A new year, a new start!

I presume some of you have started the new year with the resolution to do things differently in 2004. At least that is what the IPEC board did end of last year when they agreed that the communication committee could go ahead with implementing the new IPEC “house style”. This “restyled” newsletter is the living proof that it did not remain just a resolution. In reading “implementing a new house style”, some of you may envision a multi million Euro introduction campaign similar to those performed by some of the bigger pharmaceutical companies after one of the recent mergers. But no, none of that at IPEC. Though we like to do things well, preferably even better than some of those big spenders, we also like to do things with the right perspective and under our own control, and so our spending stays in line with our budget. That is why the house style was developed and will be implemented step by step.

After approval of the communication budget by the annual general meeting in Amsterdam last year, the communication commission started its work. The first priority was updating the text of existing brochures, organizing input for our news letter, increasing the accessibility of our internet site, etc. and finally in the middle of last year a small advertisement company started work on the new design. After the new logo was created the first examples of a new IPEC brochure, IPEC letterhead, invoices, business cards, internet lay out, etc. were presented for discussion in the IPEC board meeting of October last year.

(continued on page 2)
And even though several suggestions for improvements were made, the overall feedback was very positive. So positive in fact, that it was decided to use the suggested brochure for the CPhI exhibition scheduled to take place in Frankfurt a couple of weeks later, and to work on the suggested improvement afterwards. That is why those of you present at the CPhI exhibition may have seen a particularly proud and smiling Evert walking around waving the new brochures with the objective to bring in a couple of new IPEC members. Before long the new house style will also become visible on our internet site, visited a hundred times daily, and though small changes still will need to be made, it will gradually become visible in all our communication activities.

I imagine that some people will contest the added value of a developing new IPEC house style. Why are scarce resources spent for a non-commercial association? Why bother developing a nice package when IPEC is apparently happy with the present situation? But a consistent and appealing house style is more than just a package. It creates uniformity, visibility and provides identity. And, probably even more importantly, it also expresses a level of professionalism. If there is something that IPEC committee members deserve for all their hard work, then it is that their results are published in the same professional manner as their work was done. While it never will replace the value of the content it may certainly enhance the beauty of it. I sincerely hope that you enjoy reading this first newsletter in the new house style. Silently I also hope that it may also trigger even more of you to write copy for one of the future newsletters.

IPEC Europe News

The next Newsletter is scheduled to be issued in the month of April 2004. IPEC Europe members who would like to contribute to the Newsletter are invited to submit text electronically (maximum 1 A4) to Mr Izeboud at: eizeboud@worldonline.nl

IPEC Europe

IPEC Europe Seminar and AGM 2004

On January 29th and 30th 2004 IPEC Europe will organise its traditional « New Year » Seminar and subsequently the Annual General Meeting. The venue for the events is the Majestic Barriere hotel in Cannes, France.

Hotel Majestic Barriere, Cannes

For 2004 the IPEC Europe Board (read: Carl Mroz) has tried to present a Seminar of high quality. A seminar meant to contribute to the added value of being an IPEC Europe member. At the time of writing this article the total number of participants, the speakers and guests included, added up to 70 attendees. For your convenience the Program of the Seminar is published on page 3 of this Newsletter.

IPEC Europe membership 2003/2004

In 2003 the Board welcomed 2 new members, i.e Luzenac (pharmaceutical talc) and SPI Pharma.

The objective for 2004 (10 new members) is partly triggered by the expansion of the European Union. Already during the CPhI 2003, a start was made by approaching excipient makers and users in the 10 new EU Countries to join in May 2004.
## Program IPEC Europe Seminar

**January 29th 2004**

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
</tr>
</thead>
<tbody>
<tr>
<td>10.15</td>
<td>Chairman’s welcome</td>
</tr>
<tr>
<td>10.30</td>
<td>Regulatory update Europe</td>
</tr>
<tr>
<td></td>
<td>Dr Mike Morris</td>
</tr>
<tr>
<td>11.00</td>
<td>PhEur Cert. Scheme,</td>
</tr>
<tr>
<td></td>
<td>Mr Pieter Vree</td>
</tr>
<tr>
<td></td>
<td>Inspection experiences</td>
</tr>
<tr>
<td>11.30</td>
<td>EDQM</td>
</tr>
<tr>
<td></td>
<td>Dr Michael Wierer</td>
</tr>
<tr>
<td></td>
<td>Latest news</td>
</tr>
<tr>
<td></td>
<td>TSE Issues</td>
</tr>
<tr>
<td></td>
<td>Impurity issues</td>
</tr>
<tr>
<td>12.00</td>
<td>PhEur monographs</td>
</tr>
<tr>
<td></td>
<td>Prof Henning Kristensen</td>
</tr>
<tr>
<td></td>
<td>Substances for Pharmaceutical Use</td>
</tr>
<tr>
<td></td>
<td>Incl. Functionality related tests</td>
</tr>
<tr>
<td>12.30</td>
<td>Lunch</td>
</tr>
<tr>
<td>14.00</td>
<td>Novel use/application of an excipient</td>
</tr>
<tr>
<td></td>
<td>Dr Wouter Hinrichs</td>
</tr>
<tr>
<td>14.30</td>
<td>Introduction of a ‘new’ excipient</td>
</tr>
<tr>
<td></td>
<td>Dr Ronald Lange</td>
</tr>
<tr>
<td>15.00</td>
<td>FDA Bioterrorism issues</td>
</tr>
<tr>
<td></td>
<td>Mr Art Falk</td>
</tr>
<tr>
<td>15.30</td>
<td>Excipient Supplier evaluation</td>
</tr>
<tr>
<td></td>
<td>Mr Ignace Wallaert</td>
</tr>
<tr>
<td>16.00</td>
<td>Closing</td>
</tr>
<tr>
<td>19.00</td>
<td>Cocktail hour</td>
</tr>
<tr>
<td>20.00</td>
<td>IPEC Europe Dinner</td>
</tr>
</tbody>
</table>

### Partnership in Harmonisation, and extension to ICH activities?

Henk J. de Jong

Prior to the ICH6 Conference, on Wednesday November 12, 2004 Osaka, Japan, a Satellite symposium was organised on activities in the field of harmonization that are ongoing in non ICH regions.

In this one day symposium attended by about 750 participants, including ca. 200 coming from “non-ICH” countries, several important topics were covered:

- Non-ICH regional harmonisation initiatives [presentations by Ms Matsoso, Southern Africa; Ms D’ Alessio, Latin Americas; Mr Lim, APEC; Mr Awang, ASEAN; Dr. Rägo WHO]
- Experience of non-ICH countries with ICH guidelines [presentations from APEC, Latin Americas, ASEAN, WHO]
- New Global Cooperation Group (GCG-ICH) activities and organisation.[Dr. Abadie]

The GCG was founded in 1999 with members from the 6 ICH partners plus 2 observers and a secretary from IFPMA, with as a main objective to communicate in non ICH countries about the initiatives and achievements of ICH. Over the last years we have seen a strong interest but also some disagreement with ICH proposals in the non ICH territories. Several regional initiatives to harmonise requirements regarding registration and quality of medicines have been started, the outcomes of these initiatives sometimes differ from the ICH ones. This has been recognised at ICH Steering Committee level and from ICH6 onwards the GCG will have a new mission and composition: members from other regional harmonisation initiatives can become members of the GCG. This will result in a direct input and debate. Like always in ICH, proposals can be made to the Steering Committee for adoption leading to creation of new topics and new EWG.

(Continued on page 4)
It is recognised that the centre of interest in the non ICH countries at this time is in the area of existing medicines i.e not the new ones, this implies a high interest in generics. In the ICH countries authorities are more and more interested to apply ICH principles also to existing ingredients and products (e.g residual solvents guideline in Europe, from ICH (new substances and products) to EMEA/CPMP/QWP guideline and general chapter in the European Pharmacopoeia, mandatory for all ingredients and products).

Will be admitted to the GCG: representatives of SADC (Southern Africa, 14 member states, leaders South Africa and Zimbabwe) the Southern Africa Development Community (Health Ministers).
representatives of APEC (Asia Pacific Economic Cooperation, Network of Pharmaceutical Regulatory Science)
representatives of ASEAN(10 countries) PPWG (the Pharmaceutical Product Working Group) and probably others, the selection criterion being “a group of countries with harmonisation efforts in the pharmaceutical area”. Questions will surely arise as to other important players: India, China, and the Central and Eastern European countries that will partly become members of the EU in 2004 (and thus covered by EFPIA and EMEA).

Topics needing clarification/discussion/new harmonisation initiatives:

**Quality issues:**
- stability studies/conditions in climatic zone III/IV countries
- Certification of ingredients/products
- Status/use of GMP/PMF/DMF requirements
- Quality guidelines for existing products
- Bioavailability/Bioequivalence, Biopharmaceutical Classification system

**Efficacy issues:**
- Ethnic factors, use of bridging studies
- Good clinical practice

**General issues:**
- Common Technical Document versus Common Technical Dossier (ASEAN)

Main problems signalled by all non ICH representatives: 1) training needs in the field of drug evaluation and regulatory affairs, 2) lack of possibilities for implementation and enforcement of rules, regulations and guidelines.

The new GCG will be chaired (2003-2005) by Dr. Yves Juillet (Europe, Les Entreprises du Médicament (LEEM) France) and Dr. Mike D. Ward (Therapeutic Products Directorate, Health Canada).

**Professor Fernand Pellerin**

Evert Izeboud and Henk J. De Jong

During the 2004 Annual General Meeting Professor Fernand Pellerin will be put in the spotlight, on the occasion of the fact that he will retire from IPEC Europe.

Co-opted member of IPEC Europe, he is now emeritus Professor of Analytical Chemistry at the Faculté de Pharmacie de l’Université PARIS-SUD. His department was specialized in functional group analysis and its application to polymers used as pharmaceutical excipients and plastic materials for pharmaceutical use.

As President of the Analytical Chemistry Division of IUPAC (1984-1986) he was interested in the harmonization of collaborative analytical studies. In 1991 Professor Pellerin presented a lecture to the Open Conference on International Harmonisation of excipients standards (January 1991 - Orlando, Florida, United States) also the starting point of IPEC. In 1993, he presented his views during the First Annual General Meeting of IPEC Europe in Paris: “Strategies for acceptance of a new excipient”. The ideas he developed are still up to date. Since 1993, he participated in the activities of IPEC Europe’s Harmonization Committee.
With Prof. Henk de Jong and Anne Bonnetto (both at Servier) a first attempt was made to create a world inventory of excipients used in marketed pharmaceutical products. This first inventory was published by IPEC Europe on Internet for a future dictionary.

The experience of Prof Pellerin in the French Pharmacopoeia Commission, where he was Technical Secretary and Vice President, and also as an expert at the European Pharmacopoeia, allowed him to know the regulatory problems of Pharmacopoeias, the rules, the conception and the content of monographs.

Among the general ideas he developed in the interest of International Harmonization of quality requirements for pharmaceutical excipients, one should note the following:
- The quality of an excipient should be defined by the pharmaceutical industry in view of the role this ingredient has to play in a given formulation. Appropriate and validated methods should be chosen and defined to demonstrate quality attributes being within specifications. The pharmacopoeias play an important role in describing generally applicable methods.
- Frequently producers of excipients e.g. the chemical industry, are unaware of the final destination and use of their products. It is the obligation of the user, the pharmaceutical formulator, to verify fitness for use.
- Many excipients are used as food additives or food ingredients. These substances are scrutinized and their quality defined at International level (Food and Agricultural Organization, FAO, World Health Organization, WHO, the former EU Scientific Committee on Food). Professor Pellerin strongly promoted the idea that specifications thus already established could also be sufficient for oral or topical pharmaceutical uses.
- Excipients and additives are not limited to uses in pharmaceuticals, food and cosmetics, they also find applications in the chemical industry or in other "technical fields". The grades and qualities for the different uses are associated with sometimes very different specifications. Quality control monographs should be capable to differentiate between these qualities.

On behalf of IPEC Europe, we like to thank Fernand Pellerin for all his contributions. We wish him all the best!

New Application of Excipients: Inulin

Dr Wouter Hinrichs

Many new drug substances are either proteinous drug substances that have been evolved from recent biotechnological developments or highly lipophilic drugs that have been developed based on currently used screening methods. Despite the prospects to treat a large variety of diseases with these drug substances, several problems are encountered.

Proteinous drug substances are produced in an aqueous environment. However, in the dissolved state, these drug substances are usually not stable, limiting their shelf life. Moreover, the possibilities to develop dosage forms from solutions is limited. The aqueous solubility of lipophilic drugs is poor causing many lipophilic drugs to exhibit a poor bioavailability. Furthermore, lipophilic drugs may also be unstable, limiting their shelf life.

In this study it was evaluated whether these problems can be overcome by the incorporation of these drug substances in sugar glasses, in particular inulin glasses. Alkaline phosphatase (AP) and _9-tetrahydrocannabinol (THC) were used as models for an unstable proteinous drug substance and an unstable lipophilic drug, respectively. AP is a highly promising therapeutic agent for the treatment of sepsis and should be delivered in the intestines. THC is currently used to relieve nausea and to enhance appetite. To obtain a rapid physiological effect, rapid dissolution is required.

An aqueous solution of a mixture of AP and inulin (weight ratio 1/9) with a degree of polymerization of 14.2 or 23 (inulin DP 14.2 or inulin DP 23) was freeze dried and then stored for 6 days at 60°C and 8% relative humidity (RH). After this treatment, the enzymatic activity of AP was still about 80%. In contrast, when no excipient was used or glucose, trehalose or inulin DP 5.5 instead of inulin of higher DP, the activity of AP was fully lost[1]. Inulin DP 23 with incorporated AP could be compacted into tablets with sufficient strength and low friability without loss of activity of AP[2].
Supplied with an enteric coating the tablets also showed the desired in vitro dissolution behavior, i.e. they did not dissolve at pH 1 (pH of the stomach) but dissolved within 30 min at pH 6.8 (pH of the intestines). The desired dissolution behavior was also apparent in an in-vivo model: rats, to which the tablets were administered orally, showed increased levels of AP in their intestines[3].

THC and inulin DP 23 (weight ratio 4/96 and 8/92) dissolved in a mixture of water and tertiary butyl alcohol was freeze dried and then stored at 20°C and 45%RH[4, 5]. Pure THC was used as a control. The freeze dried material still contained about 80% non-degraded THC after 300 days while unprotected THC was completely degraded after 40 days. THC incorporated in inulin DP 23 prepared by spray freeze drying showed a similar stability as the freeze dried material. Tablets of 125 mg containing 2 mg THC prepared from the freeze dried material using mannitol and PVPP as additional excipients dissolved within 3 min for 80% making these tablets suitable for sublingual application.

It can be concluded that inulin glass technology can be used to stabilize labile proteinous and lipophilic drug substances. Furthermore, the inulin stabilized drug substances can be processed into tablets for oral administration, sublingual tablets or other solid dosage forms.

References
4. D.J. van Drooge et al. Accepted for publication. in J. Pharm. Sci.

IPEC Europe the first Ten Years

Jean-Paul Lopez

Some of us like archeology and it is perhaps why I have been asked to dig into my memory and many very useful “historical documents” to narrate some aspects of the first Years of the IPEC Europe lifetime. While it is certainly not the intention to bother you with a complete and detailed story of what has happened during the period 1991-1999, nine years during which I have been a permanent member of the IPEC Europe Board, let me try to give you some impressions, others would say a “flavor” of the scope of the activities of your Association during the “nineties”.

Well, everything started during the summer 1991 when a few colleagues among whom Rajiv Khosla (ISP), John Hogan (Colorcon) and Jeffrey Allen (Mendell), together with myself met to organize a first IPEC meeting in Dusseldorf hosted by Aqualon. We were in fact working on a similar project as the so called “International Pharmaceutical Excipient Council” which had been launched by approximately the same companies in the USA during the spring of the same year. The Dusseldorf session gathered 25 participants including a representant of the World Health Organisation. During this historical one day session the first foundations of the Association were settled. Both the function and mission, the structure, the membership of the Association were discussed, three working Committees were created among which the Membership Committee which was instrumental in inviting new members along the years to come before the IPEC Europe Board was formally established.
The year 1992 was for a large part devoted to resolve organisational and administrative problems under the Membership Committee responsibility. The Association By Laws became available in april under the french Law, IPEC Europe was officially registered with an address in Strasbourg, JP Vervoort from Seppic accepted to become Treasurer, the Harmonization and the Safety Committees started to work under the respective chairmanship of D Jackel and LC Clauss. In september 1992 your Association was including 17 members.

The first formal General Assembly of the Association took place at the Hilton/Paris in March 1993 at the end of a first technical symposium organised by IPEC. This was quite an achievement as we did everything by ourselves, but we were pleased to welcome more than 80 participants from different countries including the USA. Until the last moment we were unable to evaluate if we would cover the cost (what a lunch!) of this international meeting. IPEC has latter on sponsored a couple of symposia but we systematically called for a professional support in the preparation of Fairs and technical Events. The first IPEC Board under the chairmanship of John Hogan was composed of Henk De Jong (Servier), Dankward Jaekel (Ciba Geigy), Jean-Pierre Vervoort (Seppic), Robin Roman (Smith Kline Beecham) and Alan Henderson (Dow Chemical) and the writer representing Aqualon.

During the years 1993 and 1994 the Board had to deal with many challenges, while the Membership Committee was dissolved after its mission had been achieved, the Harmonisation Committee was progressing well but the Safety Committee met difficulties. At the same time the IPEC America partners were progressing faster which resulted in some pressure on the European colleagues. It was essential to broaden the International recognition of the Association towards the Official regulatory bodies, to organise advertising campaigns to broaden the membership, to take care of the relationships with IPEC America and the Japan PEC (IPEC). A second technical symposium was organised on the sunny belt of Europe at Nice in november 1994 this time with the support of Advanstar. All in all 1994 can be seen as the year of a consolidation of the Association’s mission and activities. With a very active GMP Committee under the leadership of Patricia Rafidison (Dow Corning), several essential meetings took place between the Board and the EDQM, the EUFEPS, the CEFIC, the other “PECs” in the US.

40 members from nine different countries had joined IPEC Europe at the time of the January 1995 General Assembly.

The next two years allowed to strengthen the relationship with the two other “PECs” in the US and Japan with several meetings (Washington, Yokohama, San Diego), at the same time new technical seminars were given at the EUFEPS Congress at Edinburgh and the Prague Symposium sponsored by the EDQM respectively in september and december 1996. The By Laws were twice modified to better reflect some administrative constraints. New Board Directors were elected replacing several “historical Directors” who had terminated their term. Because the workload of the Board Secretary was becoming unmanageable it was also decided to hire a professional support and Evert Izeboud joined the Association as Coordinator. During this period the GMP and the Safety Guidelines were published and widely promoted and distributed.

IPEC Europe has been honoured with the presence and contribution of the EDQM Director and Secretary Dr A Artiges and Dr Schorn at different General Assemblies particularly during the period 1997-1999. This was received as a very positive sign of the quality work which had been accomplished during the first years of the Association lifetime. Along this same period IPEC Europe has broadened the scope of its technical activities (Excipient Masterfile, Auditing Guidelines, Organic Volatiles Impurities and Good Distribution Practices Committees). IPEC managed to stay highly visible in the pharmaceutical industry with many contributions participating at different international events in both Europe and America. Relations with the Official Regulatory Bodies remained high on the agenda (with the Pharmacopœial Discussion Group, the USP, ICH and obviously the EDQM). It would be quite boring to report in more details the different actions IPEC has sponsored or triggered during this period, but let’s not forget advises to the launch of a “South Asia Pharmaceutical Excipient Council” in India and seminars to the Drug Information Association Annual Meetings (Boston and Denver) and the IPTS Symposium (Ankara).
When I left the Board at the end of a long 9 years term in January 2000 IPEC Europe was managed by a Board under the leadership of Carl Mroz and almost entirely renewed as compared to the first “generation” of Directors: I was the “last of the Mohicans” and it was time for me to give up. However we also should not forget Michel Malandain as he and his company Seppic took care during all these years of the finances of our Association which stayed and still are in an healthy position. We all can be proud of what we have accomplished during this early time and since then for the Excipients used in the Pharmaceutical Industry. We all now benefit from a true International Organisation with a high level of recognition and have been capable of not only giving life to a very useful “technical body” but we have been able to make it what it is today: an Association where it is pleasant and rewarding to work with highly professional colleagues.

Calendar of events 2004

Jan 29
IPEC Europe Seminar, Cannes, France
Majestic Barriere

Jan 30
IPEC Europe Annual Meeting, Cannes
Majestic Barriere

Feb 18
Tri-PEC meeting
Madrid Spain

Feb 19
Tri-PEC/PDG Meeting
Madrid, Spain

Next IPEC Europe Newsletter

The next Newsletter is scheduled to be issued in the month of April 2004.

Call for text to be published

IPEC Europe members who would like to contribute to the Newsletter are invited to submit text electronically (maximum 1 A4) to Mr Izeboud.

IPEC Europe on the Internet
http://www.ipec.org/europe.htm