International Pharmaceutical Excipients Council Europe
July 2003 IPEC Europe News

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Editorial

A hot summer for excipients

It is a really hot summer night in the Netherlands. Everything is packed for the yearly trip to the south of France for two weeks well deserved holiday. Just one little thing left before the journey can start, writing the editorial for the July 2003 issue of the IPEC Newsletter.

Some months ago the IPEC Board agreed that we would start dividing “tasks” more evenly. One of the consequences was that IPEC (Board) members would need to start contributing more to the IPEC Newsletter Henk de Jong took care of most of the editorials and probably most of the other copy in most of the issues as well!. When talent and experience are combined in one hand, others too easily rely on it and without realizing it, we may have become too depended on the Chairman’s contribution.

After several attempts earlier this evening, I now know that it will be too difficult for me to provide you with a summary of last months highlights. So you will have to miss the short overview of the progress made by the various committees, working groups, Tri-PEC, PDG and the highlights of other meetings, as Henk was able to give you, many times because of his presence at those meetings.

I would like to discuss a development that increasingly puts pressure on the profitability of our excipient business and how, sometimes indirectly, IPEC plays a role in this. The ongoing commoditization of the standard types of excipients, is being driven by suppliers that look for opportunities to reduce their costs and with increasing competition from the so-called “low labour cost” countries, has already been putting pressure on profitability for many years. Another development however, over the last

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couple of years negatively effecting profitability for excipient producers is the increasing regulatory burden enforced by governmental bodies and indirectly the pharmaceutical industry.

Each company may look for its own way to deal with these developments. Alternatives may be to look for lowering their overall cost base while others decide to invest in quality, service or innovation or look for acquisition candidates to increase critical mass. Which strategy to follow is each company's own responsibility. However there is a mutual interest to work closely together in some of the ongoing discussions and initiatives in this field. Indeed, many such initiatives are ongoing. The EU for instance is working on a community code involving a revision of the legal framework for Pharmaceutical Products including excipients. Or think of the quality regulations now being made by French government in relation to the development of excipients. And of course, many others will be forced upon us in the coming years!

It is good to realize that we do not have to deal with these developments each for itself and that IPEC is a body that represents the interests of both producers and users of excipients. Discussions on what should be obligatory or what should be kept voluntary, or even more important, on what is appropriate for excipients , can be held in the safe environment of the IPEC working committees. Subsequently the outcome of these discussions is translated into position papers so that regulatory bodies need to take notice of it.

A good example of such a "combined approach" is the ongoing discussion on impurities in excipients in one of IPEC's working committees. Much effort is made to make officials see that impurities in excipients should not be seen with the same eyes as those in active pharmaceutical ingredients. Sometimes they are an intrinsic part of an excipient and the excipient could not be produced economically without them and in some cases they even add to the specific functionality of that excipient. As in all businesses, producers of excipients need to decide on the best strategy to achieve their objectives, and they also need to realize that some battles are better fought together within IPEC than alone. This is probably the only guarantee to avoid that we all are faced with unrealistic regulatory demands. I invite you to read on the progress made in this field by some of the working groups.

Herman Ermens

IPEC Europe

During the Board Meetings in April and June 2003 the Board discussed the various responsibilities of the Board members.

IPEC Europe Board

Name	Period	Responsibility
Mrs Patricia Rafidison	2003-2006	GMP/Communication
Mr Carl Mroz	2001-2004	Symposia
Mr Adrian Bone	2003-2006	Regulatory Affairs
Mr Henk de Jong	2003-2006	Chair (till 2004)
Mr Herman Ermens	2002-2005	Secretary Communication
Mr Johnny Pallot	2002-2005	Internet /Membership affairs
Mr Michel Malandain		Treasurer

Board Election 2004, call for candidates

During the Annual General Meeting in 2004 Mr Carl Mroz will end his term as member of the IPEC Europe Board. Mr Mroz will not

stand for re-election and therefore the Board invites the IPEC Europe membership (user category) to put forward candidates for fulfilling the vacancy for the period 2004 to 2007. Detailed information about the vacancy can be obtained by contacting Mr Henk de Jong.

IPEC Europe GMP Guidance

Draft IPEC Guidance document on defining and monitoring impurities

IPEC Europe's Working Group on impurities for pharmaceutical excipients has elaborated a draft guidance document on impurities in pharmaceutical excipients. Below is a summary of the contents.

The guide provides an approach for establishing an impurity profile for existing pharmaceutical excipients. An impurity profile may be mainly used for regulatory purposes, quality consistency, manufacturing process monitoring, change control, product specification setting and as a base for safety evaluation by the excipient suppliers.

The guide should be of international application, bearing in mind that pharmaceutical excipients are diverse and often have uses other than pharmaceutical applications. An excipient is often used with a broad range of active pharmaceutical ingredients and in a diverse range of finished dosage forms. As an international guidance document, it does not specify legal requirements nor cover particular characteristics of every excipient. In addition, current guidelines like ICH Impurities for New Drug Substances do not apply to existing excipients and novel excipients which are by nature and definition pharmacologically inactive ingredients and should not be subjected to the same standards. When implementing this guide, each manufacturer must consider how it may apply to his products and processes. The diversity of excipients means that some principles of the guide may not be applicable to certain products and processes. The terminology "should" and "it is recommended" does not mean "must" and common sense must be used in the application of this guide.

The guide is divided into several sections. The first part provides background discussion necessary for considering the nature and origin of impurities and contaminants found in the pharmaceutical excipient. A section that contains guidance on establishing an impurity profile follows this. The final section contains definitions and references to other documents and websites useful in developing an impurity profile.

The next step will be reaching consensus about the contents with our American colleagues in order to obtain an IPEC guidance document.

New IPEC Europe members

During the Board meeting on April 11th 2003 the application of the French company SPI Pharma was endorsed. Below is the company profile of SPI Pharma (source: Internet site of SPI Pharma).

SPI Pharma™
Formulating Success Through Innovation

SPI Pharma is an important supplier of custom formulation solutions for pharmaceutical and nutriceutical manufacturers. By offering raw materials, processing capabilities, and advanced application technologies SPI has become a valued source for complete custom delivery systems.

SPI Pharma is an Associated British Foods company.Their product scope includes excipients, antacid actives, and formulated systems. All products are produced under appropriate manufacturing guidelines suitable for pharmaceutical and neutriceutical applications.

Their core processing capabilities include precipitation, hydrogenation, crystallization, spray drying, granulation, micronization,

suspensions, and encapsulation. Some of advanced applications include solid dosage formulation, viscous suspensions/blends, DC chewing gum, effervescent systems, chewable/quick-dissolve tablets and customized granulations.

Handbook of Pharmaceutical Excipients- 4th Edition 2003

In March 2003 the 4th Edition of the Handbook of Pharmaceutical Excipients was published. The new edition is a useful guide to the uses, properties and safety of pharmaceutical excipients. The 4th edition is available both in hard copy as well as on a CD-ROM.

The Handbook gives information on about 250 excipients of which 40 are new entries.

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PO 151, Wallingford
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Fax: +44(0) 1491 829 292
Internet: www.pharmpress.com

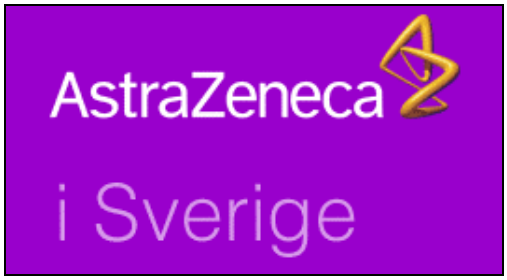
IPEC Europe membership profiles

Under the heading Membership Profiles an attempt will be made to inform the IPEC Europe membership about the major activities (Excipients) of the members. In this issue AstraZeneca, an important user of pharmaceutical excipients is put in the spotlight.

AstraZeneca is a major international research based pharmaceutical company engaged in the development, manufacture and marketing of ethical (prescription) pharmaceutical products. Our long heritage of innovation and documented ability to develop new concepts in medicine has makes this organization one of the top five pharmaceutical companies in the world.

AstraZeneca PLC has its headquarters in London with its U.S. base located in Wilmington, Delaware. Wilmington is also the global home for the company's Central Nervous System (CNS) commercial and research and development efforts.

AstraZeneca operates nine different R&D sites and has sales activities in over 100 countries and manufacturing facilities in 19 countries. With 100 years of combined experience, scientists at AstraZeneca have discovered and developed several of today's leading prescription medicines—pharmaceuticals that contribute to a higher quality of life for millions of patients and to a better health economy worldwide.



Based in Sweden, AstraZeneca's R&D organization is international in scope and comprised of approximately 10,000 researchers. Through its own resources and through collaboration with dozens of universities and strategic alliances with numerous research and biotechnology companies, AstraZeneca has broad access to advanced technologies in biomedical research, including genomics, bio informatics, chemical libraries, high throughput screening and product delivery systems.

Representative to IPEC Europe

Dr Magnus Erickson, member of IPEC Europe's Harmonisation Committee, is the official contact for AstraZeneca to IPEC Europe.

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Enlargement of the European Union

Acknowledgement

IPEC Europe would like to acknowledge Pharmaceutical Marketing for granting permission to cite from an article of Mrs Zelda Pickup, published in April 2003. Information about Pharmaceutical Marketing can be found on the Internet site: http://www.pmlive.com.

Nine countries have completed their accession negotiations in time to accede to the EU during 2004. They are the Central and Eastern European countries of Hungary, Poland and the Czech and Slovak Republics, the Baltic States of Estonia, Latvia and Lithuania, plus Cyprus and Malta. Clearly, the enlargement of the EU marketplace from 15 countries to 26 will have a significant impact and provide an entirely new marketing environment for all sectors, including the pharmaceutical industry.

As with many other changes, whether the expansion of the Union is regarded as a threat or an opportunity depends on a company's strategies, positioning in the market and product portfolio. The areas likely to be most affected by the impact of accession are cross-border trade, raising questions of whether parallel imports may increase as a result of the expansion, and concerns over the increased availability of generic products in the marketplace. In addition, regulatory matters, specifically compliance with EU regulatory regimes, will be affected.

Unified market

The basic, free trade principles of EU law generally already apply between accession countries and the European Union.

This has come about through various Free Trade and Association agreements that set out the legal framework by which countries can meet the economic and political conditions for EU accession. These agreements incorporate the principles of free movement of goods and obligations to uphold competition law.

For pharmaceutical products, however, the position is more complex and bears greater scrutiny here. Essentially, there are regulatory controls within the EU which constitute legitimate obstacles to the free movement of medicinal products from non-EU countries into the EU. Parallel trade of drugs between EU member states is only possible due to equivalent regulatory regimes in each country. Clearly, countries wishing to accede to the EU need to match this regulatory situation.

As part of the accession process, potential member states have made a commitment to reach European Union standards and comply with regulatory requirements by the date of accession (May 1 2004) or by the end of any agreed transitional period. After this date, regulatory approvals in accession countries based on dossiers which do not comply with EU regulations will lapse.

Where medicinal products are imported from a third (non-EU) country, these controls may be relaxed if appropriate arrangements have been made with the exporting country to ensure that the manufacturer has applied standards of good manufacturing practice at least equivalent to those in the EU.

With labelling and packaging requirements, all labelling and leaflets must be in the language of the member state where the products are to be placed on the market.

Regulatory compliance

The most complex area that will be impacted by accession is the adoption of EU regulatory standards. In order to be ready for accession and able to adopt EU regulatory standards, the eleven accession countries - together with the EMEA regulatory body and the European Commission - have entered into a Collaboration Agreement with Drug Regulatory Authorities in EU- associated Countries (CADREAC).

This agreement sets out a simplified procedure for the granting by the accession countries of marketing authorisations for medicinal products, which have already been authorised using the centralised procedure within the EU.

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The agreement aims to assist countries to implement Community standards, procedures and good practices, and to strengthen collaboration with EU bodies and authorities.

CADREAC has also commenced harmonisation work on a simplified authorisation procedure for products that have been approved under the EU mutual recognition procedure.

It will only be possible for authorisations granted in the accession countries to be mutually recognised by existing member states once national procedures are harmonised to EU standards. As part of the accession process, if existing regulatory dossiers are not in line with EU standards it has been agreed that authorisation for the product should be withdrawn on the day of accession (or the end of the agreed transitional period).

Consequently, both regulatory authorities in accession countries and pharma companies are working extremely hard to update the regulatory dossiers of existing products, to ensure they comply. Five accession countries (Cyprus, Lithuania, Malta, Poland and Slovenia) have asked for more time to complete this process (a transitional period).

The threat of withdrawal of approval raises some significant questions for those pharmaceutical companies operating in accession countries. These include:

• How much extra work and extra data will be required in order to obtain a new authorisation complying with the EU standards?

• How many products will be withdrawn from the marketplace rather than incur the cost or dealing with the issue of upgrading the regulatory dossiers?

It is inescapable that the requirements to update and standardise all regulatory dossier is likely to place companies that already possess EU authorisations (and, therefore, compliant regulatory dossiers) in a much stronger position in accession countries than locally-based manufacturers or generic suppliers.

Exhaustion setting in

While there are clearly some major obstacles to parallel trading for accession countries, once a dossier and resulting marketing authorisation is EU compliant parallel importing ought to be possible.

However, nothing relating to parallel imports is simple and there is an important distinction between EU and non-EU countries over the ability to use intellectual property rights to prevent parallel trade.

Under the doctrine of `exhaustion of rights', intellectual property rights are said to be exhausted if the product has been placed on the market in the European Economic Area (EEA) by the rights holder or a licensee. Exhausted rights, therefore, cannot be used to prevent parallel imports of products between EU member states.

However, these rights are not exhausted, and can be enforced, relating to products which have been placed on the market outside the EU and are being imported into the EU. As a result of these legal distinctions, accession would inevitably affect the legal position on the use of patents or trademarks to prevent importation from an accession country into an EU country.

This issue, however, was identified at an early stage and a mechanism has been negotiated which protects the intellectual property rights of patent or supplementary protection certificate (SPC) holders, which were in place in the EU at the time when it was not possible to gain such protection in the accession state.

Clearly, this mechanism could have significant impact on the pharmaceutical industry and parallel trade.

It should be noted, however, that the mechanism will be of no assistance to companies with products which were launched after patent protection was available in the accession countries.

Typically, such patent protection for pharmaceutical products came in to force between 1991 and 1994 in most of the accession countries. If the full five-year protection of the SPC is available, some products might enjoy up to 15 years' protection.

The key dates for this mechanism are:

• The filing date of the patent/SPC in an existing member state: and

• The date when patent protection became available in (presumably) the relevant accession country.
Nevertheless, a considerable number of products should enjoy a degree of protection by reliance on these patent and SPC rights.

EU regulatory requirements

• The accession countries, the EMEA and the EC have entered into the CADREAC agreement

• CADREAC sets out a simplified procedure for the granting of marketing authorisations for medicinal products

• Authorisations granted in the accession countries can only be recognised by existing Member States once national procedures are harmonised to EU standards

• If regulatory dossiers are not in line with EU standards, authorisation for the product should be withdrawn on the day of accession

• Products which gained IP rights in the EU before such protection was available in accession countries will be able to use this patent protection. If the five-year SPC protection is available, some products might enjoy up to 15 years' protection.

DEMAND Summit, Asia Pacific

As most pharmaceutical and biotechnology research and development takes place in Europe and the US, the task carried out by the industry in Asia, is to manufacture drugs and medical tools, and distribute them to the end user. Given the fact that the pharmaceutical industry is highly competitive, since most products may now be generically manufactured, it has become a necessity that manufacturers and distributors ensure that their products are made to the highest standards and distributed to the end user in a timely fashion.

In order to contribute to this objective the Congress Organizer Marcus Evans will organize a two days summit event (November 9th -11th 2003) under the name DEMAND in Bangkok, Thailand. IPEC Europe will be represented by its Chairman Mr Henk de Jong, who will address Quality issues of Pharmaceutical Excipients.

Manufacturing and distributing Pharmaceuticals in Asia Pacific

For more information on the **Demand Summit 2003**

http://www.demandsummit.com/html/event.htm

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Mrs Jacqueline Chin

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Meetings and Seminars 2003

Sept 8-9
Swedish Academy co-sponsor IPEC Europe; 3rd International Symposium on Excipients for non-parenteral dosage forms. Stockholm, Sweden.
Jeanette.jansson@swepharm.se

Sept 12
Univ de Bourgogne Dijon , France, Substances à Usage Pharmaceutique, 9ème Journée Scientifique
More Information:
yvette.pourcelot@u-bourgogne.fr

Sept 24-25
Amsterdam, IRR Symposium on Impurities;
The detection, identification and control of impurities in medicines".
Cbecker@iirltd.co.uk

Sept 30 + Oct 1
IPEC Americas, Regulatory Affairs Conference, Alexandria, Virginia, United States. Information and registration:
www.ipecamericas.org

Sept 29 + Oct 1
APGI-EUFEPS/IPEC
"New Challenges in Drug Delivery", Paris France.
Information at :
secretariat@eufeps.org

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Next IPEC Europe Newsletter

The next Newsletter is scheduled to be issued in the month of October 2003.

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