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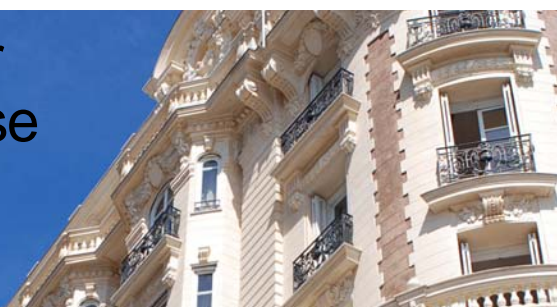
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## IPEC seminar charts a course for excipients in 2009



IPEC Europe's annual seminar in Cannes last month had a great turnout, with around 90 delegates eager to get up to date with the latest developments in excipients from the perspective of users, suppliers and regulators.

### WHO update

Kicking off the day, Sabine Kopp of the World Health Organization updated on WHO activities of relevance to starting materials, which it defines as both active pharmaceutical ingredients (APIs) and excipients.

With national and regional requirements for control of starting materials increasing in the face of continuing safety incidents - often due to lack of adherence to existing guidelines and principles - various groups are developing international standards.

For example, the International Pharmacopoeia is looking into publishing monographs harmonised by the Pharmacopoeial Discussion Group (PDG), and has been in discussion with IPEC to revise excipient monographs in Ph. Int. based on the PDG collaboration. When preparing monographs the objective is to focus not only on robustness of methods, but also on costs, to make them accessible for developing countries, she said.

The WHO is also updating its Good Distribution Practice standards for finished products, said Kopp, who congratulated IPEC on its adoption of the related Good Trade and Distribution Practices (GTDP) which cover starting materials.

The GDP standard is being revised as a result of the IMPACT anti-counterfeiting initiative and may

now be renamed *Good Distribution Practices for Pharmaceutical Products Including Measures Against Penetration of Counterfeits into the Legitimate Supply Chain*.

As IPEC Europe embarks on its own certification project (see Excipients Insight November 2008), Kopp gave an update on SMACS - the WHO Starting Materials Certification Scheme, which started development after the 1996 case in Haiti in which 85 children died after taking acetaminophen syrup contaminated with diethylene glycol.

This was a mammoth project and some nine years in development, and has been operating for a couple of years. New schemes can take a while to gain momentum, she noted, but take-up of SMACS has been very slow. This may be a result of resistance by some parties who were concerned about the level of detail demanded in the certification process.

### Heavy metals

Heavy metals testing comes under section 2.4.8 of the European Pharmacopoeia (Ph. Eur), which refers mainly to a wet chemical test for lead, and this has come in for criticism for a lack of sensitivity. There is also a lack of harmonisation in testing between the various international pharmacopoeia.

*Cont'd page 3*

# The word from the chair

Dear Members,

February 20, 2009

Welcome to the February edition of Excipients Insight, which comes to you at a time of great changes inside our organisation. Many of you will have attended our AGM and seminar last month, which was once again a great success thanks to the stimulating input of speakers and delegates and the hard work of all those involved in the organisation.

The AGM always heralds a time of change as new priorities are agreed for the year ahead, and new faces step forward to drive those efforts. This year was no exception, with a number of additions and subtractions on IPEC Europe's board and committees. You can read all about the conference and our new faces and workplan in this newsletter.

First off, please let me welcome our two new board members, Flavia Arce and Johann-Philipp Hebestreit, who are profiled on this page. Their enthusiasm for the role already apparent and I'm sure we will be hearing a lot from them as the year progresses.

As you may know Adrian Bone is stepping down from the Board. He has been a figure-

head for IPEC Europe in the last few years and instrumental in helping IPEC Europe build its action plan for the future. Happily he's agreed to continue to be our ambassador on key projects

Regretfully, work pressures mean that Kevin McGlue has had to stand down from the Board, having been a member since 2004 and an IPEC stalwart since 1995. His passion and energy for IPEC activities will be missed, but he will help with the integration of new Board members and will continue to participate in the certification project. We hope to have Kevin back in our core team in the near future.

And finally, Michel Malandain, another long-standing Board member, is leaving us to enjoy a well-earned retirement. His company has kindly contributed resources for some time to help in his role of IPEC treasurer, and we wish him all the best for the future!

On behalf of the IPEC Europe Board,

*Patricia Rafidison*

Chair to IPEC Europe



## Board Updates

### Meet the new board members...



Flavia Arce is a quality assurance manager at Eli Lilly responsible for supplier quality management, complaint handling, product stability, quality of printed packaging material development, GMP training qualification and GMP records retention at Lilly's manufacturing site in Madrid (Spain).

She joined Lilly in 1992 and has held roles within Product Development & Formulation and Process Validation. Flavia has a degree and Ph.D. in Pharmacy from the University of Pharmacy in Madrid, a post-doctoral certificate in industrial pharmacy and is the patent holder of two Pharmaceutical Formulation Patents.

Johann-Philipp Hebestreit is a global regulatory affairs manager CMC within the pharma section of BASF's Care Chemicals Division in Germany. Upon completion of a PhD in pharmacy at Humboldt-University in Berlin, he joined BASF in 2004.



Since then, Philipp has been responsible for standard, new and novel excipients produced by BASF. In the course of this work, he joined IPEC Europe to participate in the Regulatory Affairs Committee.

### ...and bid farewell to another



Sadly, due to professional reasons, Kevin McGlue has had to resign from his position on the IPEC Europe Board. His leadership and contributions will be greatly missed, and we thank him for all his efforts for IPEC over the last few years.

In light of this recent event, we have one vacancy which needs to be filled by a representative from the excipient user group.

### Call for nominations

Hence, we are calling for nominations from member user companies who are interested in joining the IPEC Europe Board. An election will determine the final nominee who will occupy the vacant seat.

Please send the name of your potential candidate no later than March 10, 2009, to: [info@ipec-europe.org](mailto:info@ipec-europe.org).

## IPEC Member's Corner



### AGM: member's minutes

At the AGM in January the Board and the committees gave presentations on activities and objectives reached in 2008 and those planned for 2009. Members endorsed the programmes, and all the presentations are available [here](#).

Election of Board members: Patricia Rafidison (Dow Corning) was re-elected, while Flavia Arce (Lilly) and Johann-Philipp Hebestreit (BASF) were elected to replace Adrian Bone (Lilly) and Michel Malandain (Seppic). The Board members are elected for a period of three years (renewable).

The 2009 budget was presented by the treasurer, Damien Kerloc'h (Roquette), and was approved by the official representatives. There was no change to the current fees.

Elena Miceli also gave a presentation on *Excipients Insight*, noting that six issues were issued in 2008, while 10-12 issues are expected this year. Among 2009 objectives are to provide more articles on science and technology and to harvest more news from IPEC members.



### Missed the AGM and seminar?



Don't worry - all the presentations are available exclusively to IPEC Europe members on our website [here](#).



### Welcome to our new members

The AGM also saw the official presentation of all nine new IPEC Europe members, namely: Abbott Laboratories (user); DSM Nutraceuticals (maker); IMCD Group (distributor); Mallinckrodt Baker (maker); National Starch (maker); Orion Corp (user); Rockwood Pigments (maker); SE Tylose (maker); and Tate & Lyle Sugars (maker).

A big thank you goes out to Evert Izeboud for his invaluable work in recruiting new members to the IPEC Europe cause!



### Frank Milek takes the helm at GDP Committee

Dr. Frank Milek has succeeded Allan Whiston as chair of the GDP Committee. He is an industrial pharmacist and has worked for 15 years in the pharmaceutical excipient industries, especially in the field of supply chain and distribution. He is Qualified Person at Hedinger GmbH & Co. KG, a specialized excipient distributor in Germany, for Quality and GMPs.



Frank is member of different committees of industrial trade associations like IPEC, BAH and APV. He is also currently chairman of the Good Trade and Distribution Practice Committee of the European Association of Chemical Distributors (FECC GTDP Committee).

## IPEC seminar charts a course for excipients in 2009 (cont'd)

The US Pharmacopeia (USP) made a proposal to the PDG in November 2008 to replace the lead test with an instrumental metal screening test. This has not met with favour with USP's counterparts in Europe and Japan, said Keitel.

While the Ph. Eur Commission recognises the need for a review, Keitel would rather see a general monograph approach similar to that implemented in the European Medicine Agency's recent Guideline on Residues of Catalysts and Reagents, which came into force last September. A Working Party will be appointed this year to look into the issue.

Keitel also noted some changes at the PDG, in recognition of the fact that progress is in general "disappointingly slow." Some steps have been taken to try to boost efficiency, such as monthly conference calls and giving responsibility to follow-up actions to the pharmacopoeia that will host the next PDG meeting.

### Quality by Design

Ulla Paulsen-Sorman of AstraZeneca gave a presentation on quality by design (QbD) from the perspective of an excipient user, adding that for drugmakers QbD demands a new science-based understanding of pharmaceutical formulations to define critical parameters for product quality. As a minimum, she said, the critical quality characteristics and functionality-related characteristics of an excipient must be considered when applying QbD principles to a drug product.

Paulsen-Sorman concluded that communication between manufacturers and distributors is a key point, citing examples where changes to an excipient suppliers test methods led to unexpected results when the material was used in batch manufacture.

"The bottom line is pharma is looking for better understanding of QbD by among excipient manufacturers," she told the conference.



### Paediatrics

The problems associated with formulating medicines for children was the subject of a presentation by IPEC Europe's Kevin McGlue, who pointed out that the vast range of body weights among the paediatric population means that appropriate doses are simply not available. That

means children are often denied access to medicines, or must be treated off-label, raising safety concerns (see also lead article on page 8). It is estimated that 90% of medicines given in neonatal intensive care units are used off-label.

To correct this, European legislation was updated in 2007 to demand that a Paediatric Investigation Protocol (PIP) for all applications for medicines. As a sweetener, the EMEA grants 10 years' marketing exclusivity for new formulations of off-patent medicines designed for use in children. However, these trials can be difficult to perform for ethical and practical reasons, said McGlue.

Paediatric medicines will require proven safe excipients, however a previous misconception that if an excipient is not suitable for paediatrics it will eventually disappear from general use is not true, asserted McGlue. However, there is a need to generate safety data.

With that in mind, IPEC Europe has joined the European Paediatric Formulation Initiative (EuPFI) which also comprises six companies, one industry association (the Association of Specials Manufacturers) and the EMEA as an observer body. One project for the EuPFI is to create a database of excipient safety data, but there are also opportunities for excipient developers, for example in the area of taste-masking.



### Excipient pedigree

Frank Milek, who recently became chair of the GDP Committee at IPEC Europe, reported progress with the Excipient Pedigree Position Paper, which is a TriPEC initiative.

This is intended as a guide for determining, documenting, and verifying the supply chain history of an excipient. This can be a monumental task considering there are more than 1,200 chemical distributors in Europe alone, the majority of which are small and medium-sized enterprises, and two-thirds of which supply the drug industry.

Currently a draft, the position paper is due to be published very shortly, said Milek. It is a more political document than IPEC's 2006 GDP Guide, he added, and outlines the necessary collaboration in the supply chain between the excipient maker and distributor and the excipient user to mitigate risk.

### Certification

On behalf of IPEC Europe's GMP Committee, Iain Moore gave an update on the certification project, saying that the objective now is to get a baseline scheme in place by the end of the year. What is clear is that regulators simply cannot inspect all excipient suppliers, and excipient users cannot audit all their suppliers for compliance with appropriate GMP and GDP standards, said Moore.

The statement in the European Commission's December 2008 pharmaceutical package that third-party certification has a role to play in qualification of API is encouraging as it suggests a similar approach for excipients could find regulatory favour, said Moore. More details on progress with the certification project are available on the GMP Committee update (page 4).

### FDA efforts

Steven Wolfgang of the US Food and Drug Administration laid out the regulatory framework for excipients in the USA, where they are clearly defined as drugs though not approved by the agency. The FDA, like the EC, is also revisiting its position on GMP for excipients, and sees a need to improve its cGMP oversight of the excipient supply chain.

To that end the agency is expanding its capacity for inspection by opening new offices around the world and forging collaborations with overseas regulatory bodies. It also wants to tackle what Wolfgang described as "challenged import screening capacity," via a combination of risk-management - identifying and prioritising the shipments that should be screened, and developing technologies such as Raman and near infrared spectroscopy for rapid, non-destructive screening of at-risk imports.

Looking to the future, Wolfgang anticipates that greater efforts will be taken to inspect the robustness of drugmakers quality systems with regards to control of components, and there will be a greater reliance on audits of excipient suppliers by third parties, such as IPEA (International Pharmaceutical Excipients Auditing) the GMP auditing arm of IPEC Americas.

### US imports

Rounding out the day, Dave Schoneker of IPEC Americas gave a US perspective on import safety in the wake of President Obama's inauguration, suggesting that there is likely to be more scrutiny under the new administration than under the old.

There is a "huge emphasis" at the FDA on third-party audits and certification, according to Schoneker, but the pharma industry is reluctant to go down this road because of a fear that the agency will not accept them. This is clearly a misconception in light of Wolfgang's earlier comments, he said.

Schoneker pointed to the new IPEC Excipient Qualification Guide (see page 5) as a pivotal new document that will improve communication between users and makers, and may also form the basis of an FDA guideline on pharmaceutical ingredient quality control. He also noted that a harmonised version of the Excipient Information Protocol guide, designed to do away with the need for questionnaires, is almost ready for publication.

Overall, the most important thing to strive for is improved communication between excipient users, suppliers and regulators, as well as an increased understanding of the systems and controls that are in place, concluded Schoneker.

*The seminar programme is freely available [here](#), and IPEC Europe members can download presentations [here](#).*

# News from the IPEC committees



All the IPEC Europe Committees met on 21 January in Cannes. The minutes of these meetings are available on the members area of IPEC Europe's website. If you are interested in joining any of them or participating in some of their activities please contact the chairs:

- GMP Committee: [Iain Moore](#)
- Regulatory Affairs Committee: [Carl Mroz](#)
- Harmonization Committee: [George Mansveld](#), or the vice-chair [Bernhard Fussnegger](#)
- GDP Committee: [Frank Milek](#).

## Regulatory Affairs

## GMP

- ▣ **Quality by Design:** a taskforce has been formed, and many members showed their interest in the topic during the AGM. A meeting is scheduled for 5 March at ECCO's premises. For more information contact [Carl Mroz](#).
- ▣ **Composition Guide:** at the November meeting the draft was reviewed and significantly updated, and sent to IPEC Americas. Comments now mostly relate to presentation. It will be published soon.
- ▣ **Excipient Master File:** a more political approach is being developed to address this problem to the attention of regulators. Meanwhile the task force would like to pose the following questions to members:
  - for excipient manufacturers: are there issues when launching new excipients in the EU where a Master File would facilitate market entry?
  - for excipient users: would the existence of an Excipient Master File for a new excipient give more impetus to innovation?

- ▣ **Quality Agreement Package:** This is undergoing the Board approval process. It will be printed out and circulated soon.
- ▣ **Certification:** A project plan is in place with team leaders assigned for the three main components: Classification; GMP; and GDP. The Auditor Competency team will be separated from the Classification team. A classification survey was launched to define appropriate GMPs for excipients in the categories, and a membership review of the GMP Annex to ISO 9001 was being requested. The outcome will be presented in the March edition of Excipients Insight.

- ▣ **Excipient Information Package:** At IPEC Americas' last meeting IPEC Europe edits were reviewed and the majority accepted. A few issues are still to be discussed, and a meeting is planned to conclude the document.
- ▣ **Significant Change Guide:** Development of this document has been set up as a priority. Developments include more risk-based analysis to determine the change level.

Please send your reply/view to the secretariat.

## GDP

## Harmonization

- The GDP Committee and all IPEC members would like to take this opportunity to thank Allan Whiston for his dedication to this Committee's activities in the past years, and welcome back Frank Milek as chair (see also page 2).
- ▣ **Certification:** The Committee will contribute to all matters relating to GDP, trying to form a joint working group with the FECC GTDP committee and colleagues from IPEC Americas. A draft GDP Annex to ISO 9001 will be delivered, taking into account imminent revisions to ISO 9001 and 9004. The working group will contribute also to the process relating to auditor competency and qualification.
  - ▣ The Committee takes care of future revisions to IPEC's **GDP Guidance documents**.
  - ▣ **Communication:** The Committee wrote an article on GDP for excipients, which will be published in Pharmaceutical Technology in May 2009.

- ▣ **Talent scouting:** A need has been identified for a list of IPEC Europe Members, contacts and other experts to consult with the Harmonisation Committee. A letter will be sent to the official representative of the IPEC Europe member companies to ask for details of their excipient portfolio and experts in charge.
- ▣ **Heavy metals:** The new method of USP Monograph <231> on Heavy Metals shall comprise 30 different heavy metals which were partly transferred from the European catalyst guideline. The discussion will be pursued between industry and FDA in mid-March 2009. The intention of industry is to keep focus on only heavy metals with high level risk (Pb, As, Cd, and Hg). The IPEC Europe Harmonisation Committee will liaise with the American colleagues on this matter in the near future.

## Committee Calendar

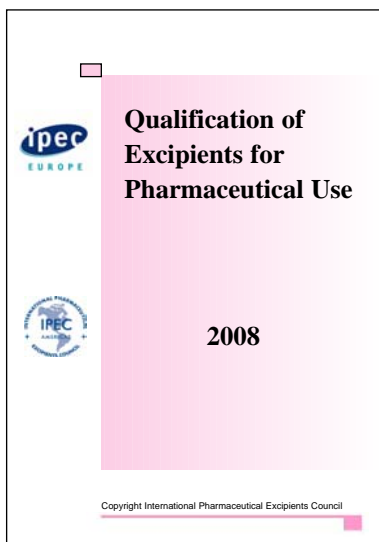
Harmonisation	21 January Cannes	16 April Brussels	8 July Strasbourg or Darmstadt	28 October Brussels	
GDP	21 January Cannes	21 April Manchester	23 June Hamburg	4 September Stuttgart	5 November Stade
Joint GMP / Regulatory Affairs	21 January Cannes	21 April Brussels	21 October Brussels		

## Excipient Qualification Guide published

IPEC Europe has published its long-awaited guide on Qualification of Excipients for Pharmaceutical Use, which is intended to facilitate communication between excipient suppliers (manufacturers or distributors) and excipient users in the selection and use of excipients.

This is a crucial document as it serves as a 'master' guide which draws together the more detailed information in all the other IPEC guides, both published and in development.

The guide details the processes in developing and sourcing excipients from the perspective of both the excipient supplier and user, and provides a discussion of the issues that must be resolved to allow for development of a commercial agreement between the two parties. Importantly, this is a consensus document that has been agreed by both IPEC Europe and IPEC Americas, so represents a truly Transatlantic position.



The qualification guide also sets out the steps needed to introduce a material as an excipient for use in pharmaceuticals, providing sound advice for those wishing to introduce or use 'new' excipients. As such it could stimulate the development of novel excipients, which are not introduced very often onto the market.

Suppliers of excipients sometimes have only a superficial understanding of pharmaceutical product development, while users generally don't understand the processes in suppliers, which tend to come from the food and fine chemical sectors.

Among other benefits, this guide helps the excipient supplier understand what the excipient user has to do to satisfy the regulators, and helps the user justify the use of a particular excipient in a pharmaceutical product. It can also help regulatory agencies in their oversight of pharmaceutical excipients, and gives pointers to the adoption of Quality by Design and Quality Space principles.

See page 8 for a complete list of IPEC guides available for download.

## Eye on Europe



### Guideline on readability of labels, inserts

The European Commission (DG Enterprise and Industry) has published a [revised version of the readability guideline](#) to be in line with amendment of Directive 2001/83/EC by Directive 2004/27/EC.

We take this opportunity to remind you that: on the outer or immediate packaging all excipients must be stated if the products injectable or a topical or eye preparation; the full qualitative composition of excipients shall be included in the package leaflet. And on both those excipients know to have a recognised action or effect.

### Revision of GMP Annex 14

As mentioned on the website of DG Enterprise and Industry, [GMP annex 14](#) on "manufacture of medicinal products derived from human blood or plasma" has been revised in the light of Directive 2002/98/EC and relevant implementing directives setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components. These directives apply to the collection and testing of blood for all uses, including the manufacture of medicinal products.

Comments can go to [entr-gmp@ec.europa.eu](mailto:entr-gmp@ec.europa.eu) and [GMP@emea.europa.eu](mailto:GMP@emea.europa.eu) through 31 July.

The requirements set up in this annex make also reference to "certain excipients" which are expected to be defined in accordance with Article 46 (f) of Directive 2001/83/EC.



### EDQM updates inspection fee policy

As of 1st April 2009, companies will be charged by EDQM for travelling and accommodation expenses of its inspectors, in a change to its [inspection fee policy](#).

The inspection fee will remain unchanged at:  
- €5000 for each inspection of an individual site; and  
- €9000 if requested by a company.

### Quality assurance activities guidelines

The EDQM's (Official Medicines Control Laboratories (OMCL) unit has published a new set of quality assurance activities guidelines, which make reference to ISO/IEC 17025 quality standards.

The guidelines are available for free downloading [here](#).

### NMR test protocol for OSCS determination

A nuclear magnetic resonance (NMR) spectrometry [protocol](#) has been drawn up by EDQM to help identify oversulphated chondroitin sulphate (OSCS), the contaminant of heparin medicines which caused tens of deaths around the world last year.

This protocol is intended to provide all users of the European Pharmacopoeia with a reference method for the quantitative determination of the OSCS in unfractionated heparins using NMR.

## International collaboration on GMP inspection: a pilot project for APIs

Regulators in the European Union, the USA and Australia have drawn up a proposal for a pilot project that could lead to greater coordination international planning of inspections.

The [proposal document](#) notes that "since the adoption of the ICH guideline on Quality Risk Management in 2005, the application of risk based approaches to the planning of inspections has increased in importance and there is increasing interest in additional international collaboration."

The pilot is based on the system currently operating in the EU where the European Medicines Agency (EMA) outlines a yearly plan for centralised inspections and invites all Member States to contribute to this based on their own inspec-

tion plans. Each regulator can reserve the right to perform their own inspection, should they consider this necessary, according to the document.

The pilot phase is initially restricted to inspections of APIs and to inspections carried out outside the participating ones. It will last 18 months from the date it becomes operational.

[Rules of engagement and procedures for participating authorities](#) have also been published.





# Eye on the world



## FDA outlines 'best practice' for importers

As announced briefly in the [January edition](#) of Excipients Insight, the US Food and Drug Administration (FDA) has issued a [draft guidance](#) on the measures pharmaceutical and other manufacturers should take to make sure imported FDA-regulated products are in line with federal statutes and regulations.

While the guide is not specifically addressed to pharmaceuticals, it applies to these products too and provides useful insight into the agency's thinking in this area.

There are four guiding principles in the document, entitled Good Importer Practice. Firstly, importers should know the foreign firms that produce the products they purchase, any other firms with which they do business and through which such products pass (e.g., consolidators, trading companies and distributors).

Secondly, they should understand the products that they import and the vulnerabilities associated with these products, as well as the hazards that may arise during the product life cycle, including all stages of production. They must ensure proper control and monitoring of these hazards.

The FDA also expects importers to be aware of the regulatory framework for the imported product, and take corrective or preventive action to ensure that they remain compliant with the requirements "throughout the supply chain and product life cycle." And finally, importers should develop a safety management programme, with defined job functions, responsibilities and accountability.

Comments should be provided by 12 April 2009.

## Submission of Laboratory Packages by Accredited Laboratories

The import practice guide its alongside another just-released document - a [draft guidance](#) on submission of laboratory packages by accredited laboratories - which is intended to enhance the quality and reliability of test results submitted by importers to demonstrate that their products meet the FDA's requirements.

The guidance advises importers how to use accredited labs and makes recommendations about the quality and type of test data and information that these laboratories should produce in support of test results submitted to the FDA.



## World Health Organization

## WHO delays "counterfeit" redefinition plan

The WHO has delayed its controversial EB 124/14 amendment that would, according to some groups, broaden the organisation's definition of "counterfeit" from its current focus on patient health to include infringements of intellectual property.

When issued last year the World Health Organization's (WHO) proposal stressed that: "disputes about, or violation of intellectual property rights [IPR] are not to be confused with counterfeiting." However, a subsequent correction to the document replaced "intellectual property rights" with the term "patents."

This revision raised fears that the rules could be used by multinational drugmakers as a way of maintaining competitiveness enforcing IP rights against generics producers in countries where patent laws are not in place.

Delaying the proposed redefinition, a move decided at the WHO's meeting in Geneva, Switzerland this week, follows considerable opposition from developing countries such as Brazil and India, where generic drugs dominate the market.

This extract of a longer article is provided courtesy of [in-PharmaTechnologist.com](#).



## USP to help fight counterfeits

The US Pharmacopeia has made its own contribution to shoring up the US medicines supply chain earlier this week with the release of standards to protect patients from counterfeit and adulterated medicines. The release of the standards, for heparin and glycerin, comes in the wake of a number of dangerous incidents involving the two ingredients.

"The decentralized, complex and global nature of today's manufacturing environment [makes it] easy for an unscrupulous supplier - driven by economic or more frightening motives - to add an ingredient to a drug product that shouldn't be there," said USP CEO Roger Williams. "Rigorous quality standards ... form a line of defense that helps to protect the public," he added.

This extract of a longer article is provided courtesy of [www.securingpharma.com](#).

## News from



## Distributors eligible for full membership

During its most recent meeting on December 9, IPEC Americas' Executive Committee relaxed its criteria for full membership, opening its doors to distributors for the first time.

A change to the organisation's bylaws now allows companies that distribute but do not manufacture pharmaceutical or other excipients, excipient blends, or finished dosage pharmaceuticals or delivery systems the option of becoming either full members with voting rights or associate members without those rights, according to IPEC Americas' latest bulletin. The amendment came into effect in January.

The rationale for the change in IPEC Americas position is rooted in recent incidents involving melamine, heparin, and diethylene glycol, according to the bulletin. These have resulted in widespread global recognition that all parties involved in the pharmaceutical supply chain need to better police and protect those areas in which they are involved, e.g. excipient and API producers, re-processors, distributors, finished drug manufacturers, packagers and government regulators.

All have responsibility for safety in their operations, which has led to various legislative proposals that will be considered by the newly-convened US Congress under President Barack Obama.

## IPEC Europe

Supporting the interests of pharmaceutical excipient developers, producers, distributors and users

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## Events Calendar



- EMEA EFPIA Info Day 2009**  
London/UK, 24 February  
For more information, view the [agenda](#) and [registration form](#)
- Formulating better medicines for children**  
London/UK, 2-3 March  
More information [here](#).
- PAT/QbD conference**  
London/UK, 10-11 March
- FECC seminar Quality standards in the supply chain of pharmaceutical, food, feed and cosmetic ingredients**  
Brussels/Belgium, 19 March  
More information [here](#).  
Programme available [here](#).
- 5th Annual Global Pharmaceutical Conference - Current worldwide regulatory and compendial expectations: impact on laboratory operations**  
Frankfurt/Germany, 2-4 April 2009  
More information [here](#).
- Expofarma Interphex 2009**  
Mexico City / Mexico, 22-24 April  
More information [here](#).
- IPEA GMP Auditing Workshop**  
Prague/Czech Republic, 27-29 April  
More information [here](#).
- PharmSciFair**  
Nice/France, 8-12 June  
Second announcement is available [here](#).  
  
Note also that a pre-satellite meeting dedicated to young scientist will be held on 7-8 June (more information [here](#))
- Paediatric drug development - tackling current and future challenges**  
Saint-Rémy de Provence/France, 17-20 June  
More information [here](#).

## Excipient industry news round-up

Like to see your news featured here? Send your releases to [info@ipeceurope.org](mailto:info@ipeceurope.org).

### German audit firm inspects Asian ingredient suppliers

German firm blue inspection body GmbH will conduct third-party API audits in Asia at the beginning of March. Manufacturing authorisation holders can take part in this audit travel to qualify their API suppliers in Hyderabad (India) and Shandong (China) regions.

The audit service provider blue inspection body GmbH will be conducting third-party audits of excipient and active pharmaceutical ingredient (API) manufacturers in Asia at the beginning of March. The company, accredited for this purpose, is seeking manufacturing authorisation holders in Europe to take part in this audit travel in order to qualify their suppliers from the regions of Hyderabad (India) and Shandong (China).

API audits are regarded as important means to enhance drug safety. The audits have to be conducted at the premises of the API manufacturer either by the pharmaceutical manufacturer himself or by a specifically qualified third-party auditor. They are a prerequisite for importing APIs into the European Union and processing them into medicinal products.

Currently, blue represents the only ISO 17020 accredited third-party API auditor for that purpose within the European Union. The recently published 'pharma package' by the EU-Commission aims to extend the European pharmaceutical directive 2001/83/EC; an accreditation may therefore become mandatory for all third-party audits by next year.

blue examines the Good Manufacturing Practice (GMP) of pharmaceutical companies around the globe. Third-party audits by blue efficiently relieve manufacturing authorisation holders, API suppliers and API manufacturers. The blue inspection body GmbH ([blue-inspection.com](http://blue-inspection.com)) is the first independent and accredited service provider for GMP audits within the EU.

More info [here](#).

### Nigeria arrests 12 accused of DEG adulteration

Nigerian authorities have arrested 12 people accused of substituting glycerine in My Pikin Baby Teething Mixture for diethylene glycol, a chemical normally found in antifreeze, which has been linked to the deaths of 84 children.

The National Agency for Food and Drug Administration and Control (NAFDAC), said that authorities were seeking the maximum penalty of 15 years in jail for those accused. Diethylene glycol has been linked to many poisoning cases worldwide. In 2006 in Panama 116 people are thought to have died after taking contaminated cough syrup and antihistamine tablets.

This article provided courtesy of [in-PharmaTechnologist.com](http://in-PharmaTechnologist.com).

### Bill seeks more inspections funded by pharma fees

A bill has been introduced to the US House of Representatives that would require pharmaceutical manufacturers pay a fee and have their facilities inspected more frequently.

The bill has been introduced by Democrats in an attempt to beef up the US Food and Drug Administration's inspections in response to the heparin contamination and other failures in supply chain security.

If passed into law the bill would require pharmaceutical manufacturers to pay an annual fee, which would be set not later than 60 days before the start of the fiscal year and be calculated based on whether the company operated foreign or domestic facilities.

In addition the bill would require facilities to be inspected every two years, or four years if the risks involved showed this to be sufficient. This would place significant strains on the FDA's current capacity, hence the annual fees, but is deemed necessary by those who put forward the bill.

Representative John Dingell, who introduced the bill, said: "Americans shouldn't have to worry about whether the medical products they use to improve their health might actually make them sick. I also look forward to continued discussions on additional improvements to the drug supply through pedigree systems." The bill can be found [here](#).

This extract of a longer article provided courtesy of [in-PharmaTechnologist.com](http://in-PharmaTechnologist.com).

### BMS to use Dow's foam granulation technology

Bristol-Myers Squibb is using a foam granulation technology developed by Dow Wolff Cellulosics for a second unnamed development product.

Unlike traditional liquid binders, Dow uses an excipient foam to improve particle coverage. The greater surface area means it can be spread more rapidly and evenly over powder beds. The foams are made by passing air into a water-soluble excipient-like methocel, ethocel, polyox or walocel. More information [here](#).

### Melamine defendants face death, life imprisonment

Four people in China are facing death or life imprisonment for their part in the melamine contamination scandal which hit headlines last year.

Zhang Yujun and Geng Jinping have been condemned to death, while Gao Junjie received a death sentence suspended for two years. That sentence typically is commuted to life in prison. Tian Wenhua, Sanlu former president, has been sentenced to life imprisonment. More info [here](#).

# Pharma additives 'pose risk to premature infants'

Difficulties in dosing medicines for premature babies mean some may be exposed to high levels of pharmaceutical excipients which, despite being pharmacologically inactive, could pose a safety risk.

That is the conclusion of researchers at Leicester Royal Infirmary in the UK, who studied the exposure of pre-term infants during routine clinical care at the hospital's neonatal unit.

In the case of one excipient, the sweetener sorbitol, infants were exposed to levels that are above the maximum recommended exposure limits for adults.

The research team looked at the records of 38 infants over the course of around one year, seven of which had chronic lung disease (CLD), a common complication in premature infants.

The babies were exposed to 20 excipients in a representative sample of the eight most commonly-used drugs, ranging from vitamin and iron supplements to the steroid dexamethasone and diuretics such as furosemide.

In addition to sorbitol, the researchers found the infants were exposed to ethanol and propylene glycol, both associated with neurotoxicity, and the food colorant Ponceau 4R.

The UK Food Standards Agency has recommended the latter be removed from products used in children because of concerns about its effect on neurodevelopment and behaviour. As expected, exposure was increased among the infants with CLD.

The study was not designed to look for any link between excipients and side effects, but the authors, led by Dr Hitesh Pandya, believe the results are a cause for concern.

The researchers concluded that regulators should "lead action to determine whether exist-

ing practice constitutes a risk" and how it could be tackled if this is the case.

The study was published in the Fetal & Neonatal Edition of *Archives of Disease in Childhood* (20 January).



## Industry challenges

Formulating drugs for use in children poses many difficulties for drugmakers. Given the huge range of body weights between preterm infants and adolescents, for example, it is hard for pharmaceutical companies to justify manufacturing a broad range of doses to serve the relatively small paediatric market.

The result is that around 10% of paediatric patients in primary care - and up to 90% of those in neonatal intensive care - receive medicines 'off-label', simply because there is no suitable dosage strength available.

Pharmacists are often forced to compound ingredients into what is known as 'extemporaneous preparations', on the order of a physician, for example by dividing and crushing tablets and dispersing them in suspending agents. While necessary, this approach is clearly far removed from Good Manufacturing Practice (GMP).

But the problem is recognised by industry and clinicians alike and, in response to the concerns, drugmakers and paediatric medicine specialists have now formed a European consortium to try to develop an answer.

The European Paediatric Formulation Initiative (EuPFI) is specifically looking at developing a database of excipient safety data relevant to paediatric formulations, as well as improved delivery devices and new ways to make medicines more palatable for children.

It will also look into the possibility of developing 'stock' medicines to replace extemporaneous preparations - for example, based on a simple powder mix of excipients and active ingredients that can be reconstituted to the desired strength.

The EuPFI is organising a [conference](#) at the Royal Pharmaceutical Society of Great Britain in London, UK, on 2-3 March.

*This article reproduced from [Pharmafocus](#) with grateful thanks.*

## IPEC Perspectives

"Care is needed with regard to the use of alarmist language when talking about this matter and we must focus on the clinical problem, not the specific materials.

"The materials in question are not harmful to adults in normal intakes, but all materials will be harmful to humans at a large enough intake.

"What this study demonstrates is the urgent need for the development of age appropriate formulations for the paediatric population, so that the intake of materials is appropriate to the patient and the potentially dangerous clinical practice of simply administering adult medicines at adjusted rates is eliminated."

*Kevin McGlue, on behalf of IPEC Europe*

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