ethnic factors have been obtained.

The global pharma R&D strategy is evolving, and although it is still US/European centric, the value of Asian countries in drug development has been further appreciated. This trend will contribute to the improvement in patient access to valuable drugs in the region.

It is critically important for each country to take advantage of this opportunity to contribute to the regional and global public health, and further efforts through the collaboration among industry, academia and government is necessary to further build clinical research infrastructure in Japan and other Asian countries to realize the full value of the region.

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This report was first published in "pharmazeutische medizin" 2015, 17/2:106-110 – journal of the "German Society of PM" (DGPharMed).

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The Flag

IFAPP WORLD is a publication of the International Federation of Associations of Pharmaceutical Physicians and Pharmaceutical Medicine.

IFAPP, a non-profit organization founded in 1975, acts as an international forum for all pharmaceutical medicine professionals' organizations worldwide by dealing with matters brought to its attention through national member associations.