Federal Institute for Vaccines and Biomedicines

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// ANNUAL REPORT 2007/2008 //
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Dear Reader,

You might find it a little surprising that it is only at the end of 2009 that you have received the Annual Report 2007/2008 of the Paul-Ehrlich-Institut, which is now also called the "Federal Institute for Vaccines and Biomedicines". To explain this would actually require us to look ahead to the contents of the next annual report, but let me briefly say this much: when we made the decision to start publishing annual reports again, no one could have predicted that 2009 would be the year of a pandemic, with all the particular challenges that that implies for the Paul-Ehrlich-Institut. Nonetheless, I believe we have succeeded in producing a readable, informative and attractively designed annual report. The years under review were full of challenges. One of these challenges comes around periodically, like a pandemic, with the difference being that it is predictable: in the first half of 2007 Germany held the EU Presidency. For the Paul-Ehrlich-Institut, this involved us conducting a few more international events than usual. The exchange with our European colleagues here at the Paul-Ehrlich-Institut or in Dresden, as one of Germany's representative cities, was both very important and highly successful.

In 2008 we organised two international conferences – the XVII International Poxvirus and Iridovirus Conference and the 12th International Paul Ehrlich Seminar on Regulatory Control and Standardization of Allergenic Extracts – yet another indication of how important it is to us to integrate regulatory activities with research. At the end of the period under review we held a symposium to mark the 100th anniversary of the awarding of the Nobel Prize to Paul Ehrlich.

The years under review have been characterised by other significant innovations. For instance, in 2007 the Paul-Ehrlich-Institut went online with its database on suspected adverse events following immunisation (AEFI). Since then, we have been informing everyone about this issue, which is a major subject of public debate, and thereby playing our part in improving the information on vaccines available to the public. In this way, we are once again giving substance to the guiding principles of the Paul-Ehrlich-Institut. The German Tissue Act (Gewebegesetz) came into force in 2007, thus bringing an entirely new and innovative product portfolio within the remit of the Paul-Ehrlich-Institut. The Institute's experts have taken on this task with a great degree of commitment and have put in place the necessary substantive and organisational framework.

The Paul-Ehrlich-Institut is also well positioned at European level. For example, in the person of Dr Christian Schneider, a PEI colleague was once again chosen as a co-opted member of the important Committee for Medicinal Products for Human Use CHMP at the European Medicines Agency EMEA, where he specialises in the quality and safety of biological medicinal products, including advanced therapies.

This is the last report which will be prepared under my direction, as on 1 December 2009 the presidency will pass to my successor, Professor Klaus Cichutek. After 28 years at the Paul-Ehrlich-Institut, including eight years as its president, my time here is coming to an end. In spite or perhaps precisely because of that, I am looking forward to the next annual report, which will cover the years 2009 and 2010.

After this brief look at the contents of our annual report, I now invite you to form your own impression of the work we do.

Yours sincerely,

[Signature]
Professor Löwer, Germany has two medicines authorities: the Paul-Ehrlich-Institut, responsible for the marketing authorisation and monitoring of vaccines and biomedicines, and the BfArM, responsible for finished medicinal products and medical devices. Does it still make sense to have this division, in view of the homogenisation of the European medicinal product markets?

Löwer: The Paul-Ehrlich-Institut is responsible for vaccines and biomedicines, in which area it has a great deal of expertise. This specialisation is important, because this product group represents a particular challenge. One advantage of having two medicinal product authorities is that there is also an element of competition between the institutions, even if they are responsible for different groups of medicinal products – and competition is stimulating. This is no longer quite so important, since our competition is now primarily at an international level. Having two authorities also increases Germany’s influence within the European bodies. If we had only one authority, we would, for example, have one national representative and one alternate on the European Committee for Medicinal Products for Human Use CHMP. As it is, however, we had the opportunity to have another member co-opted onto this committee. This means that Germany is one of the five countries who send two representatives and one alternate.

Cichutek: In my view, the two institutes complement each other very well. In future, however, we must do more to ensure that any resources present in one of the institutes will be available to both institutes, if required. For instance, the clinical assessors in the two authorities include physicians who specialise in individual indications. Take oncology and neurology for example: the PEI is responsible for tumour vaccines and has expertise in oncology, while the expertise in neurology is to be expanded at the BfArM. In this case, there is specialist knowledge which would be of benefit to both institutes. Would it not be better to merge the two authorities?

Löwer: I think the question is not so much should we merge the BfArM and the PEI, but rather whether and how the authorities which are currently obliged to follow public administration legislation can be converted into agencies entitled to use private sector management principles, given that public administration structure has strong limiting factors. What changes would agency status entail compared to public administration status?
Löwer: It would result in a greater flexibility in staffing plans. At the moment decisions are taken at a political level, rather than being determined by the market. No matter how many marketing authorisation applications come in, we must first get approval from the Bundestag to create a new position. As an agency we could respond more flexibly to the demand.

Professor Cichutek, looking at the PEI from a European perspective, one thing in particular is striking: the close linkage between regulatory activities and research. Why does the PEI assume this special role?

Cichutek: I would say it’s the other way round: the special role is primarily the result of the fact that the PEI performs particularly well on a European level. And this is precisely because we combine research and regulatory activities. Incidentally, I have the impression that we do not necessarily have a special role, but rather a pioneering role. Other agencies are also now making efforts to strengthen their research. This is because they recognise we deliver excellent quality in the area of regulatory activities, and this quality is essential.

Löwer: There is an additional point: biological medicinal products are becoming increasingly more complex and more difficult to assess. Take for example TGN-1412, the monoclonal antibody, which caused serious adverse events in the participants in a clinical trial. This can only be understood if we have an expert knowledge of the field of immunology, and this is only possible if we also carry out research. This is particularly clear in the area of gene therapy, which other medicines agencies are rather cautious about, because they are not familiar with it. We, however, conduct research in this field and can therefore assess marketing authorisation applications accordingly. This also applies to modern cell therapy. Our expertise is also reflected in the fact that the EMEA appoints PEI staff members to corresponding positions. All this encourages other medicines agencies to think about going down the same road themselves.

Research at the PEI takes place primarily at divisional level. This means that high levels of research resources need to be maintained in all the various divisions. Does that make sense economically?

Cichutek: The research must complement the regulatory activities in each division. It would not make sense to conduct research centrally, separate from the regulatory activities. In addition, the exchange of information between the staff members involved in research and those involved in regulatory activities is very important. The regulatory work of the assessor clearly benefits from their close proximity to research. It also means that everyone can make use of resources such as research platforms and large equipment.

Professor Cichutek, are there any examples of the need for research in connection with the regulatory activities?

Cichutek: The example of TGN-1412 has already been mentioned. As a regulatory authority, it is essential that we understand the underlying mechanisms in order to have an answer for similar medicinal products. Another example is the gene therapies with which some of the patients developed leukaemia during two clinical trials. In this case, the research carried out by the PEI may contribute to a better understanding of how the disease came about, as well as reducing the associated risks by improving the vectors.

The regulatory work of our assessors clearly benefits from their close proximity to research.

Professor Löwer, how do you see the further development of a single European regulatory system for medicinal products, and what role should the PEI play in that?

Löwer: At the moment there is a European network that is designed to jointly perform the regulatory duties. As part of this, there are centres of resources, institutions that have particular expertise in specific areas. A development is conceivable in either direction: will this duty continue to be performed in the long term by a network, or will ultimately everything be centralised, as with the Food and Drug Administration FDA in the U.S.? If the decentralised network solution becomes established, the PEI will have to consider whether to take the next step and become a European institution.

Professor Cichutek, how well do you think the PEI is prepared to take on this role?

Cichutek: We have one of the best starting positions, if you consider the number of marketing authorisations, the number of Rapporteurships and Co-Rapporteurships and the number of other procedures that we currently handle. We provide the co-opted member of the Committee for Medicinal Products for Human Use, and we are also represented on the corresponding veterinary committee. We provide a representative on and the chair of the committee for advanced therapies.
and several chairs of the working parties that support these committees. The situation up to now has been that the network consists, on the one hand, of the medicines agencies of the EU member states and, on the other hand, of the EMEA. The trend now, however, is not to leave the coordinating and leading role to the EMEA alone, but for the medicines agencies to play a bigger role. I believe that we are well prepared to do that.

Professor Löwer, one might argue that when it comes to the safety of medicinal products even the European dimension is too limited. Should the PEI not adopt a global perspective, especially with regard to the safety of blood products and vaccines?

Löwer: That's true. For this reason, we not only work with the EMEA, but also with the WHO. The WHO has a body that deals with the safety of vaccines. A colleague from the PEI has recently started representing Germany on that body. With regard to the safety of blood products, it is even clearer: the PEI is a WHO Collaborating Centre for blood products and in-vitro diagnostic devices used to test donated blood. We are also one of the few members of the Blood Regulators Network, which brings together the larger authorities who are responsible for the regulation of blood products. We are active on a global level and we hope in this way to contribute to the safety and efficacy of blood products and vaccines worldwide.

Cichutek: Another key body is the International Conference on Harmonization ICH, which cooperates on a global level to set standards for medicinal products in Japan, North America and Europe. There is a trend to invite countries such as China to attend as guests, to further increase the body's global influence. Once again, the PEI is represented on this body.
Professor Löwer, given that the PEI is active over such a wide area, the question arises as to how all this is funded?

Löwer: The Federal Government knows how important our global activity is. Our budget is currently such that we can carry out these activities, and hopefully this will continue to be the case in the future. Some of these, by the way, are funded by third parties. For example, the WHO pays for some of our experts’ activities and we also receive payment for the work we do for the ICH. It is therefore a question of mixed financing by international organisations and the Institute. The assumption of costs by third parties is an important theme: what is the current situation with the PEI’s self-financing ratio?

Löwer: The PEI’s self-financing ratio has increased significantly in recent years. One third of our funding is now generated by our own income. The other two thirds come from the federal budget. This underlines the fact that the Federal Government provides appropriate support for our work, in particular our research and international activities.

The PEI’s divisions carry out internationally acclaimed research.

Professor Löwer, you have been the acting head of the PEI since October 1999, and since June 2001 you have been its President; at the end of 2009 you are handing over the baton to your successor and current Vice President, Professor Cichutek. What milestones do you think the PEI has achieved during your time in office, and where do you see further potential for development?

Löwer: The key issue for me has been the consolidation of our position within the network of European medicines agencies. We have become much more visible over the last ten years and have gone from the sidelines to being a major player. I also think we have made great progress in the area of research. Whereas ten years ago our research focused on only a few areas, it is now highly diversified. Our divisions carry out internationally acclaimed research, which can also be seen from the fact that in recent years five PEI colleagues have been appointed to university professorships. Another milestone which I am pleased about is the great progress we have made in reconciling work and family life. After a long struggle, we are now able to subsidise nursery places, which makes it easier for female employees in particular to work here while placing their children in pre-school facilities nearby. The fourth point is the transition from the paper age to the electronic age. I well remember the first time I gave a presentation about the Internet here at the Institute. A lot has changed since then. We have laid a solid foundation which will in future enable us to carry out the assessment of marketing authorisation applications in electronic form.

As far as our potential for further development is concerned, this will primarily relate to us playing our part in shaping the European regulatory system and taking up an important position in it; there is also a lot of potential in the area of research. Furthermore, I believe it is important to think about saying goodbye to our public administration structure and becoming an agency entitled to use private sector management principles.

Professor Cichutek, do you share Professor Löwer’s opinion regarding the PEI’s potential for development? Where are the main points that you wish to emphasise in the future for the PEI?

Cichutek: I agree with Professor Löwer – the key issue will be for the PEI to continue to play a leading role in Europe. To make this possible, we must continue to develop and improve our efficiency in various areas. We must also think of the PEI more as a whole: regulatory activities include batch testing, product testing, inspections, pharmacovigilance, marketing authorisations, post marketing authorisation approval procedures, but also approval of clinical trials and scientific advice. We must link these areas more closely with each other, while nonetheless using specific standards for each. Another important point is our client-centred approach. This is already very good at the moment, but we need to offer certain clients – the biotechnology companies – even more advice. Some of our clients require a lot of support with regulatory issues even to get as far as the marketing authorisation application stage, and our goal is to ensure that good, effective and safe medicinal products are available for standard therapies.

Gentlemen, thank you very much for this interview.

The questions were asked by Dr Corinna Volz-Zang
Effective and safe medicinal products are indispensable in modern society – and are therefore the focus of intense public and media attention. The debate around medicinal products is coloured by both hopes and fears, and there is a great need for information. The Press Office informs the media, the professional community and the general public on all matters relating to the Institute, its mission and the medicinal products for which it is responsible.

The range of questions is enormous: a TV station that wants to broadcast an interview on a topical issue, requests from the press for background information, enquiries from parents about vaccinations, a historian who needs Paul Ehrlich’s original documents. At the same time, the Press Office often takes on the role of a translation agency, converting complex scientific and regulatory interrelationships into easily understandable language. This requires both knowledge of the subject matter and professional communication skills, which is why the staff of the Press Office have backgrounds in both science and journalism.

Susanne Stöcker, the Press Information Officer, is known for being a highly-skilled contact person, and journalists like to take advantage of the expertise she can provide thanks to her doctorate in biology. Medicinal products and their healing effect – or in the case of vaccines their preventive effect – are a hot topic of debate among the public and in the media, as is the fear of their potential side effects; these issues can quickly take on a momentum of their own, which necessitates an urgent response. The “Press and Information Office”, which is a staff unit attached to the Institute’s management, informs, explains, coordinates and ensures transparency in order to contribute to a constructive discussion. Major themes in 2007/2008 included debates on medicinal products for treating wet macular degeneration, the introduction of a freely searchable database of suspected cases of vaccine complications, initial discussions around mock-up pandemic vaccines and, in particular, the introduction of vaccination against human papillomaviruses as a cause of cervical cancer.

Internet presence
The Institute’s website at www.pei.de provides the media, the public, companies and professionals such as doctors, pharmacists and veterinarians with up to date and scientifically sound information. This is made possible by a very

// COMMUNICATING COMPLEX INTERRELATIONSHIPS IN A TRANSPARENT MANNER //
close cooperation between the experts in the PEI's sections and units, the Institute's management and the Press Office. In this way, the Institute can provide timely background information on topical issues. The web pages carry the logo of the Health On the Net Foundation HON. The Foundation is committed, among other things, to improving the quality of health-related information on the Internet. But it is not just to the outside world that the Institute communicates in this modern fashion - the intranet, which is coordinated by the Press Office, allows colleagues to share information and keep up to date with what is going on within the Institute.

A peak inside the laboratories: the Open Day

Every year the Press Office, in collaboration with colleagues from the various divisions, organises an Open Day. Visitors can conduct experiments in the laboratories and learn interesting facts about the work of the Institute, while children can play the role of young researchers; plenty of refreshments are, of course, also provided for our guests. In 2007 approximately 1,000 visitors found their way to the Institute to learn about "The European Dimension of the Paul-Ehrlich-Institut". In 2008 the Open Day was held in the evening, and the focus was on marking the 100th anniversary of Paul Ehrlich being awarded the Nobel Prize. Groups of visitors are, however, also welcome to visit the Institute on other days to learn about its work: parties of school children, groups of senior citizens, graduate schools, scientists and politicians have all taken advantage of this opportunity. In addition, the PEI takes part in the Open Day of the Federal Ministry of Health in Berlin and carries out presentations to the visitors there.

Pan-European public relations

It is not just the various divisions that are part of a European network: in June 2008 the Paul-Ehrlich-Institut was responsible, on behalf of Slovenia, for organising at short notice the meeting of EU Heads of Medicines Agencies Working Group of Communication Professionals HMA WGCP. An important issue at this meeting was the exchange of information on the question of how communication should take place in the event of a pandemic and how well prepared the various member states were. After this, four working parties reported on their initial results since the previous meeting of the group in Portugal. The issues addressed by the working parties – Communication Strategy, Communication Toolkit, Networking and Best Practice – will help to advance the goals of the group: to make coordinated and effective communication possible throughout Europe. The meeting was attended by 23 representatives from 17 countries.

Langen Science Prizes

Every two years the Paul-Ehrlich-Institut, together with the town of Langen and Stadtwerke Langen GmbH, awards the Langen Science Prize. This prize, worth €100,000, is given to researchers in various fields of infection medicine, such as virology, bacteriology and immunology, haematology, allergology and gene and cell therapy. In this way, the Institute demonstrates the importance it attaches to research, while at the same time honouring the community in southern Hesse in which it is based. In 2007 Prof. Jochen Hühn of the German Rheumatism Research Centre at the Charité University Hospital in Berlin received the award for his work on regulatory T cells.

Freedom of information

Since early 2006 members of the public have been able to submit a request in accordance with the German Freedom of Information Act IFG to view information held by a government body. This raises a large number of questions from an organisational and legal point of view: to what extent is this possible, given that the marketing authorisation documents for a biological medicinal product may fill up to 120 ring binders? What is the impact of industrial and commercial secrecy or data protection laws? The Press Office coordinates the IFG requests in collaboration with our legal advisers and the divisions. In 2007/2008 the Institute received 76 IFG requests, ranging from simple enquires to comprehensive requests for information.

Further information

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This marketing authorisation is recognised by all countries in the European Economic Area. The scientific assessment and recommendation for marketing authorisation is provided via the European Medicines Agency EMEA. In the case of biotechnological medicinal products or medicinal products with new active substances for certain diseases, such as cancer or diabetes mellitus, manufacturers have no choice – they must apply for marketing authorisation via the centralised procedure. The importance of the EMEA for the supply of medicinal products is growing continuously.

Germany represented twice

The EMEA is an agency of the European Commission. The EMEA’s highest scientific decision-making bodies for the marketing authorisation of medicinal products are the Committee for Medicinal Products for Human Use CHMP and the Committee for Medicinal Products for Veterinary Use CVMP. Each member state is entitled to one seat on the CHMP and one on the CVMP. Each committee also includes five co-opted members with specialised expertise in a particular scientific area. Dr Christian Schneider is a co-opted member of the CHMP, with expertise in the quality and safety of biological medicinal products, including advanced therapies. This means that Germany is represented by two members on the CHMP.

Many medicinal products also receive their marketing authorisation by means of the Mutual Recognition Procedure MRP or the Decentralised Procedure DCP. In the case of the MRP, a member state recognises the assessments of the country which initially granted the marketing authorisation for the medicinal product. In contrast to the MRP, with the DCP the medicinal product has not yet been authorised in any member state. This recognition considerably reduces the effort and expenditure required for marketing authorisation. In 2007/2008 the PEI was involved in 63 mutual recognition procedures, of which in no fewer than 31 cases it was the authority leading the procedure as the Reference Member State RMS.

The work of the CHMP and CVMP is supported by a variety of working parties. Their members include experts from
Centralised marketing authorisation procedure based on the example of the CHMP – the clock is running

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* Time for manufacturers to answer questions

national marketing authorisation agencies, external experts such as university professors, but also patient representatives. The working parties support the committees in the provision of scientific advice / protocol assistance, the assessment of marketing authorisations and notifications of variation and in the drafting of scientific guidelines. Scientific Advisory Groups advise the CHMP and CVMP in the evaluation of specific product groups or forms of therapy. If a manufacturer applies for a central marketing authorisation, the CHMP or CVMP will appoint certain of its members to produce reports, with one acting as Rapporteur and one as Co-Rapporteur. While in the veterinary field these appointments are distributed as evenly as possible across Europe, when it comes to medicinal products for human use the European marketing authorisation agencies have to apply for the appointment and must therefore demonstrate specific expertise for the corresponding product. Given its high level of expertise, the PEI succeeds in being awarded a disproportionately high number of Rapporteurships and Co-Rapporteurships for biological medicinal products: between 1995 and 2008 it acted in this capacity for no fewer than 70 of the 256 central marketing authorisations for biological medicinal products. All medicinal products manufactured and sold in Europe are subject to strict rules in terms of their composition, production and quality. The European Directorate for the Quality of Medicines EDQM is responsible for the European Pharmacopoeia.

This defines pharmaceutical rules, for example for manufacturing, quality, testing and storage. In 2007 the Council of Europe extended the competence of the EDQM to cover blood transfusions and organ transplants. In addition, the EDQM coordinates the Official Medicinal Control Laboratories OMCL – the PEI is recognised as an OMC laboratory for its area of expertise.

New medicinal products must be safe, effective and of the highest quality. At the same time, it is important for patients and manufacturers that there should not be an excessively long period before the medicinal products appear on the market. To guarantee this, while also giving all the experts of the EU member states the opportunity to monitor the procedure and to raise potential concerns, the course of the marketing authorisation procedure is precisely defined.

Committee for Advanced Therapies

Advanced therapies such as regenerative medicine and gene therapies are the subject of intensive research. To guarantee the safety and efficacy of therapies in this new area of medicine, the Committee for Advanced Therapies CAT was launched at the start of 2009. This scientific committee is in charge of preparing expert opinions for the CHMP containing recommendations on the marketing authorisation of new therapies. The PEI will provide the German member of this committee.

>> www.pei.de/international-en
subsequent procedures were handled by the division in 2007/2008. It also conducts research into new vaccines, for example against tuberculosis.
In March 2006 six men displayed dramatic immune reactions during a clinical trial in London. The TeGenero case could have happened anywhere.

There were no obvious errors such as contamination, incorrect dosage or protocol violations. Could regulatory guidelines be formulated that would prevent such a disaster? Scientists at the PEI set to work on this issue immediately after the incident, published their initial results and played a key role in the formulation of a new European guideline [1]. The scientists did not want to leave it at that and so in spring 2007 started work in a relatively unfamiliar field of research – regulatory research. It is based on an analysis and comparison of marketing authorisation applications, taking into account current research findings. In 2007/2008 the researchers devoted themselves to two key aspects.

- Avoiding typical errors: to prevent pharmaceutical companies from repeatedly encountering the same problems in the development of medicinal products, the experts formulated typical pitfalls in the marketing authorisation procedure and published them in November 2008 in the prestigious journal Nature Reviews Drug Discovery [2].

- Safety in the use of biological medicinal products: while vaccines should generate the strongest possible immune response, an immune response by the body to therapeutically administered proteins such as monoclonal antibodies or coagulation factors is not desirable and may be dangerous. The researchers also examined whether the immunogenicity of therapeutic proteins can be systematically evaluated [3] and whether regulatory frameworks can be transferred to new product classes [4]. Specifically, the researchers dealt with the “generic” aspect of monoclonal antibodies: while traditional generic drugs have an identical molecular structure to the original, the “replicas” of biological medicinal products, which are referred to as biosimilars, are “essentially” the same as a previously authorised medicinal product. The differences are the result of the complex molecular structure and the manufacturing process in living organisms.

Literature

1. Strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products; Dokument Nr. CHMP/SWP/28367/07 (July 2007)
More and more medicinal products are being authorised for all EU member states in a centralised procedure. For many biological medicinal products for which the PEI is responsible, the centralised European marketing authorisation procedure is in fact required by law. Individual member states are also increasingly recognising each other’s assessments and marketing authorisations in a decentralised or mutual recognition procedure, while the EMEA advises pharmaceutical companies on regulatory issues as part of the scientific advice procedure. The PEI is involved to a great extent in these European procedures and in the development of important guidelines.

To ensure that this European collaboration can benefit from the expertise of all the PEI’s divisions, co-ordination and cooperation is essential between these divisions and the various EU bodies. For this reason, in March 2007 the EU Co-operation section was integrated within the Microbiology division. It was directed initially by Dr Christian Schneider, a member of the Committee for Medicinal Products for Human Use CHMP at the EMEA. This direct involvement guarantees the interconnection between regulatory expertise, research and cooperation with European bodies. Dr Schneider was appointed acting head of the division in April 2007, and since 2009 has been its permanent head.

EU CO-OPERATION ON BIOLOGICAL MEDICINAL PRODUCTS

Focus on Europe

The EU Co-operation section is the initial contact point for the European Medicines Agency EMEA and takes care of centralised European duties. In addition, it also ensures transparency in terms of content: the section organises the scientific communication between representatives of the PEI on the various European bodies, the assessors who undertake the evaluation of medicinal products, and the research scientists. In the spring of 2007, the section launched the “Forum”, a series of internal meetings in which all scientific staff could obtain information about and discuss European guidelines which have recently been adopted or which are being coordinated. The section is also working hard on the development of an intranet-based information platform which will enable rapid access to content relating to marketing authorisations and research. On account of its expertise in the field of biological medicinal products,
the EMEA often awards Rapporteurships or Co-Rapporteurships to the PEI. To guarantee the quality and consistency of assessment reports, the section organises "peer reviews", meetings attended by experts from various divisions in order to discuss the reports. This exchange of information is also very important, because for certain indications the Institute works on a cross-divisional basis.

Since 2007 the section has been working on the development of a "regulatory memory" which should enable assessors to quickly access older marketing authorisation documents which are still relevant to current issues. The safety of medicinal products, and thus the health of humans and animals, is dependent on the quality of the marketing authorisation procedure. The regulatory research which began in 2007 analyses completed marketing authorisation procedures and international publications in an attempt to arrive at new regulatory principles.

INSPECTION SERVICES FOR BIOLOGICAL MEDICINAL PRODUCTS

On-the-spot checks

Inspections of biological medicinal products may take place at various times during the marketing authorisation procedure or after the product has been authorised. These inspections may be one of the following types:

- Good Clinical Practice GCP inspections during the approval of clinical trials or in the marketing authorisation procedure
- Inspections for the verification of the pharmaceutical company’s pharmacovigilance systems
- Inspections as part of the Plasma Master File procedure.

These inspections lie within the sphere of competence of the Paul-Ehrlich-Institut and may be initiated at both national and European level by the EMEA. These inspections, which contribute significantly to the safety of medicinal products and patients, are conducted by the section’s staff. For medicinal products in Germany which are within the Institute’s sphere of competence, such as blood products and vaccines, the Paul-Ehrlich-Institut is involved in the Good Manufacturing Practices GMP inspections, and a manufacturing licence is issued only in consultation with the Institute. For this reason, PEI staff are involved as experts in the GMP inspections carried out by the German regional control agencies (Landesüberwachungsbehörden) at the manufacturers of biological medicinal products.

The section coordinates the participation of its own inspectors or experts from various divisions in these inspections: 346 national inspections were carried out in 2007/2008, as well as 73 inspections for the EMEA. The PEI’s inspectors and specialists are in demand:

- as experts to assist the state authorities, since specific expertise is required for many biomedical devices.
- in the context of a marketing authorisation procedure, if an inspection is required on site.
- in centralised marketing authorisation procedures, in the case of inspections on behalf of the EMEA.

MICROBIOLOGICAL VACCINES

Important protection for young and old

Bacterial vaccines have become an indispensable part of our lives. They protect us against such diseases as diphtheria, tetanus, whooping cough, meningococcal disease, Haemophilus influenzae type B (Hib) and pneumococcal disease. This section is responsible for the marketing authorisation of bacterial vaccines and test antigens (tuberculins) in national and European marketing authorisation procedures. The section’s scientists also conduct research into new methods for testing vaccines against diphtheria, tetanus and whooping cough, in order to reduce animal testing.

In 2007/2008 the section handled 25 new applications for clinical trials. These included trials of new vaccines against tuberculosis using genetically modified microorganisms, and also against meningococcal B disease, for which as yet

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European countries with more than ten central marketing authorisation procedures between 1995 and 2008

<table>
<thead>
<tr>
<th>Country</th>
<th>2007/2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>Germany (PEI)</td>
<td>70</td>
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<tr>
<td>UK</td>
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<td>Sweden</td>
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<td>Italy</td>
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<td>Spain</td>
<td>11</td>
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</tbody>
</table>

27% of all central marketing authorisations of biological medicinal products are handled by the PEI as Rapporteur or Co-Rapporteur.
no vaccine is available anywhere in the world. Other important developments include: a pneumococcal protein vaccine with an entirely new mechanism of action and vaccines against Helicobacter pylori and Staphylococcus aureus. The assessment of Phase I trials, in which an active substance is used for the first time in humans, is particularly complicated. The section handled three of these Phase I trials in 2008. Once a medicinal product has been authorised, the maintenance phase begins: any variation, whether it relates to the method or place of production or to indications, must be approved. The section is responsible for a total of 70 medicinal products and in 2007/2008 handled 144 European variations and 178 national variations to marketing authorisations. Vaccines must be safe. For this reason, the PEI tests all batches of bacterial vaccines: in 2007/2008 a total of 1547 were tested, including 529 experimentally. On behalf of the WHO, the section tests the efficacy and safety of diphtheria, tetanus and Hib vaccines that the WHO uses in its vaccination programmes. In addition, the section supports the WHO in prequalification programmes: PEI experts evaluate the vaccine dossiers and inspect the production facilities on site. The section is closely involved in the development of new procedures and standard materials for testing vaccines against tetanus, Hib, diphtheria and pneumococcal disease. European or worldwide uniform standard samples are required for the testing of vaccines; these samples need to be manufactured and “calibrated” again and again.

**BACTERIOLOGICAL SAFETY**

**Novel rapid tests for increased safety**

Ensuring the microbial safety of biological medicinal products is this section’s central duty. This work includes:
- testing for microbial contamination, for example by bacteria or fungi
- the development of new rapid methods for detecting microorganisms: the new “advanced therapies” mean that more rapid detection methods are required. If, for example, cartilage cells are taken from a patient in regenerative medicine, grown in culture and then re-administered, conventional testing methods are useless because they take too long. The development of suitable test methods is a major focus of research for this section.
- testing for pyrogens and the development of alternative test methods: medicinal products must not contain any fever-inducing pyrogens or endotoxins, the decomposition

**Scientific Advice – Help in the development of new vaccines**

Many pharmaceutical companies take advantage of the scientific advice procedure to receive advice from the PEI. This can take place during the initial development phase of an active substance, or as late as the planning of clinical trials. In 2007/2008 companies received advice from the section’s experts by means of a total of 64 national specialist discussions – for example in the development of vaccines against group B streptococcus, pseudomonas, tuberculosis, Helicobacter pylori and meningococcal B disease. The staff also advise the German Standing Vaccination Committee STIKO, which issues recommendations on the necessary vaccinations in Germany.

"We are actively involved in developing and providing important therapeutics in Europe."

New medicinal products must be safe, effective and of the highest quality. At the same time, it is important for patients and manufacturers that there should not be an excessively long period before the medicinal products appear on the market. To guarantee this, while also giving all the experts of the EU member states the opportunity to monitor the procedure and to raise potential concerns, the course of the marketing authorisation procedure is precisely defined.
products of bacteria. To date, animal testing is still necessary in order to test for pyrogens. The section’s scientists are working intensively on alternative tests, which will mean that animal tests are no longer required.

- developing international bacteria standards: to date, there are no bacterial strains available anywhere in the world which are suitable for evaluating detection methods in blood components and cell therapeutics. The Institute’s scientists have therefore isolated and characterised bacteria that are to be established as WHO standards.

**BIOSTATISTICS**

New trial designs require new models

The biostatistics section supports the PEI’s divisions with mathematical and statistical expertise for

- the assessment of marketing authorisation applications in national and centralised procedures
- the testing of applications for clinical trials
- research projects
- national or central scientific advice procedures

In addition, the section’s staff also develop new biostatistical procedures.

**Selected activities/publications/appointments**

- Dr Christian Schneider, Committee for Medicinal Products for Human Use CHMP – EMEA; Similar Biological (Biosimilar) Medicinal Products Working Party BMWP (Chair) – EMEA; Committee for Advanced Therapies CAT (Chair) – EMEA
- Dr Katrin Völler, Coordination Group for Mutual Recognition and Decentralised Procedure – Human CMD(h) – HMA
- Dr Volker Öppling, Drafting Group for Vaccine Guidelines – EDQM; Vaccine Working Party VWP – EMEA
- Dr Thomas Montag-Lessing, Blood-associated Pathogens – Working Party Blood; Bacteria Group, International Society of Blood Transfusion ISBT (Chair)
- Sabine Heinz, German Regional Control Agencies’ Specialist Expert Group 02 - Inspections
- Dr Peter Volkers, Efficacy Working Party EWP – EMEA
- Dr Ingo Spreitzer, Expert Group “Monocyte Activation Test” – EDQM

>> [www.pei.de/eu-cooperation](http://www.pei.de/eu-cooperation)

>> [www.pei.de/eu-cooperation-research](http://www.pei.de/eu-cooperation-research)
3,607 batches were tested by the division in 2007/2008, including many vaccines against pathogens such as influenza.
H5N1 – the name is no longer only known to experts. There is great anxiety that the bird flu virus will change in such a way that it can also be transmitted from person to person.

It is already dangerous – more than 60 percent of those infected die. Since 2006, as part of the Federal Immediate Action Influenza Research Programme FSI, researchers from the PEI, the Friedrich-Loeffler-Institut, the Federal Research Institute for Animal Health FLL, and the Robert Koch-Institut RKI have been working together to find ways of eliminating the danger. The focus is on the development of suitable vaccines.

"Domesticated" poxviruses as vaccine delivery systems
A common feature of dangerous viral diseases is that they occur suddenly and spread rapidly. A vaccine must therefore be found quickly and produced in sufficient quantities. To date, manufacturers have mainly been growing the viruses for flu vaccines in fertilised chicken eggs. This takes several months, which means that the short-term production in sufficient quantities of a vaccine against a new pathogen is not possible.

New vaccines and production methods are needed in order to quickly produce the necessary quantities of vaccine in emergencies. The researchers in the Virology division focused on the search for an effective vaccine, a so-called vector vaccine, and have already been successful. The vector that they use could almost be described as a "pet" of the PEI: the modified vaccinia virus Ankara, MVA for short, is a highly attenuated and therefore non-dangerous poxvirus which cannot replicate in humans and has proven to be safe. It activates the human immune system in a highly effective manner – ideal for a vaccine. The virologists introduced the gene of an important membrane protein of H5N1 viruses into the genome of the MVA virus. The human immune system reacts to the protein and produces antibodies. Vaccination with this vector should therefore generate a protection against dangerous pathogens. The researchers developed the vector vaccine against two different H5N1 subtypes: one occurred in 1997 in Hong Kong during a virus outbreak, the other in Vietnam in 2004.

Successful protection against H5N1
Can cross-reactivity be generated with the two vector vaccines? Does this therefore also result in immunity to distantly related strains of the virus? The researchers vaccinated mice with each of the two vectors and then tested the vaccine protection against three different H5N1 influenza subtypes. The experiments, conducted in collaboration with virologists from the Erasmus University in Rotterdam, were successful: both vaccines gave the mice immunity against all the tested pathogens [1], they induced a cross-reactivity against various H5N1 isolates. The researchers were not satisfied with this evidence of efficacy in mice: they vaccinated cynomolgus monkeys (Macaca fascicularis) with their vaccine. They were also protected against various H5N1 isolates and they tolerated the vaccine well [2].

Overcoming bottlenecks in the production of vaccines
This vaccination not only seems to be safe and effective, the production of such MVA-based vaccines is also independent of the existing production capacities for conventional influenza vaccines. In the battle to prevent pandemics, a vaccine produced in this innovative manner could solve two problems at once: the sufficiently rapid production of adequate quantities of vaccine.

Vector vaccines
With vector vaccines, researchers introduce one or more genes of the pathogen into the genome of an infectious, but harmless virus. The virus enters the host cells. There, the foreign gene is transcribed and the corresponding protein is formed. Cells of the immune system present fragments of the formed proteins on their surface. The organism produces antibodies against the foreign protein – and thereby develops the desired immunity.

Literature
Work in focus – viruses and how we can protect ourselves from them

// COMBATING NEW PATHOGENS – PREVENTING THEIR SPREAD //

Vaccinations are the most effective protection against dangerous viral infections. Vaccines for combating viral infections are therefore among the most important biological medicinal products in the world.

The Virology division coordinates the majority of marketing authorisation procedures for viral vaccines, especially at a European level. In addition, the division's experts assess the viral safety of biological medicinal products as well as virus inactivation procedures. In its own research projects, its scientists are looking for strategies for the development of new vaccines and are working on procedures to further increase viral safety.

**VIRAL VACCINES**

Molecules that protect against serious diseases

This section guarantees the quality, efficacy and safety of viral vaccines – not just for Germany, but also to a large extent for Europe. The range of viral vaccines is now very broad: it includes 15 classes of vaccines with well over 100 products, e.g. vaccines against influenza, hepatitis A and B, mumps, measles, tick-borne encephalitis TBE and even the first HPV vaccines to protect against cervical cancer. The section's regulatory activities are equally extensive. The work involved in maintaining marketing authorisations for viral vaccines is significant: in general, around 20 follow-up measures are defined during the marketing authorisation stage, i.e. supplementary examinations are agreed. In 2007/2008 the section handled a total of 405 subsequent procedures. The batch testing of biological medicinal products is extensive. It always includes a comprehensive review of the manufacturing process documentation. In 2007/2008 the section tested 3,607 batches, 793 of them experimentally.

**Spotlight on the manufacturing process**

With chemically defined medicinal products, the molecular structure of the active substance is known and can generally be verified using physicochemical methods. With biological medicinal products, this is more difficult: in most cases, we are dealing with large molecules with a very complex structure. The higher the molecular weight of a biological active substance, and the more modifications it contains, such as special protein folds or additional attached groups of molecules, the more difficult it is to reliably characterise the final product and to check its quality. This is especially true of vaccines, which are among the most complex biological medicinal products. A precise description of the manufacturing process and a checking of this description are therefore central to the quality control of biological medicinal products.
AIDS, NEW AND EMERGING PATHOGENS
The search for the right weapon

Worldwide, more than 40 million people are infected with HIV, the Human Immunodeficiency Virus. Although many approaches have been tried, to date no vaccine is available. To combat such a versatile virus, new strategies are required. This section is conducting intensive research in this area: its virologists are investigating how the viruses mutate in patients and are searching for new ways for developing a vaccine.

"Mock-up" vaccines

The concept of "mock-up" vaccines ensures that, in an emergency situation, regulatory measures do not delay the provision of a vaccine. For pathogens which virologists consider likely to produce dangerous variants as a result of mutations, a vaccine is manufactured and authorised for a virus subtype. In the event of an imminently probable pandemic, the marketing authorisation for the mock-up vaccine is modified for the pandemic subtype in a fast track process. The manufacturers only change the virus strain – the previously authorised production process and the formulation remain the same. The division is involved in this procedure to a significant degree.

VIRAL SAFETY
Product safety starts with production

Biological medicinal products must be free of viruses. With blood products, this is guaranteed not only by the selection of donations, but also by special procedures in the manufacturing process which inactivate or remove any viruses that may be present. This section’s staff assess and experimentally check the various procedures. Of particular interest in this regard are viruses which are difficult to inactivate, such as hepatitis A, hepatitis E and parvoviruses. In addition, the staff can provide the service of assessing the viral and TSE safety (protection against prions) of biological medicinal products, as well as of investigational medicinal products in the context of clinical trials. In 2007/2008 the section assessed the viral safety of medicinal products in 125 marketing authorisation procedures and in 261 clinical trials. The PEI is the only European marketing authorisation agency where experts who conduct experimental research also evaluate viral safety.

MOLECULAR VIROLOGY
Detection methods must keep pace with developments

The work does not stop with the marketing authorisation – marketing authorisations and subsequent procedures in 2007/2008

<table>
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<th>2008</th>
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<td>Centralised marketing authorisations</td>
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<td>1 (3)</td>
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<tr>
<td>Subsequent procedures, MRP2 / DCP3</td>
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<tr>
<td>National marketing authorisations</td>
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</tr>
<tr>
<td>Subsequent procedures, national</td>
<td>55</td>
<td>37</td>
<td>92</td>
</tr>
</tbody>
</table>

1 CMS Concerned Member State
2 MRP Mutual Recognition Procedure
3 DCP Decentralised Procedure

In 2007/2008 the Virology division dealt with a total of 405 subsequent procedures.
The PEI is one of the few agencies in Europe carrying out the testing of plasma pools on a large scale.

Continuous further development of molecular biological technologies means that an ever more sensitive detection of viral components is possible in biological medicinal products. The section assesses in-house methods for the various divisions of the Paul-Ehrlich-Institut: for the detection of molecular viruses, for example, blood establishments often use (in-house) methods that their own laboratories have developed themselves. In the context of clinical trials or marketing authorisation procedures, the section tests these methods – partly by replicating them on a laboratory scale. In addition, the staff develop and establish their own methods for detecting viruses in biological medicinal products and blood products such as plasma.

According to European regulations, official medicines control laboratories must test plasma pools from which, for example, factor concentrates and albumins are obtained. The section tests plasma pools for viral contaminations: many international manufacturers opt to have this testing conducted by the PEI, but the Institute is also commissioned by other European agencies. As part of the testing laboratory for in vitro diagnostic devices, the section’s experts also evaluate the tests used there.

Reference material for rapid prion test

Since the appearance of BSE in the mid-80s, there has been a debate about testing blood donations for prions. In humans, infection with pathogenic prions results in variant Creutzfeldt-Jakob disease, vCJD. The collective term for brain diseases caused by prions is Transmissible Spongiform Encephalopathy TSE. The first blood tests are now becoming available. To assess whether the tests are effective in detecting prions, samples from the asymptomatic phase before the infection are required. In a cross-divisional collaboration, the experts from Veterinary Medicine obtained samples from primates in the incubation period. These are the only samples available in Europe for the evaluation of the tests. Other research topics include:

- In 2007/2008, on behalf of the Federal Ministry of Health, the division’s experts, working in conjunction with the Robert Koch-Institut, identified the potential risk of West Nile virus in Germany. Mosquitoes transmit this pathogen, which has resulted in several hundred fatalities in the U.S. alone. The experts consider sporadic outbreaks to be possible in Germany, but do not see any great danger.
- Can tick-borne encephalitis TBE also be transmitted from human to human via blood products? The virologists have been addressing this issue since 2008. Research funds have been applied for to investigate this topic more closely.

Colours play a major role in the laboratory as indicators

Selected activities/publications/appointments

- Prof. Gerd Sutter, Strategic Advisory Group of Experts SAGE - WHO;
  Member of the Editorial Board of the Journal of Virology
- Dr Michael Pfleiderer, Vaccine Working Party (Chair) - EMEA
- Dr Johannes Blümel, Dr Michael Pfleiderer, Biologics Working Party BWP - EMEA
- Dr C. Micha Nübling, Pharmacogenomics Working Party PgWP - EMEA;
  Working Group on Common Technical Specifications for IVDs, EU

Appointment:
- Prof. Gerd Sutter, Ludwig Maximilian University of Munich (Chair of Virology)

Event:
- 17th International Poxvirus and Iridovirus Conference, 7-12.06.08, Grainau

>> www.pei.de/virology
>> www.pei.de/virology-research
The testing laboratory for in vitro diagnostic medical devices, PEI-IVD, has a special position within the Institute: while the specialist divisions work according to the Medicinal Products Act AMG, the testing laboratory is governed by the Medical Devices Act MPG.

This was not always the case – up to June 2000 in-vitro diagnostic medical devices were also subject to the Medicinal Products Act and the PEI tested and authorised them. This situation changed as a result of European harmonisation. Since that time, these diagnostic devices have been considered medical devices for which a CE marking is compulsory. For certain high-risk products, manufacturers may not undertake this CE marking themselves, but must have the products assessed and certified by independent "notified bodies" in accordance with the applicable European directives. Manufacturers have a free choice of which notified body they wish to commission to carry out the certification. This body in turn decides with which recognised testing laboratories it wishes to work. The testing and evaluation of in vitro diagnostic devices is therefore a private-sector market. The PEI-IVD is part of the Institute, but acts externally as a private-sector organisation and is in competition with other national and international laboratories.

PEI-IVD defends its good market position

The staff are highly experienced in the evaluation and testing of in vitro diagnostic medical devices: for 25 years they were responsible for granting marketing authorisation and for official batch release on a national level, before European harmonisation was introduced. Safe and sensitive diagnostic devices make a significant contribution to the safety of blood and blood products in Germany. The aim of the testing laboratory is that the high level of health protection that was achieved under the Medicinal Products Act should continue to be maintained under the new arrangements – the new regulation covers blood screening tests for pathogens such as HIV or hepatitis B and C.

The testing laboratory works with notified bodies in Germany and Europe. Although it now faces international competition, PEI-IVD continues to be responsible for the majority of the tests used in the blood donation field, thus guaranteeing safety. In addition, the staff also conduct scientific studies and test evaluations on behalf of manufacturers. The testing laboratory has already participated in the assessment of more than 600 different in-vitro diagnostic devices. The testing capacity is around 2,000 product batches per year.

International cooperation for safe blood products

The PEI-IVD's experts are active on numerous national and international boards and are involved in a range of international studies. An example of this is the support they provide to the Collaborating Centre for the International Consortium for Blood Safety ICBS, for whom they compare test kits for use in countries with limited resources. PEI-IVD also works with the WHO's Collaborating Centre for Quality Assurance of Blood Products and In Vitro Diagnostic Medical Devices in the development of international standard materials for the detection of HIV, hepatitis B and C viruses and other pathogens. For example, in 2007/2008 the testing laboratory staff were responsible for developing an international standard for the hepatitis B antibody test (anti-HBc), which was adopted by the WHO in October 2008. For the third time in five years, PEI-IVD colleagues worked for the WHO on site in Geneva on a secondment basis.

Notified bodies

Notified bodies are neutral organisations which assess the conformity of products. Certification bodies for medical devices must be accredited in Germany as a notified body by the Central Authority of the Länder for Health Protection Regarding Medicinal Products and Medical Devices ZLG. Manufacturers of medical devices can freely choose between the various notified bodies. These bodies in turn commission accredited testing laboratories such as PEI-IVD with the assessment and testing of in vitro diagnostic medical devices.

Selected Activities

- Dr Sigrid Nick, Working Group on Common Technical Specifications for IVDs
- Dr Sigrid Nick, Joint Diagnostics Committee of the German Association for the Control of Viral Diseases DVV and the German Society of Virology GfV
- Reference laboratory for INSTAND e.V.

>> www.pei.de/ivd-en
Clinical trials were handled by the Immunology division in 2007/2008. The attenuated poxvirus is considered a suitable candidate for the development of vaccines.
Explaining these mechanisms could help to combat pathogens more successfully and make vaccines even more effective. This is why Zoe Waibler and her colleagues from the Immunology division are keen to find out more about them. For their research they selected, from the body’s various defence mechanisms, the type I interferon response. This forms part of a human being’s innate immune system and without it life would be impossible.

Useful tools for immunologists

The researchers examined two different poxviruses in mice. Smallpox has, of course, been eradicated in human beings, but since September 11, 2001 smallpox vaccines have been back on the political and scientific agenda on account of the fear of bioterrorism. In addition, there is always a risk of zoonotic diseases, the transmission of poxviruses from animals to humans. “Poxviruses are also useful tools for immunologists,” says Waibler, “because they have a large number of immunomodulators and can therefore influence the immune response of the host that they attack.” Additional genes can also be incorporated in the virus, which can then smuggle antigens into the cells as if on piggyback to create a vaccination. There are now a number of attenuated poxviruses which are being researched as promising vaccines. The modified vaccinia virus Ankara MVA is one such attenuated, and therefore non-dangerous, poxvirus. Among other things, MVA triggers a strong interferon response – unlike the vaccinia virus VACV, with which there is no detectable interferon response.

Viral Escape or attack?

The so-called Toll-like receptor 9 TLR9 is used as the cellular sensor for viruses whose genetic information is present in the form of DNA. In fact, the researchers were sure that MVA would also disappear from the immune system’s radar if TLR9 was switched off. Far from it – MVA remained visible even without TLR9 and generated the usual interferon response. “This was a huge surprise, and probably also the reason why we could publish our data so well,” says Waibler. It did not stop there. The second big surprise soon followed. Even if the scientists switched off important adapter molecules, there was still an interferon response. In this way the researchers had demonstrated that there must be another system that acts as a sensor.

If there are in fact several sensors, the question is what prevents the vaccinia virus from being seen. Does it lack the detectable structures, or does it have its own weapons with which it can disable the interferon response? The researchers found the answer by simultaneously infecting mice with both virus types. The interferon response was missing, although it was still detectable on infection with MVA. This is evidence that the vaccinia virus actively suppresses the interferon response. Viral protein B18 is involved in this inhibition: it acts like a fishing rod to catch the circulating interferon and thus prevent it from having any effect. In addition, there is a previously unknown interferon inhibitor within the cells, and in this case the working party has already identified six possible candidates.

If Waibler and her colleagues can find out what mechanisms block this interferon response, this could revolutionise the treatment of autoimmune diseases such as lupus erythematosus or rheumatoid arthritis, because chronic inflammatory conditions are often associated with high levels of type I interferon. Waibler has now taken over the leadership of the “New Vaccination Strategies and Early Immune Responses” temporary research group and is continuing to work intensively on solving this puzzle.

Literature

Therapeutically, they work by blocking the growth of tumour cells in the treatment of breast and colon cancer. They are also used for certain forms of leukaemia or lymphoma. In that case, they attach themselves specifically to tumour cells and make them visible to the body’s own immune system – the cancer cells then become fair game and can be specifically targeted by cytotoxins linked to antibodies. Other antibodies help to suppress the immune response in the case of organ transplantation or rheumatism. Scientists worldwide are working intensively on such innovative therapies.

Vaccination as therapy
This is not, however, the only innovative product group for which the division is responsible: therapeutic vaccines represent a new avenue for research. These are able to cure existing diseases by activating the body’s own immune system against the cause of the disease. The Immunology division therefore focuses on the assessment and approval of the necessary clinical trials and the assessment of these products in marketing authorisation procedures. In addition, the division’s staff advise companies that are developing such therapies.

MONOCLONAL AND POLYCLONAL ANTIBODIES
European leader in advice and marketing authorisations
Since 2001 monoclonal antibodies have been authorised via the EMEA in the centralised procedure as genetically engineered biological medicinal products – in December 2008, 18 of them were on the market. The PEI is jointly responsible for seven of them, i.e. for more than one third of all monoclonal antibodies authorised in Europe. This underlines the crucial significance of the division for the safety and efficacy of this product group, which is so important for modern therapies. Progress is also being made with polyclonal antibodies: between 2006 and 2008 a total of three polyclonal antibodies received central marketing authorisation. Thanks to its great expertise in this area, the PEI was involved in all the procedures as Rapporteur or Co-Rapporteur.

The growing importance of antibody-based cancer therapy is reflected in the greatly increased number of clinical trials to test these modern therapies. In 2007/2008 the division assessed a total of 233 applications for clinical trials. After the 2006 TeGenero disaster in London, there has also been a significant increase in the number of pharmaceutical companies seeking advice and receiving a risk assessment from the
Monoclonal and polyclonal antibodies

Monoclonal antibodies are derived from a cell clone which goes back to a single B-lymphocyte. All the antibodies of this cell clone target a quite specific section of an antigen. Polyclonal antibodies, such as those included, for example, in vaccines for passive immunisation, are mixtures of antibodies produced by different B cells. They target different surface structures of the same antigen.

PEI’s experts in advance of clinical trials. On a national level alone, the division provided 84 advisory consultations.

THERAPEUTIC VACCINES

Vaccines in cancer therapy

Unlike traditional vaccines that prevent disease, therapeutic vaccines are designed to cure an existing disease by active immunisation. The main area of indication is tumour diseases, but one day it will be possible to use them to treat neurodegenerative diseases such as Alzheimer’s, hypertension or diabetes.

By the end of 2008 no products had as yet been authorised, but pharmaceutical companies are working intensively in this area. Accordingly, the requirement for scientific advice from experts is also large. The development of new therapies entails corresponding clinical trials: in 2007/2008 the section worked on a total of 20 clinical studies. Some therapeutic vaccines are based on human somatic cells and are therefore considered to be “advanced therapies”.

With regard to the development of these novel therapies, it must be determined how they are to be tested, what needs to be considered in the marketing authorisation procedure, and what risks must be taken into account. The section’s staff are involved to a large extent in the formulation of European Commission laws and EMEA guidelines. In addition, the section also assisted in GMP inspections of production sites.

IMMUNOLOGY

IMMUNOCHEMISTRY

Focusing on pharmaceutical quality

Ensuring pharmaceutical quality is the responsibility of the Immunochemistry section. Its staff determine and experimentally assess the chemical, biochemical and physicochemical parameters of the preparations which are undergoing marketing authorisation or which have already been authorised. In addition to the active substance and excipients, such as stabilisers and preservatives, they also focus on possible impurities. The preparations’ properties, such as solubility and appearance, are also checked. The section examines not only preparations from its own division, but also the pharmaceutical quality of products from other divisions. In 2008 alone it tested 1,260 batches of medicinal products, as part of either batch testing or CAP testing.

CAP Testing — Testing of Centrally Authorised Products

Since 1998 the testing of Centrally Authorised Products has been used for the quality assurance of medicinal products authorised in the EU. Each year the EMEA selects around 40 preparations for testing. The official test laboratories in Europe apply to the European Department for the Quality of Medicines EDQM in Strasbourg for the testing of products, which is then assigned to the laboratories according to their expertise. For each product, samples are taken from three different countries and analysed in comparison with a batch that comes directly from the manufacturer. Every year, in the context of CAP testing, the PEI analyses medicinal products from different product groups, such as monoclonal antibodies, recombinant coagulation factors and also veterinary products.

In addition, the staff assess the pharmaceutical quality of monoclonal and polyclonal antibodies as part of marketing authorisation procedures and scientific advice. They are involved in the development of EMEA guidelines and European Pharmacopoeia monographs. These define requirements for

Clinical trials of monoclonal antibodies

The number of clinical trials of monoclonal antibodies has increased tenfold since 2004.
the quality, manufacturing, testing, storage and dispensing of medicinal products. In 2008 the section assisted in the revision of the monograph for monoclonal antibodies and in the development of an EMEA guideline specifying the quality requirements for medicinal products in clinical trials.

MORPHOLOGY
Looking at the little things
The morphology section is the central service unit for advanced methods in light and electron microscopy. It is equipped with transmission and scanning electron microscopes, several fluorescence microscopes, and a laser scanning microscope. It prepares microscopical specimen for all the Institute’s divisions and examines and documents them in collaboration with the relevant working groups. In its own research, the section’s staff are studying the endogenous retrovirus HERV-K, whose genome has been integrated in the human genome for millions of years. It is no longer infectious, but can form particles which are visible by electron microscopy. Why the virus genome has been retained in the human genome for such a long time, why it still produces virions, what is its function – these are questions that have yet to be answered.

Selected activities/publications/appointments

- Dr Jan Müller-Berghaus, Scientific Advice Working Party - EMEA
- Dr Thomas Hinz, Cell-based Product Working Party - EMEA; Working Party on Cell-based Products CPWP - EMEA
- Dr Siegfried Giess, Working Group MAB Monoclonal Antibodies - EDQM

Publication:

>> www.pei.de/immunology
>> www.pei.de/immunology-research
This is based on the conviction that in order for the Institute to successfully perform its regulatory duties and provide the best possible policy advice, it is essential that its own research should be on a par with that of the world’s leading research institutes and companies that carry out research. Professor Stefan Vieths, the Research Manager, and Dr Stephan Steckelbroeck, the Head of the Research Office, are responsible for co-ordinating the further development of the Institute’s research infrastructure. Every three to four years, in close coordination with the research scientists and the Institute’s management, they update the research programme and thus set out the strategic direction.

The objectives of research are clearly defined by the duties of the PEI: the optimisation of the quality, safety and efficacy of biological medicinal products. The scientists improve methods for batch testing and produce international standard preparations for experimental testing. In addition, basic research has a very important role. The priorities here are new vaccines, therapies and innovative diagnostic approaches, as well as the immune response and pathogen-host interactions.

Duties of Research Co-ordination

The research co-ordinator and research officer chair the Research Working Party, in which all the PEI’s research groups work together on the further development of the Institute’s research infrastructure. They co-ordinate joint activities and pool resources through the creation of common research equipment and service platforms. Every year a research retreat is held over several days, bringing together all the researchers for the purpose of scientific exchange, which gives rise to many cross-divisional projects. One example of this is a project on desensitization in food allergy. In addition, every year Vieths and Steckelbroeck record and evaluate the research performance by means of publication lists, lecture lists and other indicators of scientific performance. They provide support to scientists in applying for external funding from national and international research funding bodies. Another important duty is handling enquiries, for example from the Federal Budget Committee with regard to cooperation with universities. In addition, the two scientists are involved on behalf of the Ministry in matters of scientific policy, such as the elaboration of the Concept of Modern Federal Research.

PEI’s Postgraduate training is a unique feature

Around 50 postgraduate students work at the Institute. To enable them to take advantage of the unusual combination of regulation, marketing authorisation and research as an additional qualification, the Research Manager and Head of the Research Office have developed a postgraduate programme. It offers a competitive course of advanced training in the basic research areas of virology, microbiology, immunology, allergology, cell and gene therapy, as well as in the field of adverse reactions to medicinal products. A series of lectures gives the young scientists an insight into all areas of the PEI – from the Legal Affairs unit, by way of administration, to marketing authorisation, batch testing and research.

Quality assurance in federal research

Between 30,000 to 40,000 scientists in Germany work in federal research institutes. The public is hardly aware of them – unlike, for example, the Helmholtz Association or the Max Planck Society. The Working Group of the Federal Research Institutes, which was founded in early 2005, regularly brings together representatives from 38 federal research institutes for an informal exchange of experience. Other objectives include the increased visibility and acceptance of federal research, as well as quality assurance and the promotion of young researchers based on common criteria. In this regard, the PEI’s research co-ordinator and research officer have actively participated, as representatives of federal research, in shaping the “map of non-university health research”. This documents the federally-funded research taking place outside universities and companies.
of experimental animals can be saved in the testing of vaccines against rabies, thanks to the PEI alternative test.
While the efficacy of live vaccines can in general be tested in the laboratory, the efficacy of inactivated vaccines is often tested by means of challenge tests in animals. For instance, the European Pharmacopoeia still prescribes an infection study in mice for the potency testing of inactivated rabies vaccines for animals. The mice are vaccinated with various dilutions of the vaccine being tested and are then infected with the rabies virus after two weeks. The measurement of efficacy is represented by the least possible amount of vaccine that allows the vaccinated animals to survive.

Antibody assays as an alternative method

Dr Beate Krämer, laboratory manager for batch testing of viral and combined vaccines at the PEI, and her colleagues were not satisfied with this and so five years ago began working on the development of an alternative test method – alongside the routine testing. Their research should soon bear fruit: the new alternative method is based on determining the quantity of antibodies (antibody titre) formed against the rabies virus in the blood of the test animals. Krämer was able to demonstrate that the antibody titre clearly correlates with the level of protection provided by vaccination, so that antibodies can therefore be used to determine whether the vaccine is effective. The European Pharmacopoeia allows such tests if there is a large degree of consistency between the alternative method and the challenge test. The PEI researchers were also able to demonstrate this, which meant that the challenge test could be replaced in Germany.

• The serological alternative test saves around 90 percent of the test animals. For the testing of rabies vaccines, the PEI only used 1,302 animals in 2007 and 2008, instead of 13,064, i.e. 11,762 mice were spared unnecessary suffering, as they did not have to be infected with the rabies virus.
• All the European testing laboratories recognise the test results obtained with the alternative method.

Subsequently, all the vaccines on the European market were successfully tested in Germany using the alternative test method. The next step was to convince the testing laboratories of the other EU member states. Despite a certain initial scepticism, the European testing bodies and the pharmaceutical industry have already agreed to test the alternative method in a Europe-wide round robin test. If all the parties obtain consistent results in the round robin test, the challenge test can be replaced and the industry and the national European testing bodies will be able to implement the new method. The goal of the Veterinary Medicine division is to have the challenge test erased completely from the European Pharmacopoeia and replaced by the alternative test model which will be described in detail.

All these efforts proved worthwhile: in December 2008, Dr Beate Krämer was awarded the 2008 Hessian Animal Welfare Prize. This was a personal recognition for her work in the batch testing of virological medicinal products for veterinary use, and also a special tribute to the entire division. Whether inactivated rabies vaccines protect animals against the threat of infection can now be determined by measuring the antibodies against the rabies virus in the serum of mice, without, as before, having to expose these mice to the great suffering caused by a challenge test. The staff of the Veterinary Medicine division have for a long time demonstrated a commitment to improving testing methods and protecting animals: they have been working on alternative methods for almost two decades. The results they have obtained have often led to the desired changes in the relevant pharmacopoeia monographs. With the deletion of animal testing in favour of in-vitro test methods, with the replacement of challenge tests by specific antibody assays, and with the reduction in the number of animals used in each study, the Veterinary Medicine division is making an active contribution to animal welfare. For this reason, its staff have been awarded several animal welfare research prizes.
These products play a central role in veterinary medicine: the approximately 400 authorised vaccines alone account for around 20 to 25 percent of all medicinal products for veterinary use. These include the rabies vaccine for foxes in the wild, as well as vaccines for pets, farm animals and fish. The testing and licensing duties are undertaken by the sections “Bacterial Vaccines and Immune Sera” – immune sera, bacterial vaccines, parasite and fungal vaccines – “Viral Vaccines I” – viral vaccines for poultry – and “Viral Vaccines II” – viral vaccines for all other species, and also immunomodulators. The “Animal Facilities” section is responsible for looking after all the animals at the Paul-Ehrlich-Institut. Maintaining animal health, consumer protection and protecting people from zoonotic diseases are the most important duties and objectives of the Veterinary Medicine division. Scientific exchange is also high on the agenda for Veterinary Medicine: although the PEI reports to the Federal Ministry of Health BMG, the professional exchange of information by the Veterinary Medicine division is primarily with the Federal Ministry of Food, Agriculture and Consumer Protection BMELV. In addition, the division works closely with the Federal Research Institute for Animal Health – the Friedrich-Loeffler-Institut FLI – and with the Federal Office of Consumer Protection and Food Safety BVL. The PEI and FLI advise the Federal Ministry of Food, Agriculture and Consumer Protection and the federal states on the development of strategies for the official control of diseases such as rabies, bluetongue and avian influenza. It also engages in expert scientific cooperation with various universities and non-university research institutions at a national and international level.

**Product diversity in veterinary medicine**

The Veterinary Medicine division is internationally renowned for its high level of expertise. A wide range of medicinal products from the fields of virology, bacteriology, mycology and parasitology are available in Germany for a variety of animal species that live under various conditions as domestic, farm or wild animals. Consequently, the scope of the regulatory and scientific testing is considerable. This testing of the quality, safety and efficacy of immunological veterinary medicinal products always takes into account the vaccination condi-
Improving test methods in order to protect animals is a matter of urgent concern for us here in the Veterinary Medicine division. At the PEI we have been working for years on methods that can be used to replace animal testing. We would like to invite everyone to abandon old ways and to look for new test methods that will help to avoid animal testing and thus minimise suffering.

Dr Beate Krämer, laboratory manager for the batch testing of viral and combined vaccines
With both avian influenza and bluetongue disease we had to act quickly, because there was imminent danger.

**VIRAL VACCINES**

**Bluetongue disease and avian influenza**

Bluetongue disease and bird flu: two animal epidemics which called for rapid and coordinated action in 2007/2008. The first cases in Germany of bluetongue disease, a viral infection (bluetongue virus – BTV) transmitted by small blood-sucking midges (Ceratopogonidae), which mainly affects ruminants (sheep, cattle, goats and wild ruminants), occurred in 2006, initially in the border area around Aachen. By the end of the year, further cases had been recorded in North Rhine-Westphalia, the Rhineland-Palatinate, Saarland, Lower Saxony and Hesse. The recurrence of the disease in North Rhine-Westphalia in the early summer of 2007 showed that the bluetongue virus, which is not actually native to Central Europe, can survive the winter. The disease spreads rapidly to the north, south and east. Around 21,000 infected animals have been recorded in Germany alone. At that time no vaccine was available. On account of the high level of economic damage that bluetongue disease caused for owners of sheep, cattle and other ruminants in Europe in 2007, the European Union decided that a mass programme of vaccination should be carried out, with at least 80% of all endangered animals being vaccinated. This was the largest vaccination campaign since the fight against foot and mouth disease in the 70s and 80s, with around 20 million doses of vaccine being procured in 2008 in Germany alone.

Under the direction of the Hessian State Ministry of the Environment, Rural Development and Consumer Protection HMULV, a Europe-wide tender procedure was implemented for all the federal states for the procurement of BTV vaccines targeting the current serotype 8 of the bluetongue pathogen.

Thanks to the combined efforts of the Bluetongue Taskforce of the Federal Ministry of Food, Agriculture and Consumer Protection, the federal states, the FLI and the PEI, it was possible to supply vaccines against the current serotype. The application of these vaccines was enabled by an Emergency Ordinance of the Federal Ministry of Food, Agriculture and Consumer Protection, which ordered the vaccination. In accordance with this, farmers and livestock owners are obliged to have all cattle, sheep and goats vaccinated against bluetongue disease. The first vaccination campaign took place in May 2008 and was continued in 2009.

As the fight against bluetongue disease is a European concern, in 2007 the Committee for Medicinal Products for Veterinary Use of the European Medicines Agency EMEA established minimum requirements for such “emergency vaccines”, which in 2008 were formulated in a guideline, which has now come into effect. In this regard, the PEI’s main contribution is to ensure that the products used are of perfect quality and are safe for the animals being vaccinated. The

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**Withdrawal periods for food-producing animals**

Animals used for the production of food must be healthy: vaccines play a big part in this. At the same time, however, it must be ensured that consumers do not absorb the vaccine through the consumption of meat, milk or eggs. It must be tested whether the administration of such a product will affect the quality of this food. With animal vaccines – as with veterinary medicinal products – a withdrawal period may, if necessary, be defined, during which the regulated animal products from vaccinated animals may not be used for human consumption.
likely efficacy of the "emergency BTV vaccines" was estimated in Germany by the PEI based on this guideline and on scientific field trials conducted by the FLI, with subsequent challenge tests in sheep and cattle. The success of this large-scale vaccination could already be seen in the third quarter of 2008, when around 5,000 cases of bluetongue disease were recorded, compared with nearly 21,000 cases in 2007. The vaccination had therefore been successful in preventing the further massive spread of the bluetongue pathogen. This is particularly apparent in the almost complete protection that the eastern federal states received against outbreaks of BTV.

Bird flu, which is known in scientific circles as avian influenza, also called for special measures. In 2004 there was an outbreak in the Netherlands with an H7 variant of the virus. Since then, the Veterinary Medicine division has been watching developments closely. It soon became clear that the rampant bird flu in Asia also represented a threat to Europe, on account of its ease of transmission and the travel patterns of animals and humans.

For this reason, in 2006 a reflection paper was drafted by the Immunological Working Party of the EMEA’s Committee for Medicinal Products for Veterinary Use. This paper defined minimum requirements for the marketing authorisation of vaccines for such emergencies. Based on this, a guideline was drawn up specifying the requirements for the vaccination. Subsequently, companies submitted four applications for the marketing authorisation of vaccines against avian influenza at an EU level, as well as a national application for Germany. In 2007 the vaccines received marketing authorisation.

**ANIMAL FACILITIES**

Different needs are taken into account

The division looks after the animals for the whole Institute. The staff obtain the animals, care for them, attend to the legal requirements and offer their expertise in the performance of animal testing. The requirements on the keeping of experimental animals are very strict: the staff are responsible for ensuring the welfare of the animals in terms of their housing and feeding. This task is very diverse, given the different types of animals that are looked after, and ranges from supplying the right food, ensuring that the cages are sufficiently large, even down to providing appropriate toys.

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### Selected activities/publications/appointments

- Dr Manfred Moos, Committee for Medicinal Products for Veterinary Use CVMP - EMEA;
  Group 15V at the European Pharmacopoeia - EDQM
- Dr Carmen Jungbäck, Immunologicals Working Party IWP in the CVMP - EMEA;
  GEON advisory group - EDQM
- Dr Esther Werner, Co-ordination Group for Mutual Recognition and Decentralised Procedures - Veterinary CMDv - HMA
- Dr Karin Duchow, German Standing Vaccination Committee for Veterinary Medicine (StlkoVet)
- Dr Roland Plesker, German Society of Primatology (GfP)

>> [www.pei.de/veterinary-medicine](http://www.pei.de/veterinary-medicine)

>> [www.pei.de/veterinary-medicine-research](http://www.pei.de/veterinary-medicine-research)
1,725 products are the responsibility of the Allergology division. Biotechnological preparations are currently in development, such as the birch pollen allergen Bet v 1.
// NEW STRATEGIES FOR COMBATING FOOD ALLERGIES //

Allergies are on the rise among the general population. In Europe, one in four children under 10 suffers from allergies. Both symptomatic treatment with antiallergics as well as specific immunotherapy, for example against pollen or insect venom, are established treatment methods.

There is, however, still no cure for food allergies. In this case, the risk of severe adverse effects from desensitisation is too great. People with allergies to a specific food are therefore at risk of accidentally ingesting an allergen hidden in food, for example traces of peanuts or hazelnuts. For some people this can lead to life-threatening anaphylactic shock.

The Allergology division specialises in research on food allergies and pursues several approaches.

Allergy research for diagnosis and therapy

In order to develop targeted immunotherapies against food allergies, the causative agents must first be identified. The scientists are investigating which allergens in food, such as peanuts, hazelnuts or soy beans, can trigger an allergy and are examining their structure. Some allergens have an unusually high biological activity and therefore often trigger serious reactions. These molecules can therefore be considered as diagnostic markers for serious allergic reactions: allergic patients who are sensitised to these proteins are at a particularly high risk. At the same time, such allergens are important target structures for the development of innovative immunotherapeutics. The systematic identification of the allergens’ binding sites for the allergy-triggering IgE antibodies is an important prerequisite for the design of new therapy allergens with improved immunological properties.

The scientists are pursuing three different strategies to enable the best possible immunotherapy for these highly potent allergens:

- Genetic engineering of the allergen: the first strategy the scientists are employing is genetic modification of the dangerous allergen in order to reduce the rate of adverse reactions during immunotherapy. The allergen is modified so that the IgE antibodies of the allergic patient can no longer bind. It is these IgE antibodies that trigger symptoms. If binding to the allergen is eliminated or strongly reduced, serious allergic reactions are very unlikely.

Researchers want to immunise patients with these attenuated allergens so that they no longer react to the unmodified allergen later on.

- Development of fusion proteins from allergens and immunomodulators: in this method researchers fuse or link the allergen with a component of bacteria that is known to induce a desired immune response through so-called T-helper 1 cells. In allergic patients, the undesirable T-helper 2 cell response prevails. Treatment with the fusion protein should re-direct this modified balance back in the direction of a normal immune response.

- Development of a vaccine: the scientists are working together with virologists on a cross-divisional basis to introduce genes of the allergen into human cells via the modified vaccinia virus Ankara MVA so that they produce an allergen. In contrast to normal desensitisation through application of external antigens, in this method antigen-presenting cells carry fragments of the allergen on their surface after endogenous biosynthesis. In this way, the immune system perceives them differently. This should significantly decrease the risk of serious adverse reactions. In addition, the virus enhances the immune response thanks to its immunomodulatory properties. The experiments conducted on this to date are very promising.

Literature

- Holzhauser T et al. (2009): Soybean (Glycine max) allergy in Europe: Gly m 5 (beta-conglycinin) and Gly m 6 (glycinin) are potential diagnostic markers for severe allergic reactions to soy. J Allergy Clin Immunol. 123(2): 452-458

- Reese G et al. (2007): Allergenicity and antigenicity of wild-type and mutant, monomeric, and dimeric carrot major allergen Dau c 1: destruction of conformation, not oligomerization, is the roadmap to save allergen vaccines. J Allergy Clin Immunol. 119(4): 944-951

The division’s main duties are marketing authorisation and batch testing of allergen products for specific immunotherapy and in-vivo diagnostics: the staff members handle around 1,800 authorised allergen extracts from all known European manufacturers and release around 2,000 batches per year. The PEI has a leading role in allergen regulation: many manufacturers in Germany are applying for marketing authorisation for their products for the first time. For this reason, its advisory duties were significant in 2007/2008 – encompassing 30 national consultations and three EMEA scientific advice procedures. Almost all allergen manufacturers active in Europe make use of the Institute’s advice services.

TEST ALLERGENS
Large demand for marketing authorisation after changes in the law

This section is responsible for the marketing authorisation of allergens for in-vivo testing. This includes allergen extracts for various kinds of skin tests, such as prick tests or intracutaneous tests. Doctors use epicutaneous test allergens to test patients for cell-mediated allergies, such as those caused by nickel. A nasal provocation test, in contrast, sprays the allergen extract into the nose. The section is responsible for a total of 1,725 products. At the end of 2008 the section was working on 409 current marketing authorisation applications. This high number was primarily due to a change in the 14th amendment of the Medicinal Products Act AMG, according to which test allergens could no longer be marketed as so-called named patient preparations for individual patients without marketing authorisation. They were widespread in the field of allergology. The legal transition period expired on 1 September 2008. Manufacturers had to have submitted a marketing authorisation application for all test allergens sold up to that point as named patient preparations – or take them off the market.

THERAPY ALLERGENS
A new regulation for increased safety

This section authorises allergen products for specific immunotherapy which contain natural extracts. The Allergology division successfully initiated a therapy allergen regulation, which took effect in November 2008. Manufacturers must now also obtain marketing authorisation for named patient preparations that contain therapeutically important allergens such as birch pollen or grass pollen extracts. The goal of the new regulation is patient safety: on the one hand it was previously impossible to draw conclusions about the efficacy
and safety of the named patient preparations because they were not subject to marketing authorisation and therefore did not undergo any independent evaluation of quality, safety or efficacy. In addition, in contrast to authorised products there was no obligation to report adverse reactions. Without proof of efficacy, it could not be ruled out that patients were receiving ineffective allergens. This represented a risk that, because of an unsuccessful therapy, escalation might occur, e.g. from hay fever to asthma.

All therapeutically important allergens and mixtures of various extracts which contain at least one of the therapeutically important allergens are now subject to marketing authorisation. Since the regulation took effect, the PEI has also been testing the batches of the source extracts for named patient preparations. If, for example, no allergenic activity is found in the samples, the product batch is not released and will thus not find its way onto the market. There is, however, a transitional period for proving clinical efficacy, given that multiple-year clinical studies are required for this. Manufacturers do have to prove that they are implementing the corresponding development programmes. At the end of 2008 the section was responsible for some 240 authorised allergen products. In 2007/2008 companies submitted six marketing authorisation applications, the section handled 54 notifications of variation and tested 1,550 batches, 1,482 of them experimentally.

CLINICAL ALLERGOLOGY

Assessment of allergy therapies

As a service section, the staff of Clinical Allergology assist the Test Allergens, Therapy Allergens and Recombinant Allergen Therapeutics sections with assessment tasks. They assess and evaluate preclinical data, the clinical efficacy and safety of allergen preparations, as well as applications for clinical trials.

Clinical testing of allergens is difficult because there is no objective biomarker in the blood which allows one to draw conclusions about the efficacy of the treatment. The assessment is thus based on the severity of symptoms experienced and recorded daily by patients and must take into account occasions on which when medications such as antihistamines suppress the symptoms. The placebo effect is quite prominent here. Evaluating long-term efficacy, for example in hay fever patients, takes many years. Some summers are worthy of the name, while others are cold and rainy, so that there are almost no allergy-triggering pollens in the air – these disruptive factors must be considered when evaluating efficacy. This requires many years of experience in evaluating data, which the section does indeed have.

RECOMBINANT ALLERGEN THERAPEUTICS

Genetically manufactured therapeutics

While biotechnology is essential in other product classes, allergy therapy still uses extracts from natural substances such as plant pollen, mites or insect poisons. On account of their natural origin, it is difficult to standardise the active allergen components. Depending on the weather conditions, the allergen content differs in plant pollen, for example. The extract also often contain proteins and other components against which there is no allergy. In the worst case scenario, substances that are unnecessary for the treatment could sensitize the patient.

For some years now, several companies have been working on developing genetically manufactured allergens with a high degree of purity and standardisation. Several such preparations are in Phase III clinical trials and submission of the first marketing authorisation applications is expected in the near future.

This section is responsible for these innovative allergen therapeutics and for all products that have been genetically manufactured or modified. At the end of 2008 no product had yet been authorised, but the section is providing advice during the development process. Genetically manufactured biomedical medicinal products require central marketing authorisation via the EMEA. On account of its high level of expertise, the Allergology division was involved in every EMEA scientific advice procedure as Rapporteur or Co-Rapporteur. It can therefore be assumed that the section will be involved to a large extent in the marketing authorisation of these allergen therapeutics for Europe.
Advanced Therapy Medicinal Products are highly innovative medicinal products based on genes, cells and tissue. For example, lentiviral vectors can attach to cells and transfer therapeutic genes.
Lentiviral vectors – carriers of nucleic acids from a sub-group of retroviruses – enable genes to be introduced into completely different cell types. To enable them to do this efficiently, they have been equipped with VSV-G, the envelope protein of another virus (vesicular stomatitis virus), for which many human cells carry the appropriate receptor on their membrane. In this way, the virus particle can attach to human cells, fuse with the cell membrane and introduce the therapeutic gene into the cell. But even the lentiviral vectors known to date are having a difficult time with one group of cells: non-dividing cells of the haematopoietic system – such as lymphocytes – cannot be “cracked” with these vectors.

Wanted: specialists, not generalists

The multifaceted nature of these vectors simultaneously restricts their possible applications: whether for a genetic disease or cancer, usually only one specific cell type should be genetically modified. The majority of the cells should remain untouched, also for safety reasons.

Can a lentivirus be constructed with an envelope protein that transfers the genes precisely into the cells where they are needed, efficiently and in a targeted manner? This is something that the researchers at the PEI’s Medical Biotechnology division have been investigating for years. And their patience has now paid off. Their success was not, however, with the VSV envelope protein; rather they are using envelope proteins of the measles virus that have been modified in a targeted manner. The haemagglutinin protein (H) is responsible for receptor recognition on the cell membranes and the fusion protein (F) is responsible for membrane fusion.

Other research groups also attempted to integrate the measles virus envelope protein into lentiviral vector particles, but it was PEI scientists who were the first to succeed – by means of “protein engineering”, i.e. the targeted shortening of both envelope proteins – in incorporating envelope proteins of the measles virus into lentiviral vector particles.

The second problem consisted in the modification of cell recognition by the haemagglutinin protein (H), which normally attaches to a receptor which is present on a whole range of human cells. To demonstrate proof of principle for their approach, the researchers focused on CD20, a marker of B lymphocytes. Firstly, they modified the H protein by mutation so that it could no longer bind to the natural receptors. The second step was to add an antibody fragment for CD20 recognition which – like a key to a lock – fit with the CD20 marker on B lymphocytes.

In order to demonstrate selective gene transfer into B lymphocytes, the scientists equipped the engineered vector particles with the gene for a green fluorescent protein (GFP). The green fluorescence was in fact only observed in CD20-positive B cells. This showed that targeted gene transfer into desired target cells with lentiviral vector particles that carry modified measles virus envelope proteins is indeed possible.

Even dormant cells cannot escape

Selective gene transfer was a great success. What was truly spectacular, however, was a finding of which the researchers had dared not dream: their lentiviral vector with the modified envelope proteins was also capable of transferring the genes into dormant B lymphocytes – which had previously been unattainable for gene transfer.

The researchers may even have developed a weapon with their new vector system which could attack a group of cells that was previously hardly therapeutically accessible and which plays an important role in the occurrence of metastasis – cancer stem cells.
The next step should tap into additional cell types for the gene transfer. Thanks to targeted protein engineering of the measles virus envelope proteins, the scientists want to create a collection of targeted lentiviral vectors that allow highly selective gene transfer into various defined cell types.

More safety in therapy with precision processes

The cell specificity of their targeted lentiviral vector could also mean a big step forward for the safety of gene therapy. In two clinical studies, leukaemia occurred in some patients treated with blood stem cells genetically modified by retroviral vectors— as a consequence of integrating the therapeutic gene at a critical location of the cell’s genetic make-up. The risk of malignant cell degradation is thought to be dose-dependent, i.e. the more vector particles used for modification, the higher the risk. A “targeting vector” could potentially decrease the risk significantly because the therapeutic gene will only be inserted into the clinically relevant cell types. The Paul-Ehrlich-Institut’s targeting lentivectors therefore offer a model that can be used to improve the efficacy and safety of gene therapy.

Literature

• Funke S et al. (2008): Targeted cell entry of lentiviral vectors. Mol Ther. 16(8): 1427–1436
• Funke S et al. (2009): Pseudotyping lentiviral vectors with the wild-type measles virus glycoproteins improves titer and selectivity. Gene Ther. 16(5): 700–705
In order to meet the challenges of complex biological medicinal products, many scientists at the Medical Biotechnology division combine their tasks in drug regulation with research.

**ADVANCED THERAPY MEDICINAL PRODUCTS, CONVENTIONAL TISSUE PREPARATIONS**

**Regulatory task force**

Research and development of Advanced Therapy Medicinal Products has increased enormously in recent years. Although no medicinal products had yet been authorised by the end of 2008, several applications had been submitted and were being assessed. Medicinal products for advanced therapies such as gene therapy and cell therapy and tissue engineering medicinal products are not only breaking new medical ground: the assessment of the applications for marketing authorisation in European bodies such as the CHMP and CAT gives rise to entirely new questions and challenges.

In order to take on a leading role in the authorisation of advanced therapies, the division has been supplemented by a section since the beginning of 2007 which exclusively handles authorisation duties. For each project, the assessors of this section work closely with their colleagues in other sections who conduct research and grant authorisations on a product basis. In 2008 alone they jointly handled more than 20 regulatory procedures for Advanced Therapy Medicinal Products. The close connection in the division between research and regulatory duties creates an unusual expertise, which has proved effective: by the end of 2008, a total of five applications for marketing authorisation of Advanced Therapy Medicinal Products had been submitted to the EMEA – the division is involved in all of these procedures, mostly as Rapporteur. An important field of activity with regard to the development of ATMPs is the approval of clinical studies, something which takes place nationally, also for centralised marketing authorisation applications. It is exactly because intensive research into advanced therapies is being carried out here that the amount of work involved in advice and approval was significant in 2007/2008, with experts of the division often being called upon for scientific advice and inspections. Scientists of the division assisted the competent state authorities in about 60 inspections of manufacturing facilities. On four occasions the EMEA requested coordination of scientific advice, and 14 national consultations took place. In addition, our staff members frequently provide advice to the EMEA on novel therapeutics and the associated issues and are also contributing to the development of European guidelines and laws.
**NON-VIRAL GENE TRANSFER MEDICINAL PRODUCTS**

Genetically modified bacteria and plasmids

There are several processes for transferring genes into the human genome. The non-viral way can be, for example, with the aid of so-called plasmids — small, circular DNA molecules. Plasmids are being investigated for their possible application as vaccines. A totally new field of research, which was associated with the comprehensive advice given to companies by the section in 2007/2008, is the application of genetically modified bacteria. These are intended to treat gastrointestinal diseases, for example, by oral administration. The section is also intensively researching therapy with genetically modified cells.

Five clinical studies with plasmids were approved in 2007/2008. The section was involved in all of the division’s other approval procedures, clinical studies, national corporate consultations and EMEA scientific advice procedures in the area of gene therapy, even in the case of viral gene transfer. The focal points of the research are the development of lentiviral vectors for gene transfer in quiescent cells and examining the role of the viral protein Vpx in the transduction of myeloid cells.

**VIRAL GENE TRANSFER MEDICINAL PRODUCTS**

First products in the marketing authorisation procedure

Viral vector systems, which serve as transfer molecules for DNA fragments, play a key role in gene transfer. Four marketing authorisation applications for viral gene transfer medicinal products had been submitted to the EMEA by the end of 2008. The section was involved in all the procedures. Such vectors serve as means of transportation for repair genes which are intended to replace sick or missing genes. The goal is to cure genetic defects in hereditary diseases or heal cancer by reversing the mutation that leads to the abnormal cell growth.

Most of the vectors studied in the past are replication-incompetent viruses: they can transfer the therapeutic gene to the target cells but are not capable of multiplying. This limits the range of action: non-replicating viruses can affect individual tumours, but not the entire tumour mass.

For this reason, the Viral Gene Transfer Medicinal Products section is currently working on an entirely new treatment approach, which was associated with significant advice activities in 2007/2008: the use of replication-competent viral vectors, also called oncolytic viruses. These vectors are derived from vaccine strains, can multiply in patients and can therefore reach more tumour cells. Because they migrate into tumour cells and thus stimulate the immune system, the patient’s intrinsic defence system should be redirected to the humour cells with the goal of killing them. The viruses are also eliminated in this process.

**TISSUE ENGINEERING, SOMATIC CELL THERAPY**

New guideline for cell-based medicinal products

“Substantially” manipulated cells for therapeutic purposes are part of this section’s area of responsibility. This includes both somatic cells and stem cells if they are expanded and/or modified in vitro, outside the donor organism. Genetically modified cells as therapeutic agents are a topic of intense interest to more than just researchers worldwide. The political world, the general public and companies conducting research, all have an enormous need for clarification and advice on this complex subject. How should these cells be handled, and what particular issues must be taken into account during the marketing authorisation process? As vice chair of the CHMP Cell-based Product Working Party of the EMEA, section head Dr Egbert Flory contributed to the formulation of the fundamental Guideline on Cell-based Medicinal Products.

In basic research, the scientists in the section focus on the interaction between viruses and intracellular signal components in disease development and course caused by immunodeficiency viruses in apes and humans. They aim to find answers to questions like “Why can an ape’s immune system repel the simian immunodeficiency virus SIV, while people become ill from the comparable human immunodeficiency virus HIV?” In addition, they are investigating intracellular signal mechanisms in the differentiation of human stem cells.

**NON-VITAL TISSUE PREPARATIONS, XENOGENIC CELL THERAPEUTICS**

Living cells from animals as tissue replacement

Xenogenic somatic cell therapeutics contain cells that originate from other species, for example cells that are transferred from animals to humans. By the end of 2008 there were no authorised xenogeneic cell therapeutics in either the USA or Europe. Pig heart valves have, however, been used in humans worldwide for decades. These valves are not classified as xenogeneic cell therapeutics but as medicinal products due to the fact that all pig cells are killed before transplantation. Scientists are currently working on the development of pig heart valves that are overgrown with genetically modified human cells of the transplant recipient. These should enable longer functionality of the heart valves inside the patient. They are thus cell therapeutics, are classified as medicinal products for advanced therapies and marketing authorisation must occur centrally through the European Medicines Agency EMEA. The section advises companies conducting research and applies for marketing authorisation procedures.

**Suicide gene should stop tumour growth**

An example of a gene transfer for which a marketing authorisation application was submitted is the transfer of the p53 gene, which is involved in programmed cell death – apoptosis. This gene is defective from birth in patients with Li-Fraumeni syndrome and the gene is also mutated in many cancers. The result is uncontrolled cell growth. Transfer of the functionally active p53 gene is expected to prevent uncontrolled tumour growth.
German Tissue Act prompts flood of applications

On 1 August 2007 the Tissue Act took effect in Germany, incorporating European Union Directive 2004/23/EC into German law. In this new law, tissue preparations are classified as medicinal products and require approval by the Paul-Ehrlich-Institut. "Tissue" includes almost all human tissue and cells including skin – but not organs. "Conventional" tissue preparations are "not significantly manipulated" – such as heart valves, blood vessels, cornea and musculoskeletal tissue preparations. Autologous – identical donor and recipient – and targeted allogeneic – different donor and recipient – stem cell preparations from peripheral blood or cord blood, as well as medicinal products for advanced therapies such as genetically modified tissue preparations are differentiated from conventional tissue preparations. Applicants who were already present in the German market with tissue preparations before the new Tissue Act was implemented were given the opportunity after the new law took effect to apply for marketing authorisation by the cut-off date of 1 February 2008. All applications submitted thereafter were considered new applications. By the cut-off date, 341 marketing authorisation applications for tissue preparations had been submitted to the PEI. A total of 160 applications were rescinded or – in rare cases – rejected, so that the division has 181 applications to assess and make a decision on. By the end of 2008 the PEI had authorised 15 tissue preparations, including femoral head, cartilage, bone powder and tendon/ligament tissue.

As part of their research activities, staff members examined the infection risk associated with the porcine endogenous retroviruses PERV in porcine tissue. This is because such therapy can only be justified if one can exclude the possibility of xenogeneic somatic cell therapeutics infecting the human recipient with the pig's viruses, bacteria or fungi and the resultant possibility of transmission to third parties. Scientists are also conducting cross-sectional research to define quality and safety requirements for human stem cells within the scope of tissue engineering. Tissue engineering products are cell therapeutics and may contain human stem cells. Using sensitive and complex methods, in particular microarray analyses, the stem cell properties are characterised in order to create special requirement profiles for human adult stem cells. They also provide an important basis for assessing quality and safety in the manufacture and future applications of cell therapy/tissue engineering medicinal products in humans.

Clarification is necessary

Gene therapy and regenerative medicine give rise to hope, but also fear. The division believes one of its most important duties is to provide information: both to the general public with regard to the opportunities and risks of these new therapeutic developments and to researching companies and applicants with regard to research and marketing authorisation. In 2007/2008 the PEI organised two events on this subject:
- In December 2007 the PEI organised an information event for around 90 participants on the approval procedure for tissue preparations pursuant to Section 21a of the Medicinal Products Act AMG.
- ATMP meeting – at a symposium organised by the PEI in collaboration with the German Society for Regulatory Affairs DGRA in November 2008, experts gave presentations to the general public on the foundations and the current state of advanced therapy medicinal products ATMP and regenerative medicine. More than 200 interested people attended this event.

Selected activities/publications/appointments

- Prof. Klaus Cichutek, Gene Therapy Working Party GTWP (Chair) – EMEA
- Dr Egbert Flory, Committee for Advanced Therapies CAT – Cell-based Products Working Party CPWP – EMEA

Nominations and appointments:
- Prof. Christian Buchholz and Prof. Ralf Tönjes, extraordinary professorships, Johann Wolfgang Goethe University, Frankfurt am Main
- Prof. Matthias Schweizer, extraordinary professorship, Albert Ludwigs University of Freiburg
- Dr Christine Hohenadl, visiting professorship, University of Veterinary Medicine, Vienna
- Dr Carsten Münk, Heinz Ansmann Foundation professorship for AIDS research, Heinrich Heine University, Düsseldorf

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Since June 2005, the WHO’s Collaborating Centre for Quality Assurance of Blood Products and in vitro Diagnostic Devices – one of four collaborating centres worldwide for biological standardisation – has been based at the Institute. Professor Rainer Seitz is director of the Collaborating Centre, in which 14 sections and units of the PEI are involved. Its main priorities are blood safety and in vitro diagnostic devices. From summer 2004 until autumn 2005 Dr Gabriele Unger worked at the WHO as the first employee seconded by the PEI and has since then been coordinating the collaboration between the two organisations. The Institute now regularly seconds scientists to the WHO in order to impart their experience and enhance communication.

International reference materials for blood safety

The WHO Expert Committee on Biological Standardization (ECBS) manages the development of international standards (written standards as well as biological reference preparations) in order to increase the safety of blood products worldwide. PEI President Professor Johannes Löwer supports the work of the committee in his capacity as a member.

Various divisions are involved in establishing reference preparations, because without them medicinal product safety is not possible. It must be possible to rely on standards – if the reference material is not suitable, it cannot be guaranteed that the blood products are free of pathogens or that a coagulation factor is truly active. In 2007/2008, on behalf of the WHO, staff members developed the first international reference material for tests to detect antibodies against the core protein of the hepatitis B virus, the WHO International anti-HBc Standard. Standards for the surface antigen of the hepatitis B virus (HBsAg) as well as for hepatitis B DNA are currently under development and the Institute submitted applications for additional standards in 2008. The Microbial Safety section is involved in the development of international standards for detecting certain bacterial strains such as Escherichia coli and Streptococcus pyogenes.

It is not only pathogens that need to be detected in a standardised manner: The Haematology / Transfusion Medicine division is also working on an international standard for detecting the activity of the blood coagulation factor VIII.

Quick-response task force for emergencies

In order to improve worldwide cooperation on blood products and to ensure that action can be taken quickly, the ECBS recommended that a worldwide network of experienced
We have requests from all over the world, as our expertise is highly sought after internationally.

authorities should be founded. The WHO’s Blood Regulators Network BRN was established in autumn 2006. Professor Rainer Seitz was the first chairperson who headed up the network until autumn 2008. The duty of the BRN is to quickly formulate recommendations in the event of suddenly occurring threats such as influenza pandemics in order to guarantee the safety of blood products. Together with international colleagues, PEI experts formulate guidelines and recommendations and support the WHO during training courses and symposia on blood products and in vitro diagnostic devices.

The PEI aims for Collaborating Centre status
There has also been long-standing cooperation in the area of vaccines: in addition to comprehensive committee work, in 2007/2008 staff members tested a total of 21 vaccine batches for the WHO’s Prequalification Programme for Vaccines. Vaccines that meet the quality, safety and efficacy standards receive a WHO prequalification certificate. With this service the World Health Organization wants to ensure that UNICEF and other UN agencies use only safe and effective vaccines in their vaccine programmes. PEI colleagues are also involved in the authorisation and certification of manufacturers and production facilities. The Institute wants to further intensify its strong commitment to vaccines worldwide: the goal is to achieve the status of a Collaborating Centre for vaccines as well, in order to have a greater say in the development of global vaccine strategies, for example. The PEI is also putting together a xenotransplantation database for the WHO. In xenotransplantation, cells, cell structures or entire organs are transferred between different species – e.g. from animals to humans. The database documents studies conducted worldwide and the data obtained from them. Organ donors are scarce and many patients wait in despair for the organ they need. It is possible that one day animal organs could resolve this shortage. Recording all the relevant data makes an important contribution to this.

Focus on assessor training
The PEI has Memorandums of Understanding with the US regulatory authority the Food and Drug Administration FDA and the Chinese regulatory authority the National Institute for the Control of Pharmaceutical and Biological Products NICPBP. These should enhance international cooperation and the exchange of information. An important contribution to this is the training of assessors: employees of health authorities worldwide can complete an internship at the Paul-Ehrlich-Institut as part of this training programme. There is a lot of interest in this programme: 14 interns from seven countries such as Thailand, Kuwait and Croatia have spent a total of 30 weeks at the Institute. Their main interests were in the regulation of vaccines, blood products and in vitro diagnostic devices – but the demand for expertise in the fields of allergology and biotechnology is also increasing.

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of all plasma product batches in Europe are tested and certified by the PEI. Blood products must be safe because many vital medicinal products are made from them.
Patients with valvular heart disease receive coagulation factors during surgery to prevent severe bleeding. However, several years ago a certain preparation caused severe thromboses and deaths. The suspected cause were the “armed” coagulation factors in the preparations, which triggered the uncontrolled coagulation. This suspicion, however, was incorrect. Some time later scientists discovered the actual cause: an increased amount of the not yet armed coagulation factor prothrombin.

PEI scientists, however, also found a hitherto unknown component during their search. They called this component hyaluronic acid-binding protease HABP. The protein gets its name from its affinity for the sugar protein hyaluronic acid and its ability to split other proteins (proteolytic activity). Because HABP can activate coagulation factor VII, the enzyme is also called factor-VII-activating protease FSAP.

The two faces of HABP

HABP can activate blood coagulation. It can, however, also set a system in motion that stops blood coagulation. This two-faced nature makes the search for the enzyme’s predominant effect in humans difficult.

We now know that one in 10 people is a heterozygous carrier of a genetic variation of the enzyme, officially called Marburg I single nucleotide polymorphism MI-SNP. This genetic variation of HABP is discussed as being a risk factor for thromboses, because thromboembolic complications often occur in carriers. In a collaboration with the University of Giessen, PEI researchers discovered that the normal version of the enzyme rapidly inactivates coagulation factor VIII, thus inhibiting coagulation. The MI mutant, in contrast, activates coagulation factor VIII, albeit only to a small extent. This explains the increased coagulation and consequent tendency to thrombosis in carriers of this gene variation [1].

HABP – an aid for metastases?

HABP has many faces – it not only impacts blood coagulation, but also affects various cell types such as connective tissue cells and endothelial cells [2]. The endothelium is the inner lining of the lymphatic and blood vessels. While HABP inhibits the endothelium in its growth, it encourages certain cells of the connective tissue to grow. The protease also influences enzymes, which increase the cell motility, enable loosening of cancer cells from the cell structure and thus promote metastasis.

How and to what extent HABP promotes the growth of certain tumour cells is currently being researched by scientists in a cross-sectional project.

Literature

1 Etscheid M et al. (2009): The Marburg I polymorphism (G534E) of factor VII activating protease (FSAP) prevents FVII activation, but contributes to thromboembolic risk due to FVIII activation. J Thromb Haemost: 7 (Suppl 2), Abstract OC-TH110

Its staff members are responsible for both established products made from blood plasma – such as coagulation factors and blood components for blood transfusions – as well as genetically manufactured coagulation products and innovative products such as cord blood as a source for haematopoietic stem cells.

The safety of blood products is of primary importance. This is guaranteed in Germany by strict regulations and intensive checks – and the PEI makes a significant contribution to this. Two different strategies ensure safety: all blood products are examined for potential pathogens and risks. In addition, the German Medical Association and the PEI jointly issue guidelines that specify who may donate blood. Thus, there are various reasons why donors may be deferred temporarily or permanently from donating blood: for example, visiting a geographical region with a risk of illnesses such as malaria, but also circumstances associated with an increased risk for certain diseases such as HIV. All the criteria have one thing in common: they aim to exclude all preventable dangers. The safety of the recipient has absolute priority, even if this means losing potential donors. Both approaches together ensure a high degree of safety of blood products in Germany.

**COAGULATION PRODUCTS**

Blood coagulation is a complex process that works like a chain reaction and involves many proteins. The splitting of individual molecular groups arms coagulation factors, which subsequently activate blood coagulation. Those suffering from a bleeding disease are missing some of these factors. For this reason, they receive therapeutic factor concentrates containing the missing coagulation factors. These, however, must not only be free of pathogens – in addition, they may only contain enzyme precursors, but not activated factors or other proteolytic activities which could result in uncontrolled blood coagulation and severe thromboses. The work involved in the marketing authorisation of and responsibility for coagulation products is therefore considerable.

The Coagulation Products sections assess the documentation for quality and preclinical/clinical aspects and monitor the progress of the marketing authorisation procedures. The two sections are responsible for 182 products. In 2007/2008 they supplied 36 clinical studies.

**PEI CERTIFICATES FOR BLOOD PRODUCTS RECOGNISED WORLDWIDE**

The Haematology/Transfusion Medicine division provides for the safety of blood products. Since its founding in 1994, it has taken up a leading role in Europe in the marketing authorisation and testing of blood products.

Characterisation of genetically engineered coagulation factors
Safe blood products require strict surveillance

After the HIV infections caused by blood products in the 1980s and early 1990s, everyone was in agreement: blood products must be safe. In Europe, official testing laboratories test every batch. The laboratories determine measurement values that are relevant for quality and safety and comprehensively review the manufacturing records. There must be consistent documentation on the plasma donations from which the product was obtained. This traceability is important for the safety of the blood products: it is only in this way that all preparations can be taken off the market if it is discovered that the plasma of a sick donor has contaminated the pool.

Competitive market for batch testing – PEI leads the way

Successful batch testing by an official testing laboratory of an EU member state is recognised by all 26 other member states. The blood product obtained from plasma is thus immediately available to the 500 million residents of the EU. Pharmaceutical companies can choose the testing laboratory in which they have their batches tested. This has led to international competition between the testing laboratories. With around 50% of all European batch tests in the field of blood products, the PEI has carved out a market-leading position for itself. The decisive success factor lies in the efficiency of the testing: according to law, the batch testing may take up to 60 days; however, the average testing time at the PEI is only around 14 days. The batch testing database, established in 2002 and continuously updated, also contributes to this. In 2007/2008, the section experimentally tested 3,136 batches.

The Plasma Master File

Plasma products are manufactured from plasma pools. A plasma pool may consist of around 2,000 to 15,000 donations. Many different medicinal products are made from this pool. To ensure that the “plasma for fractionation” source material is safe and well documented, the German Medicinal Products Act of 2003 introduced the Plasma Master File PMF. This procedure is aimed at improving the assessment of plasma and standardising it within the EU. A PMF is a standalone document which contains all the information regarding plasma – from the individual donation to the plasma pool. This includes, for example, information on donation centres, test laboratories, plasma repositories and transporters with addresses and inspection status, information on the test kits used to test individual donations and the plasma pool, selection criteria for donors and epidemiological data on each donation centre. The most important aspect is a risk assessment of the plasma’s safety, which contains all the measures implemented by the PMF holder. In this way, the risk of an infected donation contaminating the manufacturing process can be assessed. The EMEA is responsible for certifying Plasma Master Files. To date there are a total of 12 certified European PMFs; the PEI was involved in four of these certifications as the coordinator.

Worldwide acceptance of PEI certificates and assessments

77 countries accept PEI certificates as proof of quality.

Acceptance in EU member states

Acceptance worldwide
Conventional blood donation and cord blood

Although the EMEA centrally regulates many biological medicinal products, blood transfusions do not fall under European pharmaceutical legislation but under national legislation. In Germany, blood transfusions are considered a medicinal product and are subject to marketing authorisation. The section is responsible for blood cells and plasmas, including radiated preparations for immunodeficient patients. These marketing authorisations relate to 84 blood establishments with 140 manufacturing facilities. As a result of the German Tissue Act of 2007, haematopoietic stem cells which are acquired from bone marrow or mechanically from blood or cord blood and which are used in an autologous or targeted manner – for a specific patient – also require approval. To date, more than 200 applications from around 70 establishments have been submitted.

German Haemophilia Registry DHR

Haemophiliacs are patients for whom the smallest injuries can develop into life-threatening haemorrhaging on account of a lack of coagulation factors. They are given coagulation preparations containing the missing factor. Because haemorrhages in a joint, for example, may lead to permanent damage, each patient must be treated individually in order to improve their quality of life and prevent complications. In order to further develop and optimise therapy, detailed and comparable data about the treatment courses of as many patients as possible must be consolidated and analysed. In December 2004, planning began for a registry that would record therapy-relevant data of all haemophilia patients in Germany. From the beginning, the Federal Ministry of Health supported the registry, which was designed as an online database. The software provides a state-of-the-art clinical, supraregional patient registry that complies strictly with data protection regulations. The PEI established and operates the registry in cooperation with the German Society for Thrombosis and Haemostasis Research and the two haemophilia patient organisations, the German Haemophilia Society for Combating Bleeding Disorders and the Haemophiliacs’ Interest Group. Database programming began in May 2007 and was completed in October 2008. Online operation was launched in December 2008 in a pilot phase using the patient data of a large treatment centre. The PEI will gradually approve additional centres for data input.

Cord blood as a source of stem cells

Cord blood was discovered as a new source for stem cells years ago. It contains stem cells that have a big advantage compared to haematopoietic stem cells from bone marrow: they are less immunologically defined, thus permitting greater differences between donor and recipient. Cord blood stem cells can be easily and safely obtained from the residual blood in the placenta after the birth. Stem cell preparations made from cord blood are subject to marketing authorisation. The applicant must document the production, specify the medicinal product, illustrate how donors are selected and/or tested, and prove that the prescribed criteria have been checked. Only then may the preparation be marketed.

Since 2001 the PEI has authorised eight stem cell preparations made from cord blood. These products help patients, such as those suffering from leukaemia, to repair the haematopoietic system.

EU batch release of products made of blood plasma in 2007
(figures indicate percentages)

- Italy 10
- Belgium 2
- UK 15
- France 5
- Netherlands 2
- Austria 20
- Germany (PEI) 46

46% of the released batches in the EU originate from Germany and thus from the Paul-Ehrlich-Institut.
We are proud of the fact that we test around half of all batches in Europe.

Two bodies in Germany are primarily responsible for blood components intended for transfusions: the German Blood Advisory Board (Arbeitskreis Blut) is a national expert panel that advises the Federal Government on safety issues pertaining to the acquisition and use of blood and blood products. The PEI is represented by the division’s director, Prof. Rainer Seitz. The German Transfusion Act stipulates that blood products must be tested for specific pathogens. The concrete details are defined in technical specifications. The German Medical Association – the second important body – specifies the guidelines, in consultation with the PEI, for acquiring blood and blood components and for the use of blood products.

The PEI assumes responsibility beyond Germany’s borders and is intensively involved in raising the standard for blood products worldwide in its capacity as an official WHO Collaborating Centre. PEI staff impart their experience to numerous European bodies and support the WHO by actively contributing to the organisation’s efforts to improve healthcare around the globe. It is not just the local population that benefits from this, but also travellers – blood transfusions are not something that you take on holiday with you.

Research into safer blood products

In their own research projects, the division’s scientists are working on the development of new methods for measuring the activity of coagulation factors and safety-relevant parameters and for the quality control of blood components. Another priority is investigating interactions between coagulation factors and tumour cells.

Selected activities/publications/appointments

- Prof. Rainer Seitz, Blood Regulators Network (Chair) – WHO;
- Blood Products Working Party (Chair) – EMEA;
- European Pharmacopoeia Expert Group 6B (Chair), Biological Standardisation Programme Steering Committee (Chair) – EDQM
- Dr Johannes Dodt, Expert Group P4 Biologicals, Expert Group 6B Blood Products – EDQM
- Dr Uwe Unkelbach, Advisory Group for the Official Control Authority Batch Release Network – EDQM
- Dr Anneliese Hilger, Blood Products Working Party BPWP – EMEA
- Dr Margarethe Heiden, European Committee for Blood Transfusion CD-R-TS – EDQM

Events:

- June 2007: IPFA/PEI 14th Workshop on Surveillance and Screening of Blood Borne Pathogens
- February 2008: 10th Haemovigilance Seminar
- April 2008: Third German-Czech Transfusion Days
- April 2008: KOLT 2008: Information event for quality control managers of blood establishments
- May 2008: IPFA/PEI 15th Workshop on Surveillance and Screening of Blood Borne Pathogens

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periodic safety update reports for authorised medicinal products were handled by the PEI in 2007/2008.
Transfusion-related acute lung injury (TRALI) is a very rare adverse reaction to the administration of blood components containing plasma. Data from various national haemovigilance systems show that – although the number of cases is very low – TRALI has become the most frequent cause of death in connection with blood transfusions. Previously, no precise data was available about the (notification) frequency in Germany, because the cause for the suddenly occurring lung oedema was often misconstrued. In addition, a TRALI reaction can only be confirmed if clearly defined criteria have been met and documented.

Even if TRALI is a rare adverse reaction, the Safety of Medicinal Products division has proactively initiated a Germany-wide epidemiological study, in order to obtain more information about TRALI, thereby further reducing transfusion-related risks. In collaboration with German blood donation centres, blood samples from the affected recipients and the relevant donors were examined for specific antibodies that might trigger TRALI. These leukocyte antibodies were found almost exclusively in female donors with a history of pregnancy. Moreover, most TRALI reactions occurred after administration of therapeutic fresh plasma. In 2006/2007, 44 patients were identified who developed TRALI symptoms. Eight of these patients died. Based on the data, the PEI mandated measures that should reduce the TRALI reactions even further. For example, only therapeutic single plasmas may be used from female donors who have never been pregnant or who have been proven by testing not to have any leukocyte antibodies.

What is pharmacovigilance?
The WHO defines pharmacovigilance as the science of discovering, assessing, understanding and preventing adverse reactions and other problems related to medicinal products. To test the safety of biological medicinal products and medical devices, the division’s staff continuously conduct risk/benefit analyses in close cooperation with the authorising sections.
An important tool for monitoring the safety of medicinal products and medical devices is the recording and assessment of adverse effects, including after the medicinal product has been authorised. It is only in this way that rare adverse reactions can be detected.

PHARMACOVIGILANCE I + II
Continuous recording and assessment of risks
Pharmacovigilance I assesses the safety of vaccines, monoclonal antibodies, sera, immunoglobulines and allergens, while Pharmacovigilance II is responsible for the safety of plasma, blood and tissue preparations and in vitro diagnostic devices.

In order to be able to assess risks, one must first be aware of them. Doctors and pharmacists are legally bound to report suspected cases of adverse reactions. The Safety of Medicinal Products division records these spontaneous reports. In addition, the marketing authorisation holders regularly issue Periodic Safety Update Reports PSUR, pursuant to the Medicinal Products Act. Furthermore, pharmaceutical companies and sponsors are obliged to provide the PEI any information that could affect the risk/benefit ratio of the medicinal product – including results from animal experiments. Staff members also evaluate the international medical literature for new findings regarding the safety of medicinal products.

Risk Management Plans
As part of the market authorisation of a medicinal product, the applicant generally has to submit a Risk Management Plan (RMP). This contains data regarding the safety and efficacy of the product: risks that have already been identified and potential risks. The RMP specifies how systematic examination of the risks is continued after the marketing authorisation.

In the case of vaccines, for example, this may mean a controlled study with tens of thousands of study participants. The applicant must also demonstrate whether measures are necessary to decrease the risk and how their effectiveness should be determined.

Phased plan: analysis and intervention
When conducting risk/benefits analyses, the employees of the units work closely with their colleagues from the marketing authorisation sections, the Legal Affairs unit and the Institute’s management. If the experts detect a signal – an indication of an adverse effect – they check whether measures are required and, if so, implement them immediately. Depending on the severity of the case, the following measures are possible: sind
SAFETY OF MEDICINAL PRODUCTS AND MEDICAL DEVICES

und leiten sie umgehend ein. Je nach Schwere des Falles sind folgende Maßnahmen möglich:

• Requirement for pharmacological investigations
• Requirement for observational studies, confirmatory or epidemiological studies
• Performance of in-house epidemiological studies: e.g. to investigate the risk of transfusion-related lung injury
• Variation in marketing authorisation, such as modification of the indication, exclusion of at-risk patient groups, organisation of additional studies or additional warnings in the package leaflets
• Suspension: marketing authorisation is temporarily suspended
• Withdrawal of the authorisation

The PEI can only order these measures for national marketing authorisations.

European procedure for central marketing authorisations

More and more medicinal products are being approved centrally via the EMEA in European marketing authorisation procedures. This also requires a common approach with regard to the safety of medicinal products. If the PEI is Rapporteur for a specific product, the section records and assesses the signals and puts forward suggestions in the CHMP at EU level as to how the product should be handled. If the PEI experts observe a signal regarding a centrally authorised product that is not within the scope of their responsibility, they inform the Rapporteur in accordance with the EMEA recommendations and provide a professional assessment. Notification can be made informally or in the form of Non-Urgent Information NUI or, in urgent cases, Pharmacovigilance Rapid Alerts RA. All observed risks and suspected cases of reactions for EU-wide authorised medicinal products are recorded in the EUDRA vigilance database.

Medicinal products for children: a new law for increased safety

Children are not small adults – and certainly not when it comes to therapy with medicinal products. Every age group reacts differently to different active substances and breaks them down at different speeds. A therapy regimen must take this into account. Although this has been known for a long time, many medications continue not to be approved for children – i.e. they were not tested and evaluated in clinical studies with children. In January 2007 a new European regulation on medicinal products for paediatric use came into effect in order to promote the development of medicinal products for children. The key element of this regulation is as follows: When applying for marketing authorisation for new medicinal products, the applicant must submit a Paediatric Investigation Plan PIP, insofar as there maybe paediatric diseases that could be treated with the medication. A scientific committee of the EMEA, the Paediatric Committee PCD0, must approve the investigation plan. The division was closely involved in developing the new regulation and provides the German representative on the expert committee: paediatrician Dr Dirk Mentzer.

Human and veterinary pharmacovigilance

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Since 2006, the increase of products under the responsibility of the PEI has been accompanied by an increase of reports in the human medical sphere of almost 60 percent – in veterinary medicine the increase was almost 40 percent.

1 PSUR Periodic Safety Update Reports
2 ASR Annual Safety Reports
3 ADR Adverse Drug Reactions
The approval of a clinical trial involves many people at the PEI. The safety of the study participants is our most important duty.

Safety of in vitro diagnostic devices

The Paul-Ehrlich-Institut is responsible for the recording, assessment and scientific evaluation of reports concerning in vitro diagnostic devices IVD for the high-risk group. Because these test systems detect major pathogens such as HIV and the hepatitis B and C viruses, they are very important for the selection of blood donors and must be highly reliable. The PEI assesses reports about erroneous test results and, if necessary, initiates corrective measures. Such measures may include a user warning, a batch recall or a report on the safety of the medicinal product, known as a pharmacovigilance report.

Some 84.4 percent of the reports were submitted by the IVD manufacturers themselves in past years. The user reporting rate was 8.5 percent and in 12 cases (7.1 percent) the PEI was notified by Vigilance Reports from other European authorities. In general, these concerned deficits in the tests’ detection accuracy and the stability of the reagents used. Less frequently, the reports were about insufficient sterility or identification. In the majority of cases, customer information was sent out or a batch was recalled in consultation with the manufacturers. In rare cases the report resulted in a change in the manufacturing process or the design.

PHARMACOVIGILANCE OF VETERINARY IMMUNOLOGICAL PRODUCTS AND ANIMAL WELFARE

Animal diseases call for quick action

Veterinarians assess adverse reactions and risk/benefit profiles in procedures that are comparable to those of medicinal products for human use. The unit’s goal is to motivate companies and veterinarians to report suspected cases of complications in order to create a valid database for the assessment. It has been successful: the number of reports is continuously increasing by around 20 percent each year.

A special challenge in 2008 was the vaccination campaign against bluetongue disease. In order to contain the spread of disease and limit economic losses, those responsible had to act quickly, as there was no time for a regular marketing authorisation. By means of an emergency ordinance, the Federal Ministry of Food, Agriculture and Consumer Protection made vaccines available that were not yet authorised. These measures required very careful monitoring – the unit recorded and assessed the reports and published the results very promptly.

CLINICAL TRIALS

Major hurdles before clinical application

Clinical trials are the prerequisite for the marketing authorisation and use of medicinal products. They range from Phase I studies, which investigate the tolerability and safety of the medicinal product in humans for the first time, to Phase IV studies, where the medicinal product has already been authorised. Although currently 25 percent of all clinical trials in Europe are multinational, national approvals continue to be necessary. The Clinical Trials unit must approve clinical trials for biological medicinal products in Germany. When assessing applications, this unit cooperates with the sections that are responsible for the respective products, with the Safety of Medicinal Products division and with the Viral Safety and Biostatistics sections. The experts point out any defects and formulate objections to be put to the applicant. Once their response has been received, an overall decision is made. In around 10 percent of applications, the approval is linked to conditions that the applicant must fulfil before the start of the trial. The Legal Affairs unit checks these rejections and conditional decisions. In 2007/2008 the Institute handled 424 applications for clinical trials.

Europe-wide harmonisation of clinical trials

Bodies that approve clinical trials make decisions about, for example, whether a novel active substance may be administered to humans. Strict criteria should prevent any danger to study participants. An ad-hoc working group of the EU Commission – in which the unit is represented – deals with guidelines for clinical trials.

The Clinical Trials Facilitation Group CTFG is responsible for the practical implementation of the guidelines and harmonisation between the EU member states. In the case of multinational clinical trials, the participating countries must approve the study independently of each other. This may
mean that one country approves a clinical trial, while another rejects it. To prevent this from happening the group, under the leadership of unit director Dr Hartmut Krafft, worked intensely on drafting a guideline, the Voluntary Harmonisation Procedure. Since February 2009 clinical trial applicants have been able to submit documentation centrally to the CTFG group, in which all EU member states are represented. The participating countries assess the trials jointly, so that the applications continue to be approved nationally – pursuant to the applicable laws – but are no longer assessed separately. This has two advantages: the applicant gains time and the assessors can also discuss the studies with their European colleagues and thus make decisions jointly.

LEGAL AFFAIRS

Legal compliance as a hallmark of quality

The Legal Affairs unit provides comprehensive advice on regulations regarding medicinal products and supports measures for guaranteeing the safety and quality of medicinal products. From the clinical trial to the marketing authorisation to the market launch, large sums of money are invested in the development of a medicinal product. Although this is more the exception than the rule, the PEI cannot accept every application in its full scope. Sometimes facts are revealed after an approval that make it necessary for it to be revoked or withdrawn. This may, for example, be the rejection of a clinical trial, the withdrawal of a batch release, the subsequent specification of conditions for the marketing authorisation of a medicinal product or, in rare cases, even its revocation. The sections and the Legal Affairs unit engage in interdisciplinary cooperation. The early involvement of legal experts in measures that are of a burdensome nature for the pharmaceutical industry reduces the number of opposition proceedings. Experience to date has shown that the decisions stand up well to legal scrutiny if they are contested. The main emphasis of the unit’s work is on German and European legislation with regard to medicinal products, animal diseases and medical devices. In addition, the unit’s activities include questions regarding general administrative law, the law on fees, the drafting and checking of contracts and dealing with various civil law issues.

Since early 2006 the German Freedom of Information Act IFG has allowed members of the public to request certain information from government bodies. The Legal Affairs unit deals with any legal questions in this regard.

Selected activities/publications/appointments

- Dr Brigitte Keller, Global Advisory Committee on Vaccine Safety – WHO; Pharmacovigilance Working Party PhVWP – EMEA
- Dr Dirk Mentzer, Paediatric Committee PDCO – EMEA; Pharmacovigilance Working Party PhVWP – EMEA
- Dr Hartmut Krafft, Clinical Trials Facilitation Group CTFG (Chair) – HMA
- Dr Klaus Cußler, Pharmacovigilance Working Party – Veterinary PhVWP-Vet
- Claudia Ruoff, EMACOLEX – HMA

Publications:
- Hoffmann, K. Cußler; Impfkampagne zur Bekämpfung der Blauzungenkrankheit [Vaccination campaign for combating bluetongue disease], Deutsches Tierärzteblatt 2/200

>> www.pei.de/safety-medicinalproducts
>> www.pei.de/adr-database
>> www.pei.de/ct
of our colleagues have a disability. The PEI wants to remove any obstacles blocking their route into science.
This made HR manager Klaus Posselt think – and the idea was born of encouraging people with disabilities in the field of science. In 1996 the “Tandem Partnership” project appointed non-disabled colleagues to assist five disabled employees. The project was so successful that it was expanded to include more and more people.

In 2001 an Integration division was created at the PEI in order to promote the integration of disabled people in science even more strongly. More and more disabled colleagues were working in the various divisions. They were able to gain additional qualifications and also take the strain off non-disabled colleagues.

**Promoting disabled colleagues across all borders**

Based on these positive experiences, the PEI initiated the EQUAL project “Many things are possible – tandem partners in science” in spring 2005. Together with the Robert Koch Institute RKI, the Federal Academy of Public Administration BaköV, two universities, companies and a self-help association, the PEI developed strategies in accordance with the model promoted by the European Union for supporting disabled people and integrating them into biomedical research, from education and training through to qualification.

“The tandem partnerships no longer exist in the same form as in the beginning. Today some people have assistants: wherever we need help because of our disability, we receive support,” says Annetraud Grote, legal expert and Disabled Employees Representative at the PEI. Annetraud herself is dependent on a wheelchair as a result of a congenital muscle and joint disease.

“Tandem stands for the possibility of disabled people working together with other scientists as a team,” she adds. Many people with disabilities have now found a professional home at the PEI. Another goal is to pave the way for disabled scientists and employees from the ancillary scientific professions to enter the general labour market. Nonetheless, those involved with the project at the PEI are not satisfied with this: “What is the point of providing jobs for disabled post-docs, if students don’t have the courage to go for scientific professions in the first place?” asks Annetraud Grote.

“We want to be active in an integrated manner,” she adds, and refers to the public relations measures aimed at encouraging young people with disabilities to enter the scientific field. These measures include press releases, a newsletter, workshops and trade fair booths, as well as the website www.tandem-in-science.de and a film about the EQUAL project. “People with a disability often have different ideas about how to solve problems – which is an advantage for many research projects. And our concept also makes economic sense, because with the appropriate funding projects can be pursued that would otherwise not have been possible.” The EQUAL project wrapped up at the end of 2007 – but the PEI’s commitment continues. At present, colleagues are developing an advanced qualification programme for disabled Bachelor-level graduates.

- In the past 12 years the percentage of disabled employees at the PEI has increased from 6.5 to 15 percent.
- At the end of 2008 two disabled apprentices obtained their qualifications as biology lab assistants.
- Three disabled doctoral candidates finished their doctoral theses in 2008.
- Since the start of the programme, 38 people with disabilities have participated in the qualification measures at the PEI.
From personnel and finance by way of the operation of highly secure laboratories through to emergency plans for pandemics: a future-oriented service team ensures a resilient infrastructure.

Conventional administrative duties, such as finance and personnel, are just as much the responsibility of the Administration division as areas that are required by the PEI’s particular official duties and research. The division’s staff are also dedicated to continuously creating new educational opportunities for young people, are concerned with the reconciliation of work and family life and strive to encourage people with disabilities in science.

PERSONNEL
Challenges for a modern Personnel unit
As in previous years, in 2007/2008 the Paul-Ehrlich-Institut saw a continued growth in staff numbers, which had risen to 717 by the end of 2008. The Personnel unit takes care of all their personnel issues: they see themselves as a modern service provider for everyone who works at the PEI.

Recruiting qualified personnel was also one of the key tasks in 2007/2008. An everyday challenge for the Personnel unit is that many scientists complete a part of their education at the PEI – in the form of dissertations, doctorates or advanced scientific qualifications – which results in a perceptible dynamism within the Institute. The fact that the PEI is an appealing employer for the approximately 400 permanent employees is also due to the ability to choose from around 70 different working time models, which are aimed at reconciling work and family life.

Apprenticeships in eight areas
- Laboratory
- Office communications
- Media and information services, library sciences field
- Information technology, system integration field
- Electronics for industrial engineering
- Waste water engineering
- Industrial mechanics
- Animal care, research and clinical field

In addition to the conventional administrative duties such as handling personnel issues for civil servants and salaried employees, organising business trips and travel expense accounting, the Personnel unit is also responsible for education and training. One of the Institute’s main goals is to offer apprenticeships to as many young people as possible. In 2007/2008 we again intensified our efforts in this regard and – thanks to expanding our cooperation with companies
We want to provide as many young people as possible with a wide range of educational opportunities.

and public institutions – we currently offer training in eight different fields. In 2007 we had 36 and in 2008 we had 40 young people in apprenticeship. Up to 2005 we had had no disabled people among our apprentices; in 2008 this figure was around 20 percent.

Since the Institute first started employing disabled employees within the “Tandem Partnership” project in 1996, our commitment to this issue has increased steadily. The unit’s staff are dedicated to finding funding for integration projects for disabled employees. In 2007/2008 the unit was able to secure around 1.54 million euros for this purpose. Occupational Integration Management OIM, which was introduced in 2008, serves to prevent work-related health risks, chronic illnesses and employee disability and, whenever possible, to remedy these. The Personnel unit coordinates, manages and implements these important measures.

FINANCE AND PROCUREMENT
From pens to pot-bellied pigs

The Finance and Procurement unit handles budgeting, accounting and procurement. Budget and investment volumes are increasing along with the continuous rise in the number of duties and employees at the PEI. The budget volume was 86.7 million euros in 2007/2008. As a government body, the PEI is bound by public procurement laws – with the corresponding complex processes. In 2008 alone the unit implemented 28 calls for tenders, awarded 7,440 contracts with a total value of 9.1 million euros, ordered around 10,000 items and settled almost 10,000 invoices. But it’s not only the sheer number of orders that provides a challenge – the diversity of the products is enormous. The product portfolio ranges from pens, by way of small and large technical equipment for offices and laboratories, through to animals. Whether it be a mouse, a ferret or a pot-bellied pig – the unit is not only responsible for procurement, but for all the logistics as well.

In 2006 the unit, together with the Controlling office, implemented a budgeting system that allows division managers to use allocated resources under their own responsibility. This resulted in significantly increased efficiency in 2007/2008.

PEI GATEWAY, DOCUMENT MANAGEMENT
Focusing on digital process implementation

The unit is responsible for the entire Information Lifecycle Management ILM – databases and processes. This central unit’s staff attend to the majority of the information flow at the PEI: they record and distribute incoming mail, inform the public about the Federal Gazette and update national and international databases. One such national database is the Federal Medicinal Products Information System AMIS, which makes data from marketing authorisation authorities available to the public and expert groups.

The various amendments to the Medicinal Products Act AMG have also resulted in changes to the product areas under the responsibility of the PEI. In 2007/2008 the unit was therefore very busy adding new medicinal products such as tissue preparations or individual therapy allergen preparations, improving data quality and providing additional information.

### Actual expenditure 2004 to 2008 (in thousands of euros)

<table>
<thead>
<tr>
<th></th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>Labour costs</td>
<td>3,121</td>
<td>3,132</td>
<td>3,110</td>
<td>2,196</td>
<td>3,893</td>
</tr>
<tr>
<td>Material costs</td>
<td>24,417</td>
<td>26,141</td>
<td>26,789</td>
<td>27,836</td>
<td>30,102</td>
</tr>
<tr>
<td>Investments</td>
<td>13,926</td>
<td>16,414</td>
<td>14,811</td>
<td>15,959</td>
<td>16,843</td>
</tr>
</tbody>
</table>

30,1 million euros is how much the PEI spent in labour costs in 2008.
In April 2008 the PEI, together with its sister agency the BfArM, initiated a project for a joint document management and workflow management system DMS/VBS. The objective is to implement a coordinated, integrated, electronic marketing authorisation process.

TECHNICAL SERVICES
24-hour a day operation of highly complex building technology

It would take a total of 16 football pitches to house the 86,000 m² that make up the PEI’s premises. The property consists of 10 buildings with highly complex technology: the laboratories alone take up 10,000 m², including 13 safety level 3 laboratory facilities. The technical complexity is immense: The unit’s staff monitor some 30,000 data points pertaining to ventilation and air conditioning, electrical, water, waste water and laboratory technology.

Medicinal products data – centralised and transparent

Since 2005 the unit has been working on the integrated medicinal products information system PharmNet.Bund, a federal and state information system. This system makes official data available regarding the marketing authorisation, registration and monitoring of medicinal products in Germany. Cooperating in the project are the German marketing authorisation authorities PEI and the Federal Institute for Drugs and Medical Devices BfArM, the Robert Koch-Institut RKI, the German Institute for Medical Documentation DIMDI and the Federal Office of Consumer Protection and Food Safety BVL.

An important sub-project is the electronic submission of applications: In the future, pharmaceutical companies will submit marketing authorisation and batch applications and notifications of variation entirely in electronic form. Its introduction is planned for 2010.

In collaboration with Hessisches Baumanagement (Hessian State Construction Management), the employees plan structural measures and oversee their implementation. Plans for 2007/2008 included replacing autoclaves, pressure tanks for the thermal inactivation of substances in the overpressure area. The unit also planned a new central inactivation facility for waste water from animal husbandry facilities, which will be rebuilt starting in 2011 – estimated budget: around 9 million euros. The Institute was allocated 18 million euros in 2007 via the energy savings programme for federal buildings. These funds will be used, among other things, to replace windows in the 20-year-old buildings, install photovoltaic modules and renew solar shading devices.

INFORMATION TECHNOLOGY – ORGANISATION
High-performance IT infrastructure

A high-performance IT infrastructure is a prerequisite for effective work. Colleagues use programs and databases which must, in part, be compatible with the databases of the European Medicines Agency EMEA as well as the WHO. The unit ensures continuous access to the IT infrastructure. The IT equipment includes around 850 computers and a server environment which processes the large quantities of data created daily and which guarantees its availability. In order to improve performance, in 2008 the unit’s staff increased the bandwidth of the backbone of the IT network to 10 GBit.

Reconciling work and family life

Many experts at the PEI work on international bodies: in 2007/2008 the IT unit established the technical preconditions for forms of communication, such as video conferencing, which save time, decrease travel expenses and ensure working capacity in the event of impending pandemics. In addition, the unit ensures an infrastructure that provides employees access to all of the PEI’s resources worldwide. One of the unit’s main duties is to create optimal working conditions. In 2007/2008 the focus was on reconciling work and family life – after all, 70 percent of our employees are women. PEI offers more than 70 different working time models for

An Antibody –
a sculpture by Waldemar Otto
part-time employees. Because day care places are hard to come by, in 2008 the unit concluded a contract with the town of Langen that guarantees a place in a day care facility for 10 children from the age of 1 until they start school. Working from home is also being expanded: some 15 telecommuting positions had been created by the end of 2008; in 2009 this number should more than double.

Structured selection of personnel and monitoring of training

The PEI’s most important resource is its employees, which is why personnel development starts with the employee selection process. In addition to professional skills and knowledge, personal qualifications are becoming increasingly important. For this reason, the unit implements state-of-the-art testing procedures that supplement the job interview. Another priority in 2008 was the development of a continuing and advanced education plan that provides further training to employees in a targeted and efficient manner. The key factor here is to ensure the transfer of knowledge from the seminar to the workplace.

OCCUPATIONAL SAFETY & HEALTH – PERMITS

From bandages to pandemic emergency plans

To ensure safe working conditions, this unit’s staff examine the technical prerequisites and the actual working conditions of individual employees at their workplaces. They conduct regular inspections to check whether legal regulations are being complied with.

The unit conducts the approval procedure in the area of genetic engineering and infection and radiation protection, coordinates occupational health examinations and organises safety training. If the PEI were not able to function in the event of a pandemic, the supply of blood products in Germany would very quickly come to a standstill, vaccines would no longer be available and no new vaccines against the pandemic pathogen could be tested. This is why the staff of the Occupational Safety & Health unit began working on an emergency plan after the emergence of bird flu: which employees have to come to work even during a pandemic in order to ensure that central official duties such as batch testing and authorisation of new vaccines are performed, and how many antiviral products have to be stockpiled? A particular challenge is that the pandemic plan must be continuously adapted to the current situation.

FEE COLLECTION

Based on Statutory Cost Regulations

A large part of the PEI’s regulatory services are subject to fees or compensation. The three main elements of this are:

- Official duties such as marketing authorisation and batch testing: the fees are incurred based on the statutory cost regulations in accordance with the Medicinal Products Act and the Animal Vaccine Ordinance. In 2007/2008 around 6,450 invoices were issued for around 18,000 official duties.
- Services on behalf of third parties in the healthcare sector: this includes the development and sale of reference materials, as well as projects for the EMEA and the WHO. At the end of 2006 the new Animal Vaccine Ordinance took effect as part of the implementation of European regulations. This was implemented in 2007/2008 in the draft of a new version of the Animal Vaccine Ordinance. The unit’s staff determined the associated official duties, the expenditure and the cost-neutral fees. In addition, the unit worked out corresponding fees in 2008 for new official duties resulting from the Tissue Act which had come into force.

Revenues in 2007 and 2008

(in euros)

<table>
<thead>
<tr>
<th>Service</th>
<th>2007</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>Official duties*</td>
<td>1.7 million</td>
<td>1.6 million</td>
</tr>
<tr>
<td>PEI-IVD</td>
<td>1.6 million</td>
<td>1.7 million</td>
</tr>
<tr>
<td>EMEA/WHO/reference materials</td>
<td>3.4 million</td>
<td>2.8 million</td>
</tr>
</tbody>
</table>

* e.g. marketing authorisations and batch testing

16,9 million euros is how much the PEI received in total revenues in 2008.
### Performance 2007/2008

### Completed procedures

<table>
<thead>
<tr>
<th>Completed procedures</th>
<th>2007</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marketing authorisation procedures for medicinal products for human or veterinary use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>121</td>
<td>121</td>
</tr>
<tr>
<td>Marketing authorisation decisions in the centralised European procedure according to Regulation (EC) No. 726/2004</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>a) PEI Rapporteur or Co-Rapporteur</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>b) PEI commenting agency Concerned Member State CMS</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Marketing authorisation decisions based on marketing authorisations in EC or EEA member states – <em>Mutual Recognition</em> MR and <em>Decentralised procedures</em> DC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>30</td>
<td>33</td>
</tr>
<tr>
<td>a) PEI Reference Member State RMS – the PEI recognises marketing authorisations by other EC or EEA member states</td>
<td></td>
<td></td>
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<tr>
<td>b) PEI recognising agency Concerned Member State CMS</td>
<td>13</td>
<td>18</td>
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<tr>
<td>Marketing authorisation decisions in the national procedure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>77</td>
<td>74</td>
</tr>
<tr>
<td>a) National marketing authorisation procedure for original manufacturers</td>
<td>54</td>
<td>55</td>
</tr>
<tr>
<td>b) National marketing authorisation procedure for parallel imports</td>
<td>33</td>
<td>19</td>
</tr>
<tr>
<td>Subsequent procedures: Decisions on procedures after the marketing authorisation of medicinal products for human or veterinary use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Extensions of the marketing authorisation, such as new indications, new pharmaceutical form, new route of administration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Notifications of variations which require approval according to Section 29 of the Medicinal Products Act AMG/German Animal Vaccine Ordinance or for European procedures Type II variations pursuant to Regulation (EC) No. 1084 or 1085/2003</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Extension of the marketing authorisation according to Section 31 of the Medicinal Products Act AMG/Section 26 of the German Animal Vaccine Ordinance or renewals for European authorised products pursuant to Regulation (EC) No. 726/2004 and Directives 2001/82/EC and 2001/83/EC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Fulfilment of commitments from the European marketing authorisation procedure pursuant to Regulation (EC) 726/2004 (FUMs)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>1,559</td>
<td>1,376</td>
</tr>
<tr>
<td>Decisions for products authorised in the centralised European procedure according to Regulation (EC) No. 726/2004. PEI as Rapporteur or Co-Rapporteur</td>
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<td></td>
</tr>
<tr>
<td>Total</td>
<td>248</td>
<td>300</td>
</tr>
<tr>
<td>a) Extension of marketing authorisation</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>b) Renewal or annual re-assessment of marketing authorisation</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>c) Type II variations</td>
<td>105</td>
<td>103</td>
</tr>
<tr>
<td>d) Assessment of fulfilment of commitments from the marketing authorisation procedure FUMs</td>
<td>135</td>
<td>185</td>
</tr>
<tr>
<td>Decisions for products authorised in the European mutual recognition or decentralised procedures. PEI as Rapporteur or recognising agency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>194</td>
<td>267</td>
</tr>
<tr>
<td>a) Renewals of marketing authorisations</td>
<td>23</td>
<td>21</td>
</tr>
<tr>
<td>b) Type II variations</td>
<td>171</td>
<td>246</td>
</tr>
<tr>
<td>Decisions for products authorised in the national procedure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>1,117</td>
<td>809</td>
</tr>
<tr>
<td>a) Renewals of marketing authorisation</td>
<td>426</td>
<td>192</td>
</tr>
<tr>
<td>b) Notifications of variations which require approval</td>
<td>691</td>
<td>617</td>
</tr>
</tbody>
</table>
## Completed procedures

<table>
<thead>
<tr>
<th></th>
<th>2007</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inspections: Verification of marketing authorisation-related information and documents in companies and institutions engaged in the development, manufacture, testing or clinical trials of the specified medicinal products, including in connection with a marketing authorisation according to Regulation (EC) No. 726/2004</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>183</td>
<td>236</td>
</tr>
<tr>
<td>Participation by the PEI in inspections on behalf of the European Medicines Agency EMEA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>42</td>
<td>31</td>
</tr>
<tr>
<td>a) GCP Good Clinical Practice inspections</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>b) GMP Good Manufacturing Practice inspections</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>c) PMF Plasma Master File inspections</td>
<td>31</td>
<td>22</td>
</tr>
<tr>
<td>d) PhV Pharmacovigilance inspections</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Participation by the PEI as an expert in national inspections by the competent state authorities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>132</td>
<td>188</td>
</tr>
<tr>
<td>a) Inspections in connection with the issue of manufacturing authorisations according to Section 13 of the Medicinal Products Act AMG, and permits for collection, treatment and processing of tissue and tissue preparations etc. according to Section 20 b, c of the Medicinal Products Act AMG or Section 17 d of the German Epizootics Act (TierSeuchG)</td>
<td>30</td>
<td>81</td>
</tr>
<tr>
<td>b) Inspections in connection with the issue of certificates according to Section 72, 72a, 72b of the Medicinal Products Act AMG, import authorisations and certificates regarding authorised medicinal products and for tissues and specific tissue preparations</td>
<td>24</td>
<td>30</td>
</tr>
<tr>
<td>c) Routine inspections according to Section 64 of the Medicinal Products Act AMG</td>
<td>78</td>
<td>77</td>
</tr>
<tr>
<td>National inspections, led by the PEI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>9</td>
<td>17</td>
</tr>
<tr>
<td>a) Inspections in connection with the approval of clinical trials pursuant to Section 9 of the GCP Ordinance</td>
<td>5</td>
<td>7</td>
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<tr>
<td>b) Marketing authorisation-related inspections according to Section 25 of the Medicinal Products Act AMG</td>
<td>2</td>
<td>0</td>
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<tr>
<td>c) Pharmacovigilance inspections according to Section 63b of the Medicinal Products Act AMG</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>Scientific advice for medicinal products for human and veterinary use. Scientific Advices may take place in the early development phase of a medicinal product, before clinical trials are conducted or immediately before or during the marketing authorisation procedure.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>239</td>
<td>208</td>
</tr>
<tr>
<td>a) National scientific advices</td>
<td>209</td>
<td>180</td>
</tr>
<tr>
<td>b) European scientific advice/protocol assistance by the EMEA, with the participation of the PEI as a co-ordinator – responsible for answering questions</td>
<td>30</td>
<td>28</td>
</tr>
<tr>
<td>Official batch testing of medicinal products for human use pursuant to Sections 32 and 77 sub-section 2 of the Medicinal Products Act AMG and of products for veterinary use pursuant to Sections 32 and 33 of the German Animal Vaccine Ordinance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>9,343</td>
<td>9,797</td>
</tr>
<tr>
<td>a) Release of batches based on the PEI’s own experimental studies</td>
<td>4,669</td>
<td>4,758</td>
</tr>
<tr>
<td>b) Release of batches based on the recognition of tests performed by the competent authorities of other EU/EEA member states</td>
<td>4,674</td>
<td>5,039</td>
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</table>
### Pharmacovigilance for medicinal products for human or veterinary use

<table>
<thead>
<tr>
<th>Completed procedures</th>
<th>2007</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>7,641</td>
<td>10,006</td>
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</table>

*Assessment of the updated reports, to be submitted by the pharmaceutical company on a regular basis, on the safety of authorised medicinal products for human or veterinary use – Periodic Safety Update Reports (PSURs)*

<table>
<thead>
<tr>
<th></th>
<th>2007</th>
<th>2008</th>
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<tbody>
<tr>
<td>Total</td>
<td>457</td>
<td>624</td>
</tr>
<tr>
<td>a) PSURs for products authorised in the European procedure according to Regulation (EC) No. 726/2004</td>
<td>77</td>
<td>102</td>
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<tr>
<td>b) PSURs for products authorised in the mutual recognition procedure</td>
<td>108</td>
<td>121</td>
</tr>
<tr>
<td>c) PSURs for nationally authorised products</td>
<td>272</td>
<td>401</td>
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</table>

*Assessment of reports to be submitted annually on the safety of medicinal products for human use that are undergoing clinical trials – Annual Safety Reports (ASRs)*

<table>
<thead>
<tr>
<th></th>
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<th>2008</th>
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<tbody>
<tr>
<td>Total</td>
<td>124</td>
<td>215</td>
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*Recording and risk assessment of Adverse Drug Reactions (ADRs)*

<table>
<thead>
<tr>
<th></th>
<th>2007</th>
<th>2008</th>
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<tbody>
<tr>
<td>Total</td>
<td>7,060</td>
<td>9,167</td>
</tr>
<tr>
<td>a) Medicinal products for human use</td>
<td>6,672</td>
<td>8,136</td>
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<tr>
<td>b) Products for veterinary use</td>
<td>338</td>
<td>1,031</td>
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</table>

*Clinical trials of medicinal products for human use and field trials of products for veterinary use*

<table>
<thead>
<tr>
<th></th>
<th>2007</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>476</td>
<td>508</td>
</tr>
<tr>
<td>a) Assessment of and decisions on applications for the approval of clinical trials of medicinal products for human use pursuant to Section 42 sub-section 2 of the Medicinal Products Act (AMG) and Section 9 of the GCP Ordinance</td>
<td>210</td>
<td>214</td>
</tr>
<tr>
<td>b) Participation in the approval of laboratory trials / field trials of products for veterinary use pursuant to Section 17 sub-section 4 paragraph a) of the German Epizootics Act (TierSeuchG)</td>
<td>266</td>
<td>294</td>
</tr>
</tbody>
</table>

*Other duties in connection with the marketing authorisation of medicinal products for human use*

*Assessment of Paediatric Investigation Plans (PIPs) pursuant to Regulation (EC) No. 1901/2006*

<table>
<thead>
<tr>
<th></th>
<th>2007</th>
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<tbody>
<tr>
<td>Total since the end of 2007</td>
<td>N/A</td>
<td>70</td>
</tr>
<tr>
<td>a) PEI as Rapporteur</td>
<td>N/A</td>
<td>18</td>
</tr>
<tr>
<td>b) PEI as Peer reviewer</td>
<td>N/A</td>
<td>20</td>
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*Assessment and annual reassessment in connection with the (re-)certification of Plasma Master Files (PMFs)*

<table>
<thead>
<tr>
<th></th>
<th>2007</th>
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<tbody>
<tr>
<td>Total since 2004</td>
<td>11</td>
<td>11</td>
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<tr>
<td>PEI as Co-ordinator</td>
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N/A not applicable – new procedure, as yet no final assessment
Allergy 62: 897-904

Vaccine 25: 4818-4827

Mol Nutr Food Res 51: 135-147

J Immunol 178: 5839-5847

J Allergy Clin Immunol 119: 1489-1496

Akt Neurol 34: 444-447

Immunol Rev 217: 96-104

J Virol 81: 4991-4999

AIDS Res Hum Retroviruses 23: 782-793

J Biol Chem 282: 37836-37843

Xenotransplantation 14: 366-373

Virology 4: 105

Emerg Infect Dis 13: 89-96

J Neurosci 27: 9451-9457

Vaccine 25: 3934-3945

J Virol 81: 9601-9604

J Virol 81: 11925-11936


Allergy 62: 1243-1250

Allergy 62: 897-904

Eur J Cancer Supplements 5: 29-32

Vesicular stomatitis virus glycoprotein displaying retrovirus-like particles induce a type I IFN receptor-dependent switch to neutralizing IgG antibodies.
J Immunol 178: 5839-5847

Clinical characteristics of soybean allergy in Europe: A double-blind, placebo-controlled food challenge study.
J Allergy Clin Immunol 119: 1489-1496

Migraine: Is it a Question of the Genes?
Akt Neurol 34: 444-447

Crosspriming in mast cell activation and type I hypersensitivity reactions in the conjunctiva: in vivo and in vitro studies.
Immunol Rev 217: 96-104

La Crosse bunyavirus nonstructural protein N5s serves to suppress the type I interferon system of mammalian hosts.
J Virol 81: 4991-4999

Evaluation of modified vaccinia virus Ankara as an alternative vaccine against smallpox in chronically HIVType 1-infected individuals undergoing HAART.
AIDS Res Hum Retroviruses 23: 782-793

Identification of a lysosomal peptide transport system induced during dendritic cell development.
J Biol Chem 282: 37836-37843

Recombinant murine gammaherpesvirus 68 (MHV-68) as challenge virus to test efficacy of vaccination against chronic virus infections in the mouse model.
Vaccine 25: 3934-3945

Repair capacity for platinum-DNA adducts determines the severity of cisplatin-induced peripheral neuropathy.
J Neurosci 27: 9451-9457

Crosspriming of cytotoxic T-cells dictates antigen requisites for MVA vector vaccines.
J Virol 81: 11925-11936

HBsAg non-reactive HBV infection in blood donors: Transmission and pathogenicity.

A rapidly evolving technology – Are the hurdles being addressed?
Eur J Cancer Supplements 5: 29-32


Wangorsch A, Ballmer-Weber BK, Rösch P, Holzhauser T, Vieths S (2007): Mutational epitope analysis and cross-reactivity of two isoforms of Api g 1, the major celery allergen.
Mol Immunol 44: 2518-2527

Bundesgesundheitsbl - Gesundheitsforsch - Gesundheitsschutz 50: 209-229


J Immunol 179: 7624-7634

Exp Cell Res 313: 3459-3471

Virology 364: 330-341

J Gen Virol 88: 3469-3478

// PUBLICATIONS 2008 //

Mol Nutr Food Res 52: S186-S195

J Gene Med 10: 1324-1333

J Cell Mol Med Aug 14

Trends Biochem Sci 33: 80-90

Curr Opin Allergy Clin Immunol 8: 270-275

Vaccine 26: 3835-3841

Vaccine 26: 3835-3841

Biosci Rep 29: 183-192

J Med Virol 80: 192-200

Transfusion 48: 790-791

J Gen Virol 89: 567-572
Mol Nutr Food Res 52: S241–S250

J Allergy Clin Immunol 122: 882–889


Allergy 63: 597–609


Mol Immunol 46: 416–421

Xenotransplantation 15: 290–306

Transplant Proc 40: 959–961

J Gene Med 10: 177–186

Bundesgesundheitsbl – Gesundheitsforsch – Gesundheitsschutz 51: 731–739

Int Immunopharmacol 8: 166–170

Mol Ther 16: 1427–1436


Allergologie 31: 314–325

Nat Med 14: 1256–1263


Immunity 28: 675–686


Transfus Med Hemother 35: 421–430


J Dtsch Dermatol Ges 7: 70–77


J Food Prot 71: 2263–2271


Schneider CK (00): Monoclonal antibodies – regulatory challenges.


Schneider CK (00): First-in-human trials with therapeutic proteins: regulatory rethink?


Bundesgesundheitsbl – Gesundheitsforsch – Gesundheitsschutz 51: 703–704


Transfus Med Hemother 35: 374–390

Schneeweiß B, Pfeiderer M, Keller-Stanislawski B (00): Impfsicherheit heute.

Dtsch Arztebl 105: 590–595
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<td>COMMUNICATION</td>
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<td>PEI IN EUROPE</td>
<td>8</td>
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<tr>
<td>EU CO-OPERATION AND MICROBIOLOGY</td>
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<td>VIROLOGY</td>
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<td>PEI-IVD</td>
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<td>VETERINARY MEDICINE</td>
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<tr>
<td>ALLERGOLOGY</td>
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<td>MEDICAL BIOTECHNOLOGY</td>
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<td>PEI INTERNATIONAL</td>
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<td>HAEMATOLOGY/TRANSFUSION MEDICINE</td>
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