New Year Editorial

Henk de Jong, IPEC Europe Chair

Dear IPEC Europe members and other readers of this Newsletter:

On behalf of the IPEC Europe Board I would like to wish you all a Happy and Healthy New Year. I hope you had a nice (short) holiday break with family and friends after the turmoil of last year.

In October we celebrated the 10th Anniversary of IPEC Europe around a seminar organised together with APV. With about 80 participants and a selection of very good speakers this event was a nice renewal of our collaboration with APV.

A special thanks goes to our colleague and member Frank Milek, the main IPEC Activator, party organiser and co-chair of the seminar, who made things happen. At this anniversary we received congratulations from the “founding father” of IPEC (Americas), Mr Lou Blecher, and from a permanent supporter and scientist in Japan, Mr Mitsuru Uchiyama, former president of the Society for the Japanese Pharmacopoeia. Mr Blecher underlined the announcement by “Pharmaceutical Technology” listing the main events of the 20th Century regarding health related topics, where 1991 is marked with the creation of IPEC.

To find ourselves listed together with events such as the discovery of antibiotics, the vaccine against polio etc. makes a nice picture. Both congragulators, in their very personal way, are fortunately still happy with the IPEC idea: having producers and users of pharmaceutical excipients together in one organisation to make progress with these essential ingredients of pharmaceutical products. They also wished us another fruitful 10 years of activity (at least).

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Just after this meeting another one was waiting: the Tri-PEC meeting including our get-together with the Pharmaceutical Discussion Group (PDG) in Strasbourg at the premises of the EDQM. Some in depth discussions took place around our position paper on the purpose and scope of a pharmaceutical monograph on excipients, and a polished version of this document will be prepared for spring 2002. Tri-PEC could also report on the feasibility to perform a round robin test, in a 6 month time frame, when the problem is well defined, sample availability and not too many questions about the test protocol do arise. The PDG planned and did sign-off a number of “almost harmonised” monographs. Some sticking points will be in the feedback to IPEC.

The same week a WHO expert meeting on quality of starting materials for medicinal products took place in Geneva. From IPEC Europe, Patricia Rafidison, Board Member and Chair of the GMP Committee took part in the discussions.

Last but not least the end of last year was marked for IPEC with the publication of our updated GMP Guidelines, fruit of a strong interaction between the American and European branches of IPEC, and now available through our co-ordinator.

By the time you read this, all our professional operations have been reactivated and IPEC is heading towards its Annual January tradition: the seminar on hot topics and our General Members Assembly.

Later on this year there will be two major scientific events organised with significant input from IPEC Europe.

-First the International Symposium organised by the EDQM on 4 and 5 April in Brussels, on “Excipients, Classical quality requirements and Functionality testing”. The setting of specifications for the major classes of excipients will be presented and discussed, next to the interesting but not so easy to handle functionality related characteristics.

-Second, the EUFEPS (European Federation for Pharmaceutical Sciences) congress, October 22-24th in Stockholm on the theme: New Safe Medicines Faster including an IPEC track (three half day sessions) on New Excipients, Safety aspects, and Regulatory issues, respectively. The congress theme has been a major initiative developed over the last two years from within EUFEP’s Committee on Industrial Relations in collaboration with EFPIA and with support from the European Commission.

In Stockholm the drug discovery/development process will be highlighted while focussing on rationalisation/optimisation, integrated approaches to problem solving and much more. Interaction possibilities with the 6th framework program for research in the European Union will also be discussed during special afternoon sessions.

IPEC, in joining with the general theme of the congress has found an extraordinary speaker panel to present a very interesting program. Look for detailed information that will be posted soon on our web-site. By the way you must have noticed that an important revamping of the site has been undertaken. We as the Board hope to provide you with a user-friendly tool organising the information we feel useful for our members. Contributions to this and other activities are always welcomed.

Looking forward to seeing you all at our January Meetings and have a good 2002!
Evert Izeboud

I would like to add my best wishes to the whole membership for the New Year to those of the Chairman of IPEC Europe. At the beginning of a new IPEC Europe year it is worthwhile to reflect on what happened with the IPEC Europe member companies in the past year.

New Full Members

In 2001 the IPEC Europe Board welcomed five new member companies:

1. Galderma (user)
   Mrs Veronique Zanzi
2. Solvay (user/manufacturer)
   Dr Wolfgang Dilla
3. Aventis (user)
   Mr Alan Whiston
4. Cabot (manufacturer)
   Mr Laurent Kosbach
5. Stiefel Laboratories (user)
   Mr Colin Sanders

The IPEC Europe membership now stands at 67 full members, contributing to IPEC Europe’s objective of being THE association for excipient suppliers and users. The updated list with communication co-ordinates of the IPEC Europe membership is available on the Internet site.

Associated members

The University of Bourgogne represented by Mrs Professor Yvette Pourcelot joined IPEC Europe as an Associated member. Together with The Universities of Groningen (NL) and Lille (F), IPEC Europe can rely on professional scientific expertise, when needed.

Co-opted members

In 2001 Mr Dankward Jaekel (EDQM) was appointed as an Honorary Co-opted member to IPEC Europe. Mr Henk de Jong acknowledged Mr Jaekel during the Annual General Meeting of 2001 for his impressive work as Chair of IPEC Europe’s Harmonisation Committee.

From an administrative point of view two important events came into effect in 2001. First of all, the amended articles of IPEC Europe, allowing distributors of pharmaceutical excipients to become an IPEC Europe member were officially accepted by the Tribunal d’Instance in Strasbourg, where the legal seat of IPEC Europe is based.

Secondly, Michel Malandain, IPEC Europe’s Treasurer, has provided the French fiscal authorities with convincing evidence that IPEC Europe is a not for profit association and therefore exempt from the French tax legislation.

Internet site revamped!

Under the supervision of Mr Johnny Pallot of Roquette, in 2001 the ground work was done to make IPEC Europe’s Internet site more user friendly. The current structure of the site consists of three levels:

1st level: Public domain
2nd level: Information on IPEC Europe
3rd level: Committee work

During the Annual General Meeting a presentation will be given on the contents of the various pages. Also the access parameters of the restricted part of the site will be redefined. For 2002 the objective is to construct a Library with a search engine in order to provide the membership with a useful data base with documentation of interest for pharmaceutical excipients.
Good pharmaceutical trade and distribution practices (part 2)

The article below has been published in the WHO Drug Information in July 2001. IPEC Europe acknowledges the WHO for permission to publish the text in IPEC Europe’s Newsletter. Part 1 has been published in the July 2001 Newsletter (available on IPEC Europe’s Internet site)

H. Leblanc, The European Chemical Industry Council (CEFIC)

F. Milek, International Pharmaceutical Excipients Council (IPEC)

Supply chain characteristics of excipients

During the past decade, the excipient market has changed from a regional to a global market. Companies have become international, manufacturing products from only a small number of sites for the whole global market. New competitors have appeared, especially in Eastern Europe and Asia. This situation has led to a movement of excipients throughout the world. In this environment, distributors become more involved in the supply chain.

The incident in Haiti of contaminated paracetamol illustrates the extent and dramatic consequences of improper handling of excipients by supply chain brokers. Several distributors were involved in this incident, the product was shipped all around the world from Asia via Europe to Haiti, with no traceability, insufficient controls and documentation lacking. Other similar incidents have also been reported (10).

In many countries, distributors are in charge of the excipients business because pharmaceutical companies have low consumption of these products compared to the large quantities used in food production, or for cosmetic and technical applications. Of course, some exceptions exist concerning particular excipients used exclusively for pharmaceutical applications. However, most distributors dealing with excipients are involved in trading to businesses with technical applications and often supply similar products for different uses. In these other business lines, processes involving mixing or minor cross contamination, are not viewed with the same precision as they are in pharmaceutical production. Traceability and documentation are not strictly required, nor do customers wish to pay for this service when using such materials for technical, food or cosmetic applications.

Given this situation, managing the distribution of pharmaceuticals requires sensitivity of the issues and knowledge of how to deal with the different requirements for the many similar products and their different applications. Incidents with contaminated excipients in the past showed that there is a lack of good practice in this area but no detailed regulation yet exists that provides standards for industry and regulatory authorities.

Current legislation and guidelines on good distribution practices (GDP)

The latest harmonised ICH Guideline: Good Manufacturing Practice for Active Pharmaceutical Ingredients (Q7a), approved in November 2000 includes a chapter entitled Agents, brokers, traders, distributors, re-packers, and re-labelers.

Within that chapter, special requirements for distributors are defined regarding traceability, stability, repackaging, transfer of information, complaints and recalls (5).

The French Medicines Agency (AFSSAPS) is currently preparing an exhaustive guide for good distribution practices covering both active pharmaceutical ingredients and excipients. This is still a draft working document, but it is likely to be published and implemented before the end of 2001.

The International Pharmaceutical Excipients Council (IPEC) has also issued an audit-style questionnaire specifically designed for assessing distributors of excipients and is

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based on IPEC GMP Guidelines for Bulk Pharmaceutical Excipients (11). This document is intended to be used by pharmaceutical companies for auditing their supply distributors as part of their supplier evaluation system, as well as certifying distributors against IPEC standards. It should be used as a tool to assess the actual GMP/GDP level of distributors, to raise awareness and improve knowledge of supply chain actors, and thereby improve GMP compliance.

The European Association of Chemical Distributors (FECC) and other traders organisations have also published a discussion paper entitled GMP for Active Pharmaceutical Ingredients in Distributive Trade (12). However, there is so far no final agreement amongst traders and brokers on these requirements and on the implementation of the principles set out in the document. Furthermore, there have been substantial comments made by some trader's organisations on the GDP requirements of ICH Draft Q7a, claiming that these requirements will lead to substantial price increases in Europe.

The European Chemical Industry Council (CEFIC) has published Guidelines for Handling and Distribution of Propylene glycol USP/EP (13) as part of their Responsible Care Program. The Guidelines were created by European manufacturers of propylene glycol USP/EP and contain relevant instructions and procedures to ensure safety and quality of propylene glycol from the manufacturing site down to the end user, bearing in mind special applications in pharmaceuticals, and consumer health protection measures. Similar ideas and strategies are included in the European Single Assessment Document for Chemical Distributors (ESAD), a document published by CEFIC and FECC in 1999 (14). In this document, specific guidance is given for the distribution of excipients, food and cosmetic ingredients. It can be used either by manufacturers to assess their distribution partners, or by customers to find out what level of GMP/GDP distributors of excipients have achieved.

Do these regulations suffice to safeguard public health?

Maintaining quality standards and product safety has a price, but negating the need for requirements with purely commercial arguments is unacceptable when the implicit risks to human health are considered. The need for global recommendations and control is crucial: if the expense of applying quality and safety practices risks forcing the compliant companies out of business because they charge higher prices than their unscrupulous rivals, then this is obviously a horrifying prospect! It is possible that the current GMP practices dealing with active pharmaceutical ingredients (API), excipient trading and distribution are not sufficient to guarantee product quality and safety.

Several guidance documents require full traceability back to the original producers. However, a re-packer or re-labeller is also often considered to be a manufacturer, so that traceability to the last manufacturing step is clearly insufficient. Other guidelines require a reference to the original producer on the certificate of analysis. The traceability requirement clearly needs to be bi-directional and is best reflected in section 17.60 of ICH Q7a which states: "Agents, brokers, distributors, re-packers, or re-labellers should transfer all quality or regulatory information received from an active pharmaceutical ingredient (API) or intermediate manufacturer to the customer, and from the customer to the API or intermediate manufacturer."

The API industry endorses these requirements. However, as long as there are no stringent verification and enforcement regulations in place, it is likely that fraudulent practices will continue to prosper. Europe intends to amend its Starting Materials Directive (75/319 EC) which will create a legal basis for the implementation of these GMP / GDP requirements. This will also create a legal basis for inspections covering manufacturers that are exporting products into the European Union, or intend to do so. However, in the current draft text of the Amendment, the decision to inspect is being left to the discretion of each Member State.

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Considering current budget restrictions in several countries, industry fears that substandard products, or products made by different processes to those declared in regulatory filings, will continue to enter into the European Union. This particularly concerns generics and over-the-counter (OTC) products, for which controls are minimal. OTC products are generally not even inspected, so similar concerns apply to imports of these products.

Recently, market prices of pharmaceutical ingredients for generics and OTC products have been forced to below economic levels. The inroad onto the market of products manufactured under inadequate or even in the absence of systems that should secure their quality and safety seems to be one important causative factor for this development. Omitting the use of such systems allows for lower manufacturing costs and therefore offers an important competitive edge. The implicit risks to humans are evident: such products are often sold to very large populations. For example, it is estimated that annually about 70,000 tons of paracetamol (acetaminophen) are consumed world-wide, representing a total of 150 billion tablets. A substandard product could have a more lethal impact than an atom bomb in such cases!

Similar requirements will certainly also be needed with regard to trade in pharmaceutical ingredients world-wide. The first steps that have been taken in this direction by WHO will hopefully lead to increased safety of medicines on a global scale.

In conclusion, the API manufacturing industry looks forward to presentation of a final text for Amendment of 75/319/EC for approval by the European Council and European Parliament. After all, it is the safety of patients which is at stake.

References


Good Distribution Practices Committee

A meeting of the GDP committee was held as a first kick off meeting to define the work plan and strategy of the committee for the next year. The GMP committees of IPEC Americas and IPEC Europe decided not to have a single chapter in the revised IPEC GMP Guide on distributors, traders and brokers of excipients like in ICH Q7a for APIs but to have a separate document with guidance and audit questions. Therefore the GDP committee received the task to revise the existing GDP Audit Guide leading to a document with complete GDP Guide and an audit questionnaire which can be used as one single tool to assess the supply chain of excipients.

Dr Frank Milek, Chairman
Program “Hot Topic” Seminar

January 31st 2002

10.00 Introduction
Mr Carl Mroz
(Colorcon, Vice-Chair of IPEC Europe)

General Monograph on Excipients
Mrs Anne-Sophie Bouin, EDQM

Functionality Related Testing
Prof Dominique Chulia, Univ. of Limoges

11.30-12.00 Coffee Break

Water for pharmaceutical use
Mr Paul Hargraeves (MCA)

Aflatoxins sources in excipients
Mr Thierry Ferron (Roquette)

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LUNCH 12.30-14.00
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14.00-15.30 BSE/TSE issues

Views from the gelatin industry
Mr Keith Hutchison (RP Scherer)

Views from the oleochemical industry
Mr Ad Hinze (APAG)

Views from the lactose industry
Mr Armand Janssen (DMV International)

15.30 Question time

16.00 Closure of the Seminar

Aperitif

An aperitif (19.00-20.00 PM) will be offered by the IPEC Europe Board in order to allow the participants to interact in a non-formal atmosphere.

IPEC Europe Dinner

Following the aperitif the participants are invited for dinner, starting at 20.00 PM

IPEC Europe Seminar/AGM 2002

Evert Izeboud

For a sparkling start in the 2nd decade of IPEC Europe’s existence, the IPEC Europe Board has decided to organise a “hot topic” Seminar on the day preceding the Annual General Meeting. Like in 2001 the venue is the Hotel “Le Plaza” in the centre of Brussels. The program (left) will pay attention to subjects relating to compendial monographs for pharmaceutical excipients and to the BSE/TSE issue.

Seminar room, Le Plaza, Brussels

The participation to the Seminar is restricted to the IPEC membership, and is free of registration costs. IPEC Europe members (not only the official representatives) who still have an interest in participating are welcome and are invited to inform Mr Evert Izeboud, mailto:eizeboud@worldonline.nl, and your participation will be arranged. The day after the Seminar, on February 1st 2002, is the traditional Annual General Meeting. Besides looking back to the past year, a lot of attention will be paid to informing the membership of what can be expected in the coming year. The Board and Committees will present their work programs for 2002. Looking forward meeting you all!
Calendar of Events

January - April 2002

January 30th
Board Meeting
Hotel Le Plaza, Brussels

January 31st
IPEC Europe Seminar
Hotel Le Plaza, Brussels

February 1st
Annual General Meeting IPEC Europe
Hotel Le Plaza, Brussels

February 21st
IPEC Europe TSE Committee
Hilton, Airport Amsterdam

February 26th
Harmonization Committee
Sheraton, Brussels Airport

April 4th and 5th
EDQM Symposium
Classical Quality Specifications for Excipients and Functionality-Related Test
Brussels

Next IPEC Europe Newsletter

The next Newsletter is scheduled to be issued in the month of April 2002.

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

Deadline: April 1st 2002.

Revised IPEC Good Manufacturing Practices Guidelines available!!

On the 5th of December 2001 the newly revised IPEC Good Manufacturing Practices Guidelines were published.

This revision updates the original 1995 guide and includes the new ISO quality management system requirements. The ISO 9001:2000 numbering system is utilised throughout the document with requirements specific to excipient manufacturing included under each ISO heading.

The revised guide is the result of significant collaboration between IPEC-Americas and IPEC Europe. As a harmonised guide, excipient manufacturers and their customers can be assured that the provisions of the guide reflect internationally accepted good manufacturing practices.

As in 1995, the newly revised guide will be offered and promoted to the global pharmaceutical industry. It also will be offered to international regulatory authorities and the major compendia for endorsement and acceptance as an industry standard.

Copies of the IPEC GMP guide can be ordered by downloading an order form from the public domain of IPEC Europe’s Internet site at http://www.ipec.org/europe.htm (IPEC Europe publications) or by contacting:

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