INV-1

Implementing 3R principles at national & institutional level: The Turkish case
Orer, Hakan S.
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Institutional "laboratory animals ethics committees" was formed according to a regulation issued from the Ministry of Environment and Forestry in 2007. The regulation was based on relevant EU directives and aimed to implement 3Rs at national level. The new regulation also created a National Ethics Committee for Animal Experiments, a watchdog to monitor local committees. All institutions using laboratory animals should appoint a local ethics committee to monitor the usage, breeding and husbandry of the laboratory animals. The committee should review all laboratory animals use demands (research projects, use of animals for education, testing procedures, approve experimental protocols in line with the 3R principles. The committee should supervise the conditions of the animal facilities and monitor their anesthesia and euthanasia protocols. All individuals who wish to perform manipulations on living animals should receive a theoretical and practical training of minimum 80 hours. Training programs should be approved by the Ethics Committee and should include alternative methods to animal use.
Local ethics committees should report their activities to the National Ethics Committee for Animal Experiments. National committee acts as the highest competent authority to implement policies on animal use and resolve disputed issues.

INV-2

Alternative methods and innovation
Gribaldo, L.
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The European Centre for the Validation of Alternative Methods (ECVAM) is part of the European Commission's Joint Research Centre (JRC), and was established in response to Article 23 of Directive 86/609/EEC on the protection of laboratory animals. ECVAM coordinates and funds validation studies on non-animal test methods; furthermore, it conducts research in several areas of toxicology relevant to the safety testing. The cost of drug development has increased sharply in recent years, while approval of innovative drugs has declined. This "productivity gap" represents a major challenge for the pharmaceutical industry in Europe and throughout the world. One of the main reasons for the lack of new, innovative drugs is the high attrition rate during drug development. Three factors are major contributors and represent 66% of the causes for termination of drug development projects: toxicity in animals (20%), non-acceptable unwanted effects in humans (11%) and lack of therapeutic efficacy (25%) . Both lack of efficacy and unpredicted toxicity is due to the paucity of mechanism based and predictive preclinical toxicity testing approaches. Moreover, there is a trend toward stronger recognition of alternatives, due to increasingly evident shortcomings of current approaches. Amendments of the EP into the JRC FP7 have added the obligation to address alternative methods in this field.

INV-3

Dynamic Gastro Intestinal model with high IVIVC as alternative for animal studies
Havenaar, Robert; Zeijdner, Evelijn; Verwei, Miriam; Salmon, Florence
TNO, Biosciences, Zeist, Netherlands

Increasing numbers of drugs present a low bioavailability due to poor solubility and/or permeability. Its crucial to identify the limiting factors and to determine quantitatively which kinetic factors are responsible for low bioavailability. Due to differences in physiology between animals and humans, the predictive quality of preclinical studies is often insufficient. Especially food effects show large mismatches between results in animals and humans. TNO developed and validated the 'TIM system' (TNO Intestinal Model), a computer-controlled, multi-compartmental in vitro system simulating the successive physiological processes in the stomach, small intestine, and large intestine of humans. This system provides information on release and dissolution of hydrophilic and lipophilic compounds in the GI tract under fed and/or fasting conditions, as wll as related to age and health status. These data can be combined with data on

intestinal absorption in recently developed software 'TIMpk' to predict human blood levels. Comparison with human blood levels after intake of different dosage forms, demonstrated the high predictive quality of this combine methodology.

INV-4

Nanodevices: Where animal tests fail to meet testing needs
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Engineered nanomaterials have infiltrated several key markets including a number of medically relevant areas. In terms of drug delivery, nanomaterials used as drug delivery systems –herein referred to as nanodevices – are increasingly being investigated as tools that obviate problems bioavailability, systemic toxicity and biodistribution. Application-based variants of nanoscale materials raises other important questions, not least whether existing animal studies are capable of providing adequate safety information and whether representative nanomaterials can inform the risk assessment of other nanomaterials to minimize cost and animal welfare implications of the EU Chemicals Policy.
The relevance of animal models for evaluating nanodevices is discussed along with the role of in silico approaches, such as biokinetic modeling, structure-activity relationships and mathematical modeling of toxicity pathways, in guiding the selection of suitable alternative tests and developing relevant in vitro models and testing strategies. Specific reference will be made to models of skin, gastrointestinal and airway absorption, looking at the ways in which barrier function differs in vivo, ex vivo and in vitro as well as between species.

INV-5

In vivo drug absorption: experience from clinical models
Lennernäs, Hans
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The majority (~85%) of the 50 most-sold pharmaceutical products are given orally. This route of administration presently dominates drug therapy and is likely to continue to do so in the foreseeable future because in addition to causing minimal discomfort to the patient, it is safer, more efficient and more easily accessible than alternative routes such as intramuscular, subcutaneous, rectal and pulmonary delivery.. However, despite these advantages many of the mechanisms of drug uptake following oral administration remain to be fully characterized. Previously, for example, drug development projects were frequently terminated on grounds of poor gastrointestinal absorption and bioavailability. Today, however, it is fully recognized that it is important to consider the biopharmaceutical and pharmacokinetic variables for any drug candidate if a pharmaceutical product development program is to succeed. Over the last decade, these variables have been in focus in drug discovery/early development and consequently, the number of development failures has decreased. However, current pharmacokinetic prediction tools and strategies are constantly under development and can be significantly improved. This is especially true when predictions must be made from chemical structure and/or *in vitro* data. It is expected, therefore, that quantitative structure-activity relationship (QSAR) in pharmacokinetics would benefit from applying a chemical space that is large and as unrestricted as possible. Colonic absorption of drugs may differ significantly compared to the small intestine as a consequence of several physiological, physicochemical and biopharmaceutical factors. In general, permeability and solubility are considered to be the two most fundamental determinants of intestinal absorption, regardless of region. These two parameters also constitutes the basis of the Biopharmaceutics Classification System (BCS) for IR products It is also of major interest to more precisely identify the rate-limiting step(s) and improve our understanding of the mechanisms underlying gastrointestinal solubility, dissolution, chemical and enzymatic stability issues, membrane permeability and first-pass extraction. In order to improve the understanding these processes is to perform in vivo studies with various clinical models.

INV-6

How stable is gastrointestinal transit as a parameter in populations?
Wilson, Clive
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Gastrointestinal transit is a recognised as a key measure of efficacy in oral drug absorption. It dictates the absorption number and the dissolution number. The gut is designed for the absorption of nutrients and in adults, SITT, as measured as gastric t50% emptying to caecal t50% filling of (range 90 - 330 minutes) are sufficient to achieve complete assimilation. The whole small intestine does not greatly influence transit times per se, rather it is the interplay between duodenum and gastric emptying that influences supply into the small intestine, and the bowel habit imposes the final value on mouth-to-anus transit. Entry into the caecum is dictated by food intake and the neural information transferred between the stomach and the large bowel. Food, or more completely the composition of the meal and its total size relative to body mass and activity is the single most dramatic influence on transit. For true stabilisation of gastrointestinal transit, the contents of the meal have to be uniform and calorific value sufficient to trigger a fed response in gastric emptying. It is possible to control elements of transit by selection of appropriate meals which we have applied. The effect of this manoeuvre on colonic filling and emptying has not been investigated although the low residual volume (since the nutrients will be completely absorbed) is unlikely to affect colonic transit.

INV-7

Nanoparticle formulations of poorly soluble drugs
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A significant proportion of drugs on the market are poorly soluble in water and it is expected that this will be even more pronounced in the future. Formulations of poorly water-soluble compounds offers a challenge to the formulation scientist, from the early discovery phase through the development to the launch of the pharmaceutical product. Liquid formulations of poorly soluble compounds can be e.g. aqueous pH-shifted solutions, provided the molecules are ionizable, mixtures of water and organic cosolvents, or by solubilization in cyclodextrin or micellar systems. With the exception of the pH-shifted aqueous solutions, significant amounts of additives are often needed to increase the solubility into a practical range, which may induce unwanted side effects. An interesting alternative to these formulations is aqueous nanosuspensions with typical particle sizes of the order of 100 nm, and such suspensions can contain crystalline or amorphous particles.

In the presentation the preparation of crystalline as well as amorphous nanosuspensions will be described as well as the characterization of such systems. The latter will focus on stabilizer adsorption, Ostwald ripening and the dissolution rate of drug nanoparticles.[1-3]

References:
1) Lindfors et al, *Langmuir*, 22, 906 (2006).
2) Lindfors et al, *Langmuir*, 22, 911 (2006).
3) Lindfors et al, *Langmuir*, 23, 9866.

INV-8

Galenos Euro-PhD in advanced drug delivery
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Some 15 years ago, the GALENOS Network in Pharmaceutical Sciences was formed to promote and foster the education of young researcher especially in the area of Drug Delivery. Its membership meanwhile has grown to approx 70 partner institutions.
A startling initiative of the GALENOS Network is the establishment of a formal European

postgraduate certificate: The Galenos Euro-PhD in Advanced Drug Delivery, a certificate on top of the "regular" doctoral degree obtained from the student's home university. The Euro-PhD certificate distinguishes young pharmaceutical scientists who have participated in international research training and completed a significant piece of research at competitive level. Euro-PhD candidates must have (1) successfully completed a doctoral thesis on a subject relevant to the field of Drug Delivery, (2) published at least one paper in a peer-reviewed journal, (3) worked for at least 12 months at a research facility in a foreign country, and (4) have attended a significant number of approved postgraduate courses.
The GALENOS Euro-PhD program received substantial funding from the Marie Curie Program of the EC from 2004-08. More than 40 fellows were enrolled, and until now 20 have completed all Euro-PhD requirements. They have published 39 papers and 4 patent applications, won numerous awards and were offered attractive positions in academia and industry.

INV-11

Conventional cyclodextrins for the formulation of particulate systems
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We describe modern and attractive uses of cyclodextrin ability to include molecules for the preparation of particulate systems.
Beads were prepared from α-cyclodextrin aqueous solution and oil by continuous rotational stirring for several days. This allows the encapsulation of lipophilic drugs in beads of 1 to 2 mm in diameter. Beads have great potential in pharmacy or cosmetology for oral or dermal applications.
Nanoparticles were prepared with poly(isobutyl-cyanoacrylate) and various cyclodextrins which initiate the monomer polymerisation process and increase the drug loading capacity. Poly(γ-benzyl-L-glutamate)-β-cyclodextrin nanoparticles were also prepared; a number of free empty cyclodextrins remain available for inclusion of active ingredient.
Self-assembled nanogels were prepared by mixing aqueous solutions of β-cyclodextrin polymer and hydropobised dextran. Hydrophobic chains enter cyclodextrin cavities and lead to self formation of nanoassemblies. Extra empty cyclodextrins allow the nanoparticle drug loading.
In these examples, cyclodextrins demonstrate their unique potential and exceptional characteristics by participating in the particle formation process, particle loading and drug release modulation.

INV-12

Cyclodextrin derivatives as functional drug carriers
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Throughout the past decades, cyclodextrins and their semi-synthetic derivatives, have gained increasing interest as “active” excipients in drug formulation because they may form soluble inclusion complexes with many hydrophobic drugs and prevent degradation of labile molecules. Recently, CDs have been exploited to produce supramolecular carriers for controlled drug release and targeting. CD containing polyamidoamino and polyacryloilmorpholine have been synthesised to deliver anticancer and antiviral drugs, controlling either their release or passive distribution into tumours. Biodegradable PEG, CDs and camptotheicn self assembling supramolecular bioconjugates have shown excellent anticancer performance in a number of in vitro and in vivo studies. Lactoside-displaying pseudopolyrotaxanes have been found to rapidly and efficiently precipitate Gal-1, a dimeric lectin that regulates cancer progression and immune responses.
In this realm, new CD supramolecular derivatives (CD-PEG-folic acid) have been developed for active tumour targeting where the cyclomaltoheptaose acts as a drug “shuttle”,e PEG confers solubility and flexibility to the targeting moiety folic acid used for targeting malignant tumours. All these studies together open new interesting perspectives for application of CDs in tailoring supramolecular drug delivery systems with enhanced therapeutic performance.

INV-13

Amphiphilic cyclodextrins as potential gene delivery vectors

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Cationic cyclodextrins (CDs) and their supramolecular assemblies have been developed as a new class of synthetic DNA and siRNA vectors.
CDs have well researched pharmaceutical and toxicological profiles as excipients, and as oligosaccharides are unique in possessing multiple equivalent sites for chemical conjugation. In common with other non-viral vectors, polycationic CDs neutralise the charges on the phosphate DNA backbone and promote its condensation to a compact nanoparticulate complex for cell delivery. Further, it has been found that amphiphilic polycationic CDs are at least five times more efficient again, that is 20,000 times more efficient in transfection than uncomplexed DNA, and comparable to commercial cationic vectors.
After polycationic compaction of DNA or of siRNA however, there remains the need to remedy the toxicity of the polycationic nanoparticles in vivo, and to target possible neutral or negatively charged particles. Approaches to solving these problems will be discussed.
Other general ways in which cyclodextrins have been exploited as core molecules in the development of gene vectors will be compared.
Amphiphilic Cyclodextrins – Advances in Synthesis and Supramolecular Chemistry, F. Sallas and R. Darcy, Eur. J. Org. Chem., 2008, 957-969.

INV-14

Amphiphilic beta-cyclodextrin nanoparticles for cancer therapy

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Amphiphilic cyclodextrins (CD) are obtained by modification of primary or secondary face of natural cyclodextrins by grafting aliphatic esters. Amphiphilic CD nanoparticles were demonstrated to have favorable size, surface, drug encapsulation, drug release and stability properties to be used as delivery systems for cancer therapy for eventual accumulation of anticancer drugs in tumor tissues throuygh EPR effect (1). In this technique, nanoparticles were prepared directly from pre-formed inclusion complexes of drug with amphiphilic CD. This approach allowed 3-fold increase in loading efficiency with various lipophilic drugs (1).
In our research group, different anticancer drugs such as tamoxifen, paclitaxel and camtothecin have been incorporated into amphiphilic cyclodextrin nanoparticles. Amphiphilic CD nanoparticles were found to be safer in terms of hemolysis, re-crystallization and cytotoxicity to healthy cells for paclitaxel delivery as well as significantly higher anticancer efficacy (3). Camptothecin loaded CD nanoparticles have been evaluated for in vivo antitumor efficacy in rat glioma model in comparison to PLGA or PCL nanoparticles proving that amphiphilic CD nanoparticles provide a longer in vitro release and significantly higher survival time in vivo.
1) Bilensoy, E, J. Biomed. Nanotechnol., 4, 293-303, 2008 2) Bilensoy, E., et al, Int. J. Pharm., 347, 163-170, 2008

INV-15

Preclinical safety considerations for biotechnology products, scientific and regulatory aspects

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The aims of preclinical safety evaluations for pharmaceuticals are to identify potential target organ toxicity, to provide a safe starting dose for clinical trials, and to establish dose-response relationships. As such, these objectives are similar for small molecules and biotechnology-derived pharmaceuticals. However, biopharmaceuticals are products with complex structural and biological characteristics. In addition, biopharmaceuticals span a range of product types as well as therapeutic categories. As a consequence, for biopharmaceuticals it is often not possible to follow the standard safety testing program used for small molecules. Rather, individual approaches have to be applied. For preclinical safety testing, general as well as product-class

specific guidelines have been developed. Although originally designed with small molecules in mind, in today's non-clinical guidelines for biotechnology-derived products the unique nature of biopharmaceuticals is recognized. Accordingly, pre-clinical testing should also take into account factors that are not generally applicable to small molecules such as the pharmacodynamic responsiveness of the pre-clinical model, species specificity as well as the impact of antibody formation in the repeat-dose toxicity studies. In conclusion, a flexible and product-specific approach to safety evaluation is emphasized.

INV-16

Species selection for safety studies of biologicals
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Species-specificity is in particular inherent to many biologic drug candidates. This is a scientific and regulatory challenge emphasising the need for careful selection of the preclinical models and cautious data interpretation.
Species selection must be based a thorough knowledge of the target including its distribution, biological function and conservation across species. The validation process includes assessment of species differences in target expression, drug candidate affinity and response to binding. Evaluation of relevant *in vitro* and *in vivo* pharmacology and comparison to test systems based on human material are necessary.
In some instances, no relevant conventional species exists for testing the human drug candidate directly. Then, alternative animal models may be useful: animal homologues of the drug candidate, surrogate molecules targeting biologically similar pathways in animals or transgenic models allowing use of the human drug candidate in an otherwise non-responsive species.
For a safe transition into man, the preclinical *in vivo* data should be supplemented with *in vitro* data from human systems and data from naturally occurring disease. Selecting the best animal models and understanding their limitations are of key importance. This enables a qualified selection of the clinical starting dose and dose-escalation scheme and identifies areas for clinical monitoring.

INV-17

Clinical aspects of protein drug immunogenicity
Ross Pedersen, Christian
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The majority of protein drugs induce an unwanted immune response leading to the formation of anti-drug antibodies. The frequency and consequence of anti drug antibodies vary significantly from low levels of binding antibodies with no clinical effects to high levels of neutralizing antibodies interfering with the efficacy of the drug and potentially inducing severe side effects. The EMEA immunogenicity guideline focus on a risk based approach. The definition of risk is the probability times the consequences. A high immunogenicity risk can be associated with a low probability of antibody induction if the clinical consequences are severe (e.g. EPO). Several new technologies including transgenic animal models and T-cell epitope analyses have recently been suggested in order to try to predict potential immunogenicity of protein drugs in preclinical phases. Unfortunately, at present there is no evidence of any predictive value of these analyses. History has shown that some neutralizing anti-drug antibodies (e.g. EPO and IFNs) have been recognized several years after approval, underlining the difficulty of predicting an immunogenicity problem already in the preclinical phase that might occur 15 years later. The presentation will include a state of the art overview of protein drug immunogenicity, pitfalls during drug development and clinical consequences of anti drug antibodies.

INV-18

Academy and Pharmaceutical Industry – How do they cooperate to meet the new demands on product development and quality assurance?
Wahlgren, Marie

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In this presentation, I will give a personal view on the scientific challenges posed by the growing demands on securing quality based on a scientifically sound work. Focus will be on how to understand the link between product quality and variability both in process and in starting material. The presentation will take its starting point in the Q8 guidelines and the Quality by Design concepts. This state that quality by design should be achieved by a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management. The presentation will focus on the need for academia to support the industry with the possibility to deliver sound science in the field of understanding quality of pharmaceutical technology. Emphasising the need of better understanding concerning

- Arrested state and non equilibrium processes
- Understanding the affect of imperfections
- Understanding variability in starting materials and how to adept processes to these
- Combining the sciences of physical chemistry and fluid dynamics. In order to improve computer simulations.

The presenter will also give examples from her own and others work showing how these issues can translate into the academic field.

INV-20

Demands on the quality organisation in the pharmaceutical industry

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The changing environment with rapidly increasing of cost, longer time to market and specialisation of the different activities in the pharmaceutical value chain, puts pressure on the industry to find new ways to meet the market need. This presentation will summarize how to fit quality control and quality by design with the demand of high efficacy in product and process development along with "lean" manufacturing. Highlights on how to organise and handle the contract organisations (CROs;CMOs) in order to keep high quality products.

INV-21

Molecular imaging: from NMR over X-ray and beyond

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X-ray crystallography and NMR spectroscopy can be used to determine the structure and dynamics of globular and membrane proteins. The joint application of crystallography and NMR spectroscopy is rare and an application to the solution of the structure of a membrane protein will be shown.
In the second part of the talk, NMR spectroscopy and further techniques will be shown to characterize the conformational transitions of largely unfolded proteins that are involved in neurodegeneration. From those, toxicity models and treatment approaches will be derived and discussed in the talk.

INV-22

Fluorescence nanoscopy

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Far-field fluorescence microscopy is the most frequently used type of microscopy in biomedical research today. The method has long suffered from a relatively poor spatial resolution but since the invention of stimulated emission depletion (STED) microscopy and subsequent high-resolution techniques enables nanoscale imaging. Because STED microscopy is most efficiently implemented using ultrashort pulsed lasers STED microscopy has been notoriously associated with complex setups and costly and high-maintenance laser systems. Recent developments in supercontinuum laser technology have led to powerful, inexpensive and easy-to-operate light sources which allow a STED microscope to be built at a fraction of the cost and complexity of previous designs. It is shown that spatial resolutions down to 20 nm in 2D or 45 nm x 45 nm x 108 nm in 3D can be achieved. Unlike traditional (monochromatic) lasers, the broad spectrum of the supercontinuum source allows to choose basically any fluorescent marker which can be excited at a wavelength above 480nm. Also, multicolor operation is readily conceivable.
References: D. Wildanger, R. Medda, L. Kastrup, S. W. Hell, "A compact STED microscope providing 3D nanoscale resolution", submitted to *J. Microsc.*
D. Wildanger, E. Rittweger, L. Kastrup, S. W. Hell, "STED microscopy with a supercontinuum laser source", *Opt. Expr.* **16**, 9614 (2008).

INV-23

Potential of positron-emission-tomography for drug research

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The physical features of positron decay and the use of a corresponding bio-mathematical model allow quantifying molecular processes in man with positron-emission-tomography (PET). Using suitable radiotracers, physiological and pharmacological processes can be determined without interference of equilibria. This finds increasing interest for research in drug development. Given the sub-microgram doses applied with short-lived, no-carrier-added radiotracers, even toxic compounds can be studied. By authentic labeling of a compound with carbon-11 the measurement of its biodistribution is limited due to the short half-life (20.4 min). However, labeling by fluorine-18 (109.8 min) or other PET-nuclides with still longer half-lives expands possibilities to follow dynamic processes. Further, labeling in different positions or double-labeling can help to elucidate metabolic processes in vivo (fate of the label). A still wider spectrum of drug research is exploited by therapy-control studies. Here the behavior of a non-labeled drug is monitored by an established radiotracer. Thus, metabolic and pharmacologic interferences can be measured rather independent of the time of administration of the examined drug (pre and post). Given the small radiation burden with short-lived radionuclides, also repeated probing can be done. This is of great interest for proof-of-principle and dosing studies.

INV-25

Pharmacoinformatics – combining experimental pharmaceutical sciences with in silico methods

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The past decade was characterized by a huge increase in the amount of data retrieved from high-throughput technologies on the genomic, transcriptomic, and proteomic level as well as data arising from structural genomic, compound screenings and from imaging techniques. Searching, combining and mining these data represents one of the most challenging tasks for in silico sciences and definitely requires development of new methods and algorithms both from information technology and mathematical sciences. In parallel, pharmaceutical industry is facing the problem of steadily decreasing numbers of compounds brought to the market. Key issues for successful drugs include proper ADME properties as well as low toxicity and low potential for drug/drug interactions. With our increasing knowledge on the molecular mechanisms involved in these issues the importance of transport proteins became evident. We will highlight approaches

targeting compound profiling by combining experimental data and in silico modeling in the field of ABC-transporter. This includes data driven protein homology modeling of ABC-transporter, experimental data guided ligand docking and scoring, prediction of substrates using machine learning and rule fit models, pharmacophore based selectivity profiling, up to monitoring P-gp activity in vivo by PET ligands.
Supported by the Austrian Science Fund, grant SFB 35

INV-26

Adverse drug events as cause of hospitalisation
Leendertse, Anne J[1]; Egberts, Antoine CG[1]; Stoker, Lennart J[2]; van den Bemt, Patricia MLA[1]
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Background: Medication related hospitalisations have been the subject of many studies, which were often limited to one hospital.
Methods: A prospective, multicenter study was set up to determine the frequency of medication-related hospital admissions. Within this study a case-control design was used to determine risk factors for potentially preventable admissions. All acute admissions in 21 hospitals were assessed during 40 days. Controls were patients admitted for elective surgery.
Results: 13,000 acute admissions were screened, of which 714 (5.6%) were medication related. 46% of these admissions were potentially preventable, resulting in 332 case patients matched with 332 controls. Main determinants for preventable admissions were: impaired cognition [OR 11.9 (95%CI 3.9-36.3)], 4 or more co-morbidities [OR 8.1 (95%CI 3.1-21.7)], dependent living situation [OR 3.0 (95%CI 1.4-6.5)], impaired renal function [OR 3.1 (95%CI 1.9-5.2)], non-compliance [OR 2.3 (95%CI 1.4-3.8)] and polypharmacy [OR 2.7 (95%CI 1.6-4.4)] [1].
Conclusion: Adverse drug events are an important cause of hospitalizations. The identified risk factors provide a starting point to prevent medication related hospital admissions.
Reference: 1.Leendertse AJ, et al. Frequency of and risk factors for preventable medication-related hospital admissions in the Netherlands. Arch Intern Med 2008;168:1890-96.

INV-27

Modern tools of genotyping drug related SNPs: The DMET chip
Brew, Fiona
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Affymetrix has worked with the community to develop a solution which contains the most comprehensive, cost effective panel of known pharmacogenetic markers for standardizing drug metabolism studies. The product contains 1,936 markers in 225 drug metabolism and transporter genes, DNA markers in all ADME genes validated by FDA guidance and more than 90 percent of the PharmaADME Core markers. This has been coupled with a streamlined assay and automated analysis tools including star allele translation.
Published examples demonstrating the use of this product to provide market differentiation for a new drug, Prasurgrel (1) and determining Warfarin dose (2) will be discussed.

(1) Mega et al. (2009) Cytochrome p-450 polymorphisms and response to clopidogrel. NEJM, 360(4): 354-362
(2) Caldwell et al. (2008) CYP4F2 Genetic Variant Alters Required Warfarin Dose. Blood, 111:4106-4112

INV-28

Genetic basis of drug-induced liver injury linked to commonly prescribed drugs
Daly, Ann K
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A number of currently licensed drugs are associated with idiosyncratic liver injury. This drug-induced liver injury (DILI) is relatively rare but potentially serious, sometimes leading to death

or requiring a liver transplant. The genetic basis for susceptibility to this disease is still poorly understood. The DILIGEN study is a UK-wide study on the genetics of DILI focussing particularly on co-amoxiclav and flucloxacillin. DNA from DILI cases and controls has been genotyped for a range of candidate genes. More recently, genome-wide association studies have been initiated. It appears that the mechanisms underlying co-amoxiclav and flucloxacillin DILI are different but both are HLA-related with strong associations detected with HLA-B*5701 for flucloxacillin DILI (Odds ratio 80.6 (95% CI 22.8-284.9)) and with HLA-DRB1*1501 for co-amoxiclav DILI. DILI due to other drugs does not show a strong HLA association and, here, genotypes relating to drug disposition or oxidative stress may be more important predictors of susceptibility.

INV-30

Measuring and mapping scientific research
van Raan, Anthony F.J.
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We present an overview of measuring and mapping science based on advanced bibliometric methods. The two main lines are discussed. First, the measurement of research performance is addressed including aspects such as interdisciplinarity, collaboration, 'knowledge users', and scientific excellence. It is demonstrated that advanced bibliometric methods are an indispensable element in research evaluation procedures, particularly at the level of research groups, university departments and institutes. Second, an introduction to mapping of science is presented, focusing on basic concepts and issues of practical application of science maps. These maps enable us to discover patterns in the structure of scientific fields, to visualize the dynamics of scientific developments, and to identify processes of knowledge dissemination, particularly toward applications and technological innovation. We will present examples of the application of advanced bibliometric measuring and mapping methods in pharmaceutical research.

INV-31

Peer review: A status report
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According to Sir James Black "The anonymous peer review is the enemy of scientific creativity". Nevertheless, within EUFEPS it was felt important to discuss the peer review process and how it might be used to increase the impact of the pharmaceutical sciences, albeit with as little bureaucracy as possible. A EUFEPS workshop on institutional peer review was held in Leiden in January 2008 with attendees from different parts of Europe and from different sub-disciplines of the pharmaceutical sciences. Specific points of discussion were:
1. A definition of pharmaceutical sciences
2. How to ensure quality in the pharmaceutical sciences and to demonstrate it within and outside academia.
3. Development of criteria for the assessment of the quality of research in the pharmaceutical sciences across Europe.
4. The prospect of developing pan-European Networks of Excellence.
5. How to maximise appreciation of the benefits of pharmaceutical research to society.
Actions included stimulation of further discussion at PharmSciFair and prior to the call for EU funding through the IMI 7th Framework Programme, circulation of the report to the European Commission and other organisations to appraise policy makers of the need for continued support for European pharmaceutical sciences, and lobbying to separate 'pharmacology and pharmacy' in current citation systems.

INV-32

Public-Private-partnerships in the pharmaceutical sciences at the national level: the position of Ph.D. students and postdocs
Crommelin, Daan
Dutch Top Institute TI Pharma, Leiden, Netherlands

Public-private-partnerships (PPPs) are research initiatives where scientists from industry and academia are closely working together. The Innovative Medicines Initiative (IMI) is an example of a PPP at the European level. But, PPPs can also be found at the national level. In the Netherlands the Dutch Top Institute Pharma (TI Pharma) is a PPP where (foreign) and Dutch pharmaceutical companies (global players and SMEs) are collaborating in a number of consortia. Pre-competitive research (concept-driven) is performed in consortia where between 3 and 15 partners (companies and academic groups) work together. The projects have a running time of 3 -4 years. About 600 Ph.D. students, postdocs and technicians are employed in this virtual institute.
An important ambition of TI Pharma is educating and training a new generation of pharmaceutical scientists. Therefore, we offer our Ph.D. students and postdocs trainings courses where the translational character of the pharmaceutical sciences is emphasized. Moreover, TI Pharma/EUFEPS developed a course catalogue where all courses in the life sciences in the Scandinavian countries and the Netherlands are listed and categorized (http://www.etplatform.eu/database).
PPPs perfectly fit into the open innovation model, which is now (partly) adopted by a number of global Pharma companies. And, more national PPPs are already entering the active, operational phase or are being set up. Therefore, one can foresee that the PPP-model will become a major driver of innovation in Europe in the coming years.

INV-33

Vaccine delivery: past, present and...?
Jiskoot, Wim
Leiden University, Drug Delivery Technology, Leiden, Netherlands

This presentation will serve as a general introduction to the session "The Future of Vaccines: Trends in Tailored Vaccine Delivery". Concepts of vaccine delivery, adjuvants, delivery systems, immune potentiators, antigens... will be explained and illustrated with examples from own work and data from the literature.

INV-34

Dendritic cells: Why and how to target them
van Kooyk, Yvette
VUmc, MCBI, Amsterdam, Netherlands

Dendritic cells (DC) are specialized in the recognition of pathogens and play a pivotal role in the control of immunity. Yet DCs are also important for homeostatic control recognizing self antigens and tolerizing its environment, indicating that the nature of the antigen it recognizes may steer a DC towards immunity or tolerance. Dendritic cells have been used as vaccins for their potential to induce immunity by ex-vivo loading them with antigens. However future strategies are focussed on targeting DC in-vivo in order to directly modify antigen specific immune responses in the host. For in-vivo targeting strategies the presence of dendritic cell specific receptors are vary valuable. Moreover DC express various receptors are not only DC specifically expressed but also facilitate antigen uptake and presentation. We have shown that the C-type lectins that recognize specific glycan structures on antigens are specific antigen uptake receptors that process antigen for presentation to T cells. Glycan modification of antigen targeting C-type lectins can strongly affect the antigen uptake and presentation capacity of DC and instruct antigen specific CD4 and CD8 T cell responses. Our goal is to instruct DC using glycan modified antigens as protein/peptide or particulate compositions to tailored immune responses that control immunity against cancer.

INV-35

Intralymphatic administration enhances immunotherapy
Kundig, TM[1]; Senti, G[1]; Bot, A[2]; Johansen, P[1]
[1]Zurich University Hospital, Zurich, Switzerland; [2]MannKind Corp. USA, Valencia, United States

During the era of live vaccines the route of vaccine application was an issue that received relatively little attention. In fact, for live vaccines the intramuscular or subcutaneous administration is usually efficient, as live vaccines represent rather stable particles which drain into secondary lymphatic organs to induce immune responses. The situation is different for non-replicating vaccines and especially for subunit vaccines, where the classical intramuscular or subcutaneous administration may not be the optimal route to stimulate the immune system. Like for any other drug, the dose, the route of administration, the formulation, the duration of administration and the pharmacokinetics of the vaccine are of crucial importance. We find that non-replicating vaccines induce the strongest immune responses if administered directly into secondary lymphatic organs, and if the dosing of the vaccine follows an exponential increase over several days. We find that these principles hold true for full length protein vaccines used to induce CD4 T cell and antibody responses, as well as for naked DNA, RNA and oligopeptide based vaccines to induce CD8 T cell responses. Apparently the immune system interprets delivery into lymphatic organs and exponential vaccine dosing as "danger signals", as these characteristics are hallmarks of spreading and replicating pathogens threatening the host.

INV-36

Trends and technologies in vaccine formulation

Gander, Bruno
ETH Zürich, Zuerich, Switzerland

Present endeavours in vaccine development consider delivery systems with adequate in-built immunological properties. They include, e.g., a morphological and molecular mimicry of microbes or cancer cells. Morphological mimicry is achieved through particulate nature of the delivery system. Solid and liquid particles in the nanometer to low micrometer size range can be ingested by antigen presenting cells (APCs), e.g., macrophages and dendritic cells, which are important sentinels of the innate immune system. Prominent particulate delivery systems, made primarily from biodegradable lipids or polymers, encompass, oil (o) or water (w) droplets of w/o- or o/w-emulsions, liposomes and virosomes, virus-like particles (VLPs), nanoparticles, saponin-based complexes (ISCOMs), microparticles. Molecular mimicry is achieved by associating immunogens and immunostimulatory molecules with the particulate delivery systems. Immunostimulatory molecules may be divided into unspecific "danger signals" (e.g., saponins, surfactants, certain lipids and polymers) and receptor-binding molecules (e.g., those binding to Toll-like receptors, TLR). Association of the molecular stimuli with the particulate system can be achieved by a large variety of chemical and physical techniques, affording entrapment or attachment of the immunologically active compounds inside or on the surface of the delivery system.

INV-37

The role of the European Pharmacopoeia and EDQM in ensuring API quality

Spieser, Jean-Marc
EDQM/Council of Europe, Strasbourg, France

The presentation will focus on the contribution of the European Pharmacopoeia (Ph. Eur.) over the years in optimising the control of APIs. Particular emphasis will be given to the impurity profile which may change depending on the source and on how adequately to control it (process linked impurities, solvents and catalysts are very important). In this context the usefulness of the Certificate of Suitability of the Ph. Eur. Monographs (CEP) will be studied as a tool for better control of APIs in a global market.
New perspectives currently under discussion for possible development in the near future at EDQM will also be presented, particularly as regards combating eventual counterfeits.
Finally, the contribution of market surveillance to ensuring the supply of high quality products to the European patients will also be developed.

INV-38

The commission's legal proposal on falsified medicines

Atzor, Sabine
European Commission, Bruxelles, Belgium

On 10 December 2008 the European Commission has adopted a legal proposal on falsified medicines. This proposal for an amendment of the Directive on Pharmaceuticals includes a tightening of the legal framework to protect the legal distribution chain from counterfeit medicines to enter. The legal proposal has three pillars: Protection of the product through safety features and enhanced GMP requirements, tightening of requirements for wholesale distribution and trading and an enhanced framework for active substances. It also includes the legal basis for the Commission to establish implementing legislation on technical aspects, such as related to the safety features. The legal proposal is currently subject to discussions by the European Parliament and the Council, representing the 27 Member States.

INV-39

Present regulatory requirements for API manufacture – sufficient to protect public health or a trade barrier?

Oldenhof, Chris
ZENTIVA GROUP a.s., Quality Assurance, Prague, Czech Republic

The presentation will clarify how the safety of the API supply chain has significantly decreased over the past years. The present regulatory requirements for API manufacture will be assessed in terms of their effectiveness and weaknesses in the systems will be highlighted. In addition an evaluation will be presented on how the new EU Draft Directive on "Falsified Medicines" should be optimized in order to secure the safety of the API supply chain in such a way that the safety of patients will be adequately protected.
It will also be discussed which types of API regulatory requirements can be regarded as "Trade Barriers". Examples of existing API Regulatory Trade Barriers will be presented and tools available for breaking down such barriers will be briefly described.
Finally the question will be answered whether current or future EU regulatory requirements for APIs could be considered as Trade Barriers.

INV-40

Sourcing API - challenges for a (generic) pharmaceutical manufacturer

Petr, Jan
ZENTIVA GROUP a.s., Quality Assurance, Prague, Czech Republic

Sourcing API is one of the key processes for generic pharmaceutical company determining whether the company succeeds in heavy competition. Nowadays it is not usually a problem to find several sources for API of interest for at least "modern" API. Many manufacturers especially in the third world react quickly to API fashion as well as to patent situation offering products of desired quality and maintaining appropriate quality system. It enables quick qualification of API source. What becomes a real challenge for big generic pharmaceutical company is to maintain the pool of all API sources to ensure the quality and availability of all marketed products. Big competition between API manufacturers creates a risk that positively qualified API source could stop the deliveries or even worse start deliveries of the products potentially risky for the patients. Also possibility of other potential risks as repacking, reckless transportation or even intentional frauds should not be underestimated these days. All these factors impact significantly the strategy of generic pharmaceutical companies on API sourcing and maintaining of qualified sources.
Generic pharmaceutical companies market hundreds of brands on markets in the Central and Eastern Europe. Company strategy for own API manufacturing, API sourcing, qualification of sources, and maintaining of the qualified sources is presented.

INV-42

Registration and continuing professional development for toxicologists concerned in safe use of chemicals: the EUROTOX view

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Registration is important for Toxicologists whether investigators or regulators. A European Registered Toxicologist (ERT) is a member of a society of Toxicology affiliated to EUROTOX, or perhaps a EUROTOX IM. This gives access to products and services both basic and advanced (for examples of recent courses see: http://www.eurotox.com/doc/CEC.pdf). Professional Development is a cornerstone of our working life. Through encouragement of Registration and regular Re-Registration, EUROTOX offers support to toxicologists, to the point of Registration and beyond. Successful Registration provides an individual with improved credibility, trust and respect from colleagues, customers and employers, and provides greater flexibility of employment. Over the last 10 years, EUROTOX, Asian and American societies of Toxicology have been moving towards a global understanding of what is needed in the various regions of the world and greater harmonisation of standards. In Europe, we have good access to training opportunities and mentors. Whether reviewing, reporting, or regulating, scientists in Safety Sciences, Registration, Contract and Academic Research can become ERT: European Registered Toxicologist. At this time (5th April, 2009) there are 1301 ERTs listed by EUROTOX. All ERTs, by definition, are considered to be contributing to globally significant improvements in the safe use of chemicals.

INV-43

Industrial and regulatory needs for drug safety education and training

Muchitsch, Eva-Maria
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Experts from a number of different disciplines contribute to investigating the safety of candidate drugs before medicines are released to the market. However, the high specialization within each discipline can lead to a lack of an overall picture of drug development, which can result either in inefficient and delayed progress or in drugs failing in human clinical trials. Therefore a new type of scientist is needed to provide a more holistic approach to the evaluation of the safety and efficacy of drug candidates. Training and education should allow better assessment of *in vitro*, animal, and patient safety data. Therefore the scientist should be trained in scientific skills such as translational medicine approaches and in skills associated with industry, such as industrial know-how including an appreciation of safety aspects and their impact on drug discovery, development and use, to become better equipped to judge the safety data and profiles of new and existing medicines. Both a critical understanding of general safety testing approaches and an ability to identify cases where adaptations of standardized studies are necessary are important.

INV-44

European Modular Education and Training Programme in Safety Sciences for Medicines (SafeSciMET)

Vermeulen, Nico P.E.[1]; Guentert, Theodor W.[2]; Vermeulen, Nico P.E.[3]
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In current drug safety education and training in Europe, an integrative and translational approach is lacking. This shortfall has been identified by EUFEPS, IMI ('Strategic Research Agenda'), FDA and EMEA. We present a new and unique pan-European education and training network, which solves this shortfall by establishing a comprehensive modular Education and Training Programme in Safety Sciences for Medicines (SafeSciMET). A network, consisting of 19 academic top institutes for drug safety education and research and 16 industrial pharmaceutical companies, all EFPIA members, have successfully proposed to IMI-JU a new type, high quality and sustainable programme for education and training in Safety Sciences for Medicines. This programme will fulfil the needs of pharmaceutical industry, regulatory authorities and academia.

The tailor-made training courses will encompass the safety, ethical, regulatory and societal aspects in all phases of drug development, with emphasis on integrative, translational and 3Rs aspects of drug safety assessment. Individual safety professionals who wish to address specific knowledge gaps will be able to follow single courses. The modular set up also provides an excellent opportunity for dedicated subsets of courses, to be accredited for Continuing Professional Development (CPD) and an accredited Master of Advanced Safety Sciences of Medicines (MAS2M).

INV-45

Switching from better making to making better products using PAT/QbD philosophy
Sam, Tom
Schering-Plough, Women's Health & Medical Devices, Global Regulatory Affairs CMC, Oss, Netherlands

The PAT/QbD philosophy stimulates innovation through the promotion of better development of drug product manufacturing processes. This is however only part of the story, since the true added value of Quality by Design is in the development of better products, that are better aligned with the needs of the individual patient and the health environment. Key is to optimally define the Quality Target Product Profile for the patient and to translate this for the drug product to be developed into quality attributes that are critical for patient safety, efficacy and use. An iterative and adaptive cycle during development based on increased knowledge and adequate management of the risks, should lead to such a better product.
An example of better developing drug products that could benefit from QbD and PAT approaches is continuous manufacturing. An example of developing better drugs is to use QbD and PAT to produce customized, individualized medicine.

INV-46

Combining modern powder characterisation techniques with real processing experience
Freeman, T
Freeman Technology, Welland, United Kingdom

Powder processing represents a major part of pharmaceutical manufacturing and yet few predictive tools exist, relying instead on the skill of the individual operator. There is surprisingly little information regarding the factors that effect powder processing and what can be measured to predict potential problems and answer questions like "will this batch compress well?"
Recent advances in modern technology provide new opportunities to measure process relevant characteristics of powders, enabling a database of flow properties to be established for every raw material, intermediate and final blend. When combined with the extensive qualitative knowledge that the process operators have in regard to which formulations work well on specific equipment, materials can be ranked for processability and this can be correlated with the measured flow properties.
Powder processing is challenging, but with the tools to quantify powder behaviour, there is real opportunity for improvements in efficiency and ultimately cost savings due to reduced time to market and fewer lost and reworked batches. In addition, a quantified knowledge of processability can be fed back into the development environment providing a design space for formulators, so that flow properties and processability can be considered at this early stage – the essence of QbD.

INV-47

Near-infrared spectroscopy - pat's favourite pet
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Near-Infrared Spectroscopy (NIRS) is by far the most likely tool to use for a PAT project. It has been used for process analyses for decades, so there is a vast reservoir of experience in the

literature. Why NIR? Analyses by NIR are routinely run on "as is" samples; this allows the analyst to measure physical as well chemical parameters. NIR was the first method to utilize multivariate software in the 1980s (Principal Components and Partial Least Squares), so the software currently used in NIR is already routinely compliant with FDA and EMEA regulations (including 21CFR part 11). Instruments are small, fast, quiet, sensitive, often wireless, and rugged. These instruments may be located at multiple locations along a process stream, reporting such chemical information as moisture levels, API levels, and distribution of excipients and APIs. Physical information comes from the fact that 1) the product is not treated, so shape, size, and physical properties are easily correlated, and 2) NIR, based on OH, NH, and CH bonds, is highly sensitive to hydrogen bonding. Physical measurements include hardness, surface area and particle size, degree of crystallinity, crushability, porosity, and polymorphic form; all now critical to any QbD program. Dosage forms are measured for dissolution profile (prediction), hardness, and levels of coating. Is it any wonder NIR is a crowd favorite?

INV-48

Gaining understanding of the blending process using on-line NIR spectroscopy
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Bruker Optics, Marne La Vallée, France

In this study we implemented near-infrared (NIR) spectroscopy as a tool to assess a pharmaceutical quality assurance parameter, blend uniformity, in the manufacturing step prior to compression. An on-line system based on Fourier-Transform (FT) technology and configured for diffuse reflectance measurements was used to rapidly collect spectra of common pharmaceutical blends including materials such as lactose, talc, stearic acid magnesium stearate and active pharmaceutical ingredient (API). By using peak integration methods and statistics based on moving block standard deviation calculations, the blend uniformity end point was predicted by the NIR. This approach has many advantages over conventional NIR spectroscopy as a model-free approach is used. This makes it unnecessary to capture samples via a thief and calibrate using HPLC as the primary method. The non-contact FT-NIR sensor was mounted on-axis and focused on the material being blended through a sapphire window on the rotating container. Container volumes from 4 litres to 60 litres were used in this study. It was found that blend uniformity can be predicted accurately and repeatably even when low levels of certain excipients, typically less than 1%, were being blended.

INV-49

Swelling-controlled release 30 years later: Responsive intelligence and delivery bydesign
Peppas, Nicholas
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In recent years, there has been considerable work in preparing intelligent biomaterials and finding new uses for nanoscale structures based on such biomaterials. Uses such as microchips, micropatterned devices, materials for biosensors, systems for biological recognition, and carriers for controlled and targeted drug delivery have shown the versatility of these biomaterials. Of specific interest are applications for the formation of nanoscale three-dimensional structures. These micropatterned structures may be used for a host of applications including cell adhesion, separation processes, the so-called "factory-on-a-chip" microscale reactors, and microfluidic devices. In recent years there has been an explosion in the field of novel microfabricated and nanofabricated devices using intelligent hydrogels. They include nanoparticulate systems, recognitive molecular systems, biosensing devices, and microfabricated and microelectronic devices. Certain techniques can change the chemical nature of surfaces and produce areas of differing chemistry as well as surfaces and polymer matrices with binding regimes for a given analyte. Biomimetic methods are now used to build biohybrid systems or even biomimetic materials (mimicking biological recognition) for drug delivery, drug targeting, and tissue engineering devices.

INV-50

Dome Matrix: a new technology for oral delivery and polytherapy

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The health system in developed Countries is facing challenging issues related to the rapid increase of aging population and the need to adapt medicines to personalized therapies. The expansion of the knowledges on the physio-pathological processes offers nowadays, new insight for a more specific drug targeting also for the oral administration route. Moreover, poly-pharmacy, namely the administration of different drugs in a single dosage form, will become crucial in the near future for the simplification of the therapy and the improvement of the patient compliance.
Dome Matrix® is a new and flexible drug delivery technology for the oral delivery of precise drug doses, in the desired time and in a particular portion of the G.I. tract (stomach or colon). This delivery system is obtained by assembling two or more individual modules, containing one or more drugs. According to the assembling mode, it is able to co-deliver different drugs with predefined and specific kinetics or, to prolong the transit time of the dosage form in the G.I. tract through its flotation on the stomach content. This last feature can be exploited for improving the bioavailability of drugs that present a specific absorption window in the upper part of the gut.

INV-51

Swellable matrices as coatings/shells for time controlled delivery

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Swellable hydrophilic polymers are widely used in the field of modified release of bioactive compounds. Over the past decade, they have been proposed as coating agents for the achievement of oral pulsatile delivery systems intended for chronotherapy or site-controlled release. In this presentation, the design, preparation and performance of coated delivery systems and capsular devices based on hydrophilic cellulose derivatives are addressed. Press-coating, spray-coating and powder-layering techniques were employed to prepare HPMC-coated systems, whereas hot-melt extrusion and injection molding (capsule-like mold dies) were used to manufacture HPMC- or HPC-based shells to be filled with the drug formulation.
Both coated and capsular devices were proven capable of delaying the onset of release for programmed time periods. When enteric-coated, the systems also yielded selective release of drugs into the distal gastrointestinal regions, as assessed by scintigrafic studies. According to the results obtained in terms of feasibility and physical-technological as well as release characteristics of the proposed devices, these were shown as innovative pulsatile delivery platforms based on swelling/erosion of barrier matrices. Moreover, thanks to the possibility of combining differing barrier/shell compositions and core/content types, highly versatile release performances could be achieved.

INV-52

Challenges and limitations of translating pharmacogenetics into clinical practice

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Adverse drug reactions and non-effectiveness is a limitation of drug treatment, causing extended hospitalization and substantial costs. Partly they are due to foreseeable genetic traits. In particularly the pharmacogenetics of drug metabolizing enzymes but also of transporters have been investigated extensively in the last decade. Major determinants are gene amplifications leading to diminished drug bioavailability and loss of function mutations, causing elevated risk of side effects and toxicity. More recently there is also a better understanding of genetic traits leading to interindividual differences of drug response due to polymorphisms of drug receptors or factors, involved in hypersensitivity of drugs. However, pharmacogenetics of many known drugs is currently not yet considered in clinical practice due to the lack of large prospective studies, investigating the clinical and economic benefit and due to the reluctance of cost refunding for diagnostics by many health insurances. On the other side consideration of

pharmacogenetics is worthwhile in the use of drugs having a narrow therapeutic index, long lasting therapy, and functional consequences and considerable allelic frequency of the genetic variants. As a consequence the label of selected drugs was exchanged in the recent years, recommending or demanding pharmacogenetic diagnostics prior to drug treatment.

INV-53

Genetically based therapy of warfarin

Caraco, Yoseph; Bezarano-Achache, Idit; Shaul, Hanan; Blotnick, Simha; Muszkat, Simha
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Warfarin is the most prescribed anticoagulant world-wide. Yet physicians are often reluctant to use it because of its inherent narrow therapeutic window and the marked inter-individual variability in its effect. The common clinical approach was until recently to prescribe small initial warfarin doses combined with frequent INR monitoring. This trial and error approach is far from being an ultimate solution as it does not eliminate the risk of bleeding or the likelihood of recurrent thrombotic events. The identification the genes encoding for two key enzymes involved in warfarin metabolism and effect (i.e. *CYP2C9* and *VKORC1*) holds a great promise for the vision of personalized warfarin therapy. In a multi stage study, the extent of reduction in S warfarin clearance among carriers of different *CYP2C9* genotypes was characterized and used to construct CYP2C9 adjusted algorithms that were subsequently shown to improve the safety and efficacy of warfarin therapy in a randomized control study. Next the contribution of *VKORC1* genetic polymorphism was incorporated yielding *CYP2C9-VKORC1* combined genotype corrected algorithms that further improve the ability to predict the individual's dose requirement during induction. Current research focusing on the as yet 40-50% unaccounted variability that cannot be explained by genetic, demographic and clinical details will be reviewed.

INV-54

Pharmacogenetics and pharmaceutical industry

Raaijmakers, Jan A.M.
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In the early days of the description of the human genome, expectations on its use in the development of insight of diseases, underlying mechanisms and the development of innovative and personalised medicines for important diseases where very high. Now it’s easy to say that most stakeholders were overoptimistic: genes are only part of the full spectrum determining the effects of a drug in terms of efficacy and safety. Proteins provide the function and translation therefore is an important aspect of the influence of a genetic phenomenon. Next to that, there may be parallel processes and/or compensating mechanisms that overcome a certain genetic deficiency. However, although we are far from resolving all existing diseases by therapeutics developed on the basis of genetics, pharmacogenetics has shown it's use in the development of relevant knowledge dealing with pharmacotherapy. Industry is starting to embed this knowledge in the designing of innovations and applications leading into the direction of more personalised medicine. Next to existing examples, both in terms of efficacy and safety, it seems logical that future will bring more applications. However, current knowledge leads to an integrated approach of pharmacogenetics as part of systems biology, providing a more complete image of reality surrounding disease and therapy, including i.e. environmental factors and behaviour

INV-55

Improvement of leukemia treatment

Matthias, Schwab
Margarete Fischer-Bosch Inst of Clin Phamacology, Stuttgart, Germany

The individual reaction toward a given drug varies between individuals, and may depend on many factors. Pharmacogenetics is well known affecting biotransformation and clinical outcome. Treatment results in childhood acute lymphoblastic leukemia (ALL) are one of the true success stories of modern clinical oncology (cure rates of >80%). Modern regimens consist of several

elements: 1) induction phase using multiple cancer agents; 2) consolidation to eradicate residual leukemic blasts; 3) extra-compartment therapy (e.g. CNS-directed therapy), and 4) maintenance period to further stabilize remission. Adjustment of therapy acc. to the risk of treatment failure has become a common feature in management of ALL. Research on clinical and biological aspects of ALL has identified numerous features with prognostic potential. These factors mostly include clinical, immunological and genetic characteristics. 6-mercaptopurine is an essential component of treatment protocols for ALL. Insights into thiopurine pharmacology led to the development of strategies for improving efficacy and toxicity. One important route of metabolism for thiopurines is methylation by the enzyme thiopurine S-methyltransferase (TPMT). TPMT is subject to phenotypically relevant genetic variation, but the validation of this information and its potential translation into clinical practice is still an ongoing process.

INV-56

Biomarkers (BMs): What are we talking about? And the regulators' view
Flamion, B.
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The term BM can be interpreted in many different ways, with different implications. An FDA-based consensus definition of a BM is "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention". A BM is usually a biochemical entity, such as a protein or DNA/RNA sequence, or a physiological measurement such as blood pressure. The FDA and EMEA have recently established a formal process for the qualification of BMs with the aim to determine if a BM is "fit for purpose" during drug development. Through that process in 2008 seven urinary BMs including Kim-1 and clusterin were officially accepetd for the detection of acute drug-induced nephrotoxicity in preclinical studies. The value of a BM is determined by its specificity, sensitivity, prediction, robustness, and capacity to bridge the pre-clinical–clinical domains. BMs should be non-invasive and accessible. To act as surrogate endpoints, they require additional qualification including demonstration of clinical utility. The increased use of BMs in drug development is expected to help control PK variability, define new disease subsets and allow early detection of poor responders and adverse events. In a word, BMs should lead the way to targeted therapy and personalised medicine.

INV-58

Biomarkers in oncology drug development
Orr, Maria C M
AstraZeneca, Oncology Therapy Area, Macclesfield, Cheshire, United Kingdom

The pharmaceutical industry is facing the challenge of high clinical development costs and declining drug discovery success rates. This is particularly true within the field of oncology where only approximately 5% of all drugs successfully make it to the market. Biomarker analysis has become an essential component of oncology drug development, particularly in the era of targeted therapy. Analysis of biomarkers can ensure that clinical studies are testing the appropriate biological hypotheses and can help to ensure that drugs, with the greatest chance of success, are progressed. For those drugs taken forward, effective development and use of biomarkers has the potential to positively impact the drug development process by helping to choose the appropriate dose, schedule and patient population. In this talk I will present data to support the use of biomarkers throughout the drug development pipeline to aid early and effective decision-making.

INV-59

Biomarkers or hard clinical endpoints for registration in lipid lowering agents, osteoporosis, diabetes
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There are doubts on the value of biomarkers in certain disease areas. In osteoporosis the value of BMD (bone density) has been questioned as predictor for fracture risk. Certain medication increased BMD without reducing fracture risk and vice versa. More doubts rose because the change in BMD underestimated the fracture effect of bisfosfonates. Other markers such as for bone turnover came of interest. It is clear that different drugs have divergent effect on BMD, turnover and fracture risk.
Cholesterol and especially LDL are long times seen as a validated markers for the complications of atherosclerosis. HDL was seen as a marker for protection. Recent studies indicated that both markers were not fully predictive for new drugs. In these studies changes in LDL and HDL were not predictive for changes in media intimal thickness of the carotid artery, believed to be a relevant marker.
In diabetes blood glucose levels and especially HbA1C has long seen as the ultimate predictor for diabetic complications. Newer drugs with different mode of action showed that this correlation was not as strong as believed before.
In general these markers as such were correlated in epidemiologic studies with CHD, diabetic complications and osteoporotic fractures. For some medicines this was confirmed, the relationship between markers and disease progression exits. Newer drugs were developed on the basis of these biomarkers. Huge clinical trials were started based on this correlation with disappointing results.
This all has major consequences for registration requirements. Authorities want to be seen clinical outcome data for new drugs. The ultimate questions is, do we need these date at the time of registration or should registration be based on the long believed markers and should those studies be finalized after registration. If not, it will be a huge barrier for placing new drugs on the market. The public is in doubt. Patients want to have early access to new drugs; other public bodies do not hesitate to ask for final data before treating patients.

INV-60

Preclinical modeling in translational research of active immunotherapies
Bot, Adrian
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During the last decade, there was little success in translating the concept of 'therapeutic vaccination' to oncology. Thus, active immunotherapy of cancer remains a goal in light of the failure of current therapies to achieve disease control over a long interval. Numerous attempts to develop investigational vaccines for cancer failed due to several reasons including the overreliance on preclinical models. The indirect nature of the mechanism of action of vaccines, species-specific immune responsiveness and last but not least, the difficulties in modeling human tumors – all contributed to the underestimated translational gap between preclinical modeling and clinical setting. Herein, exemplifying with concrete evidence resulting from translation of novel investigational vaccines, we propose a paradigm change to expedite their development: 1) first, understand the limitations of specific preclinical models; 2) formulate accordingly, the right questions to ask in such models and 3) use complementary information (obtained in vitro or in clinic) to optimize accordingly the development process. Application of this paradigm highlights several major challenges, as well as opportunities for this class of investigational agents as 1) adjunctive therapies in indolent, bulky disease; or 2) monotherapy for rapidly progressing, disseminated disease of limited burden.

INV-61

Ex vivo skin models for screening intra-dermal vaccine delivery
Birchall, James
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The skin contains a network of dendritic cells (DCs) that can be activated to initiate an immune response. To exploit this opportunity a range of technologies are being developed to target delivery of vaccine candidates to epidermal and dermal compartments. Animal models are not reliable for intra-dermal immunisation studies due to significant interspecies variations in skin morphology, permeability, biology and immunity. Ex vivo human skin could provide a valuable pre-clinical model to complement in vivo animal models and bridge the gap between pre-clinical

and clinical studies. DCs are however likely to be activated indiscriminately by physical stimuli and therefore the ex vivo skin model requires optimisation to maximise explant viability and minimise artefactual DC activation. Our studies aim to demonstrate preserved viability of ex vivo skin through histology, expression of exogenous DNA and DC activation. Subsequently, the model is exploited to demonstrate the ability of microneedle devices to deliver peptide and DNA vaccines to human epidermis. We conclude that full-thickness human skin can be cultured for a minimum of 72 h to study gene expression and immune cell activation and therefore provides an ideal and clinically relevant substrate in which to assess early cellular responses to intra-dermal vaccines delivered via microneedles and alternative modalities.

INV-62

Dealing with HIV-1 diversity

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Introduction: One of the big roadblocks in development of HIV-1/AIDS vaccines is the enormous diversity of HIV-1, which could limit the value of any HIV-1 vaccine candidate currently under test.
Methods: To address the HIV-1 variation, we designed a novel T cell immunogen, designated HIVconsv, by assembling the 14 most conserved regions of the HIV-1 proteome into one chimaeric protein. Each segment is a consensus sequence from one of the four major HIV-1 clades A, B, C and D, which alternate to ensure equal clade coverage.
Results: The gene coding for the HIVconsv protein was inserted into a number of vaccine vectors, which alone and in a prime-boost combination induced HIV-1-specific responses in mice and non-human primates.
Discussion and Conclusion: This vaccine approach provides an attractive and testable alternative for overcoming the HIV-1 variability, while focusing T cell responses on regions of the virus that are less likely to mutate and escape. Furthermore, this approach has merit in the simplicity of design and delivery, requiring only a single immunogen to provide extensive coverage of global HIV-1 population diversity. Phase I clinical trials in healthy and HIV-1-infected individuals testing HIVconsv vaccines have been funded and are under preparation.

INV-63

The future of vaccination: Novel indications and applications

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Non-communicable, chronic diseases are currently the major cause of death and disability worldwide and many of these maladies have reached epidemic proportions. According to WHO these disorders, including cardiovascular and respiratory diseases, diabetes, obesity and cancer, now account for 59% of the 57 million deaths annually and almost half of the global disease burden. WHO identifies comparatively few risk factors, namely smoking, alcohol abuse, obesity, high cholesterol, and high blood pressure as the cause of many of these chronic conditions. We are developing a new class of medicine, based on vaccines approaches, to treat both risk factors and their associated chronic diseases. Two such vaccines, targeting smoking cessation and hypertension, have now clinical proof-of-concept and preclinical as well as clinical results will be presented for both vaccines. The current data indicate that therapeutic vaccination may indeed be a new modality to treat chronic diseases.

INV-65

Multidisciplinary approach to the physical characterisation of pharmaceutical solids

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Among the many challenges in the development of drugs from pure compounds to dosage forms, suitable for safe and efficacious use in patients, increasingly important problems are crystalline polymorphism and poor aqueous solubility of many small molecular weight drugs. With the advent of combinatorial chemistry these problems are likely to become even bigger in the future. Investigation of the polymorphism of pure drugs and drugs in dosage forms is therefore an area of intensive research both in the pharmaceutical industry and in academia. A lack of knowledge about the polymorphism of drugs may have severe consequences not only for efficacy and safety of drugs, but also for patenting of drugs and registration of dosage forms.
To increase the solubility of drugs, and thus their bioavailabilty, crystalline drugs may be converted to amorphous forms, either on their own or together with polymeric excipients. Lack of knowledge about the physical stability of these systems is a major obstacle in the rational development of such dosage forms.
To be able to tackle the problem of polymorphism and to be able to formulate drugs in the amorphous state, it is of great importance to rapidly and reliably detect and quantify the solid state properties (crystallinity, polymorphism) of drugs, both alone and in pharmaceutical dosage forms. Currently x-ray diffraction and thermal analysis are mainly used to investigate these properties
The aim of this presentation is to investigate a multidisciplinary approach, including the use of a range of spectroscopic techniques, to perform qualitative and quantitative analysis of the solid state properties of drugs alone and in pharmaceutical dosage forms, in which the drug is present in different solid state forms. Research from our group will be presented, covering the use of Raman spectroscopy, terahertz pulsed spectroscopy, terahertz pulsed imaging and second harmonic generation in the above-mentioned areas.

INV-66

Molecular level understanding and controlling of solid phase transformations
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The majority of active pharmaceutical ingredients (APIs) and excipients can exist as multiple crystalline forms, such as polymorphs, solvates/hydrates, and cocrystals. Such an ability implies that interconversions (i.e. phase transformations) among solid forms of the API (and/or excipient) may occur during its processing and formulation (e.g., milling, granulation, drying, compaction). Owing to the dependence of the properties of pharmaceutical crystals on the solid-state structure, these phase changes can adversely affect their clinical performance, stability and/or processing characteristics. The control over the solid-state form of pharmaceutical crystals is, therefore, essential for both product performance and compliance reasons. This control can be achieved through the knowledge of phase transformation behavior of pharmaceutical materials. More precisely, understanding of the mechanisms governing these phase transformations at molecular level is required for building-in the consistent quality and reliable performance into the drug product.
In this presentation, the overview of modern approaches to detecting, understanding and controlling of solid phase transformations in pharmaceutical systems will be provided.

INV-68

Health economic aspects of adherence to lipid lowering drugs
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The clinical efficacy of lipid lowering therapies, primarily the statins, is well documented in many large clinical trials. There is also a large number of health economic studies assessing their use, indicating statin therapy to be cost-effective, that is to say to provide good value for money, in large groups of patients in both primary and secondary prevention. This is particularly true in the present situation where large price decreases are observed due to patent expiration on several products. In spite of this, adherence to lipid lowering therapies has been shown to be quite low in actual clinical practice with as many as 30 – 50 % of patients ceasing to renew their prescriptions in a few years time. Studies based on registry data indicate that this have

potentially serious health consequences, and also an impact on resource use and costs. The association between decreased adherence and increased risk of cardiovascular events has also been confirmed by findings in open-label follow-up of trials such as ASCOT-LLA. The bad health economic outcomes (bothin terms of costs and I terms of health) associated with low adherence raises the questions how adherence can be improved – in a cost effective fashion. This is an area which merits future attention from the research community.

INV-69

Can better drug treatment improve long-run financial sustainability of NHS in Italy? The case of statins

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The aim of this research is to empirically estimate the aggregate potential savings that could be obtained by reducing CVD hospitalization rates through improved drug treatment in both primary and secondary prevention.
We use a sample panel of patients obtained from the Health Search database, run by the Italian Society of General Practionners (SIMG). The selected panel includes a representative sample of the Italian population aged between 40 and 70 years, with at least one prescription of a statin-based drug over the period 2001-2006. More than 11,000 patients have been followed from a minimum of 6 months to a maximum of 60 months (from January 2001 to December 2006).
Our results show that better compliance with drug treatment may save a significant amount of money both in the short and long run period by reducing direct and indirect costs. Estimates of the total potential savings range from 3.8 billion euros per annum in 2010 to 5.2 billion in 2040. Furthermore, we find that long-run saving profiles are very different across the 20 Italian regions, suggesting the need to implement different regional health policies in the future.

INV-70

Hypolipidemic agents in chronic therapy. A compliance study in the Italian ASSET cohort

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In the 2000-2005 five years period, the utilisation of statins showed a threefold increase, from 16.5 to 52.3 DDDs/1,000 weighted residents, while the admissions for myocardial infarction decreased only marginally from 1.40 to 1.30 admissions/1,000 weighted residents. In the same period, the Italian National Healthcare System invested cumulatively over 4 billion euro to fund the prescribing of statins in primary care.
This study poses the question about the value of current utilisation of statins in general practice. The objective of the study was to evaluate the percent of persistent and compliant subjects twelve month after initiating statins' treatment in a controlled cohort of over 3 million Italian residents (the "Asset" cohort). Persistence was defined as the rate of subjects without an interval between two consecutive Rx < DDDs prescribed + 30 days. Compliance was defined as the rate of persistent subjects with total number of DDDs prescribed/365 > 80%. Out of the 33,139 patients enrolled, only 7% were persistent and 6% compliant (84% of persistent) The rate of persistent patients rapidly increases by relaxing the time interval between consecutive RXs.
A focused emphasis on individual compliance to treatment would significantly increase the expected outcomes and, consequently, the economic value of statins prescribing in general practice.

INV-71

Polysaccharidic particulate hydrogels for biomedical applications
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Polysaccharides are abundant in nature and readily available from renewable sources such as the algal and plant kingdoms, cultures of microbial selected strains, as well as through recombinant DNA techniques; thus, they have a large variety of composition and properties that cannot be easily mimicked in a chemical laboratory, and the ease of their production makes numerous polysaccharides cheaper than synthetic polymers. Hydrogels, according to Peppas, "are three-dimensional, hydrophilic, polymeric networks capable of imbibing large amounts of water or biological fluids". These networks, that can be classified into two main categories according to the type of cross-linking among the macromolecules, whether chemically or physically based, show significant similarities with living tissues and are consequently very useful for a wide variety of pharmaceutical and biomedical applications. The combination of the two statements reported above makes polysaccharidic hydrogels of particular interest in the field of pharmaceutics and they have been actually thoroughly studied in the form of monolithic and erodible matrices and as well as of particles. An overview, from preliminary studies to recent advances and perspectives (preparations, characterization, applications), on uncoated and coated particles of different types (beads, capsules) and sizes (nano, micro) will be presented here.

INV-72

Particle engineering for gene delivery and contrast agents
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We propose here two strategies to improve the delivery of DNA. The first consists in targeting the hyaluronic acid (HA) CD44 receptor, present on several tumoral cells using hyaluronic acid-modified lipoplexes. When containing a HA-DOPE (Dioleylphosphatidylethanolamine) conjugate, lipoplexes were found to transfect more efficiently CD44+ tumor cells. Transfection was inhibited in the presence of Anti CD44 Hermes-1 antibody and less internalized when the receptor was blocked. The second strategy uses the possibility of formulating DNA with the amphiphilic polymers Tetronic 304 and Pluronic L64 that both allowed significant improvement of gene transfer to the skeletal muscle with reference to naked DNA. No influence of temperature and medium was observed for Tetronic/DNA systems while Pluronic L64/DNA formulations exhibited high efficiency only at 37°C in Tyrode, conditions for which ITC showed a slight interaction between DNA and Pluronic. Very surprisingly, in these conditions, no particles were formed reconsidering the fact that only nanoparticles can induce good transfection efficiencies. Finally, the presentation will introduce the design of nanotechnologies containing contrast agents for molecular imaging by echography and MRI. To reach this step, we have designed novel polymeric capsules containing perfluoroctyl bromide, a compound that can provide dual imaging.

INV-73

In vitro testing of nanocarriers for drug delivery
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Drug delivery systems in the submicron range have been around for a long time and categorized as colloidal carriers. The increasing interest in these systems, now called nanocarriers, aiming at overcoming biological barriers, increasing drug stability, reducing toxicity and ultimately improving drug therapies, is presently driven by the explosion of nanotechnology and nanomedicine. The performance characteristics that actually make the difference between nanosystems and other multiparticulates are their peculiar mode of interaction with biological/mucosal surfaces and their distinct mechanisms of absorption/cell internalization. Moreover, possible peculiar mechanisms of toxicity can't be overlooked. Therefore new and improved testing methods should be used. Aim of the presentation is to discuss the in vitro/ex vivo tests needed as preliminary screening for selecting the better formulations for in vivo

studies. The screening includes testing cell toxicity and compatibility, either by measuring cell viability or by histological examination, evaluating the adhesion to mucosal surface and the residence time at the site of application, tracing cellular uptake, transport across biological barriers and intracellular fate. The in vitro/ex vivo tests used in the development of some chitosan based nanosystems intended for buccal, vaginal and ocular administration will be described.

INV-74

Challenges in proteomic biomarker discovery: From hypervariable datasets to individual biomarker candidates

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The biomarker discovery phase is characterized by the analysis of a limited number of well-classified samples. 'Omics' analyses generally lead to a large number of signals relative to a limited number of analyses. The main goal of the discovery phase is to find statistically significant differences in protein profiles between groups of pre-classified samples. The fact that there are many more measured proteins relative to the number of samples requires that the obtained statistical models be carefully validated to avoid that observed differences are due to chance.
Pre-analytical factors are particularly critical when it comes to proteomics analyses. Studies from the literature give guidelines on how to approach this complex and largely unsolved problem.
Biomarker discovery may lead to so-called "biomarker candidates" that require further validation. There are a number of ways of biomarker validation, many of which rely on immunochemical techniques such as immunohistochemistry or ELISA. More recently the combination of liquid chromatography with mass spectrometry using triple quadrupole mass analyzers in the Multiple Reaction Monitoring (MRM) mode is gaining acceptance. This approach has the advantage of being able to quantify multiple biomarker candidates in a single analysis without the need for well-characterized antibodies.

INV-75

lc-ms-based methods for global metabolite profiling in metabonomics

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Metabonomics is the study of the changes that take place in the metabolic profiles of biofluids and tissues in animals or humans in response to change such as such as growth and aging, the development of disease, response to a pharmacological intervention or a toxic insult. Here the use of LC-MS-based techniques to obtain these metabolic profiles to discover metabolic markers of these various conditions will be described and illustrated with examples. Such profiles can be obtained both from biofluids such as urine, bile, plasma and tissues or their extracts. However, a number of analytical challenges await those wishing to undertake this type of analysis. In particular the methods used for producing comprehensive metabolic profiles by LC-MS require careful control to ensure repeatability so that reliable data can be extracted from samples. Approaches that ensure the reliable generation of such profiles, from which biomarkers characteristic of the disease or toxic insult can be derived, will be described as will their analysis using advanced statistical pattern recognition techniques. Careful interpretation of the resulting data can provide mechanistic information leading to a better understanding of the effects of disease or of the pharmacology or toxicity of xenobiotics. The current state of the art in metabonomics will be described, with pointers towards future directions.

INV-76

A metabolomic approach to diabetes in children through GC-MS

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Despite vast knowledge of Type 1 diabetes epidemiology, a definite solution for the prevention of the disease or its deleterious effects is still not forthcoming. The rapidly growing field of metabonomics (metabolomics) is an ideal method of providing a wealth of information on the complex systems involved in this metabolic disorder. Human urine samples (10 diabetic and 11 control children) were pre-treated and subsequently analysed by an optimised and validated Gas Chromatography-Mass Spectrometry (GC-MS) method. Traditional problems associated with peak migration, multi-alignment and instrumental errors were countered by using a dynamic programming algorithm and internal standard. Principal Component Analysis (PCA), Partial Least Square Discriminate Analysis (PLS-DA) and Orthogonal Partial Least Square Discriminate Analysis (OPLS-DA) data of the aligned chromatograms were used to provide rapid and accurate sample classification, which was followed by metabolite identification. Diabetic urine samples showed significantly increased levels of glucose, myo-inositol and a non-identified monosaccharide compared with controls and significant decreases in D-turanose and glycine, all with confident intervals of 95%. The altered metabolite levels may aid further understanding of diabetes related mechanisms and possible studies on novel therapies.

INV-77

New insights in intact protein analysis with CE-TOF/MS

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CE-MS is an attractive option for intact protein analysis. On the one hand, CE presents features such as high speed, great efficiency, and low solvent and sample consumptions. Moreover, CE allows working under aqueous conditions and without stationary phase. On the other hand, MS provides selectivity and ability to identification. TOF analyzer is particularly well suited to protein analysis, due to high mass range, mass accuracy, mass resolution, and sensitivity. This lecture presents two CE-TOF/MS methods for intact proteins analysis. In a first application, an efficient, rapid, and simple method was developed to analyze natural human growth hormone (hGH) and recombinant growth hormones (rhGH) without sample preparation. The method presented original analysis conditions that allowed distinguishing hGH from rhGH. It was successfully applied to seized samples in a forensic case. In a second application, a complete analytical strategy was developed to detect intact hemoglobin-based oxygen carriers (HBOC) in plasma samples collected for doping control. HBOC (such as Oxyglobin and Hemopure) are purified proteins obtained from polymerized bovine hemoglobin that are misused as performance enhancers. The complete methodology was successfully tested with plasma samples enriched with Oxyglobin, and was also applied to blood samples collected from healthy volunteers infused with Hemopure.

INV-78

Creating zinc monkey wrenches: Disease modification through epigentics

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To date considerable research activity has focused on understanding the "histone code", and in particular on the design of HDAC inhibitors as novel therapeutics for the treatment of a wide range of disorders including cancer, as well as neurodegenerative diseases, and even malaria. In our efforts to identify HDACIs that may show an improved therapeutic profile, we have sought to identify compounds that may show enhanced levels of HDAC isoform selectivity, as it

is believed that some of the undesirable side effects of these agents may relate to their overall lack of enzyme selectivity. We have thus been investigating the design, synthesis, and testing of compounds containing various CAP residues that may interact differentially with the surface areas of these enzymes outside their catalytic gorge regions, as well as to more broadly assess the effect of variations in the zinc binding groups. In this presentation I shall summarize our current efforts in this exciting field of research, and present results pertaining to the possible use of these compounds in various diseases.

INV-79

Combining virtual and biological screening to identify novel lead structures for epigenetic targets

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Chromatin modifications have emerged as new fundamental regulatory mechanisms for the control of gene transcription and are associated with many cellular processes. It is increasingly recognized that epigenetic modifications constitute important regulatory mechanisms for the pathogenesis of malignant transformations. The present talk will highlight the results obtained for several epigenetic targets where we used a combination of in silico methods, including molecular docking and binding free energy calculation, and in vitro assaying in order to identify novel lead structures. For the analyzed histone modfying enzymes HDAC, PCAF, PRMT1 [1] and Sirtuin [2,3] we were able to develop novel bioactive molecules. The identified small molecule inhibitors can be used to further analyze epigenetic regulation in different tumor cell lines.

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INV-80

Small molecule chromatin modifying agents: therapeutic applications

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After 10 years from its birth, the science called "epigenetics" has been defined, in a modern manner by Allis et al. in 2007, as "the sum of the alterations to the chromatin template that collectively establish and propagate different patterns of gene expression (transcription) and silencing from the same genome" [1]. The control of the enzymatic machinery implicated in the (un)packing of chromatin, such as the reversible acetylation/deacetylation of lysines, methylation/demethylation of histone lysines or arginines, phosphorylation of serines or threonines, and ubiquitylation or sumoylation of lysines, is an important step in the regulation of transcriptional events. As a consequence, chromatin-remodeling enzymes, such as histone deacetylases (HDACs and SIRTs), acetyltransferases (HATs), methyltransferases (HKMTs and PRMTs), and demethylases have recently emerged as new promising targets for the treatment of many diseases including (but not only) cancer [2,3]. In this lecture we will cover some aspects of the therapeutic usefulness of small molecule modulators of the above epi-targets (epi-drugs).

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INV-82

Simulation of powder mixing and segregation

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Powder is an important and complex structure of material. However its behavior is still poorly understood. With direct measurements several aspects of powders can be studied. These include flowability, packing and segregation. While these can be monitored with experiments, the fundamental principles which cause the differences between solids may still remain unknown. Using of simulations as a tool can ease this problem.
Simulations of powder packing, mixing and segregation has been done in these studies. Forces included in these simulations are gravity, support forces between particles and particles and walls, and friction forces between particles and particles and walls. Particles are approximated as symmetrical spheres. The computing power needed is scaled so that a modern PC computer is able to perform any used simulation within few days.
The effect of elasticity, friction and size distribution on the packing density were studied. Mixing was studied by changing the direction and amplitude of mixing force between simulations. During this study a new kind of method for determining the effectivity of the mixing was developed. Segregation as a phenomena is also visible in the simulations, which indicates that the effects of single particle properties on segregation can be studied further in details with these kind of simulations.

INV-83

Particle size determination during fluid bed granulation

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Fluid bed granulation (FBG) is an example of a multivariate process where effective and reliable process control tools are important to ensure end product quality. Although PAT (Process Analytical Technology) tools have been developed and applied also in FBG environment, the determination of particle size distribution during the granulation is not straight-forward due to the challenging environment during the FBG. Optical windows used in in-line probes are prone to foul during the granulation and therefore reliable monitoring of the particle size growth is not always possible. Due to the challenges related to in-line particle size measurement in FBG, on-line and at-line techniques have also been developed and applied. We used spatial filtering technique (in/at/off-line) and a new image analysis method (on-line) to study the granule growth and the feasibility of the methods in lab-scale FBG. In addition to the granule growth monitoring different process phenomena could also be monitored. A novel on-line sampler attached with an image analysis method was found to be a promising PAT tool for FBG studies.

INV-85

Whole Blood Fatty Acids as Biomarkers of Nutrition and Disease Risk

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Fatty Acid (FA) profiles in biological samples, and especially levels of PolyUnsaturated FA (PUFA), allow to : a. correctly evaluate FA intakes in populations, b. establish correlations between levels and physio-pathological parameters, and c. evaluate the bioavailability of FA, e.g. the Omega 3, in relation to formulations and matrices. FA profiles of whole blood lipids are indicative of the FA status in the body, more than those of plasma lipids or red blood cells, representing both the plasma and cell compartments. An analytical approach based on collecting blood drops from fingertips on a special absorbent, thus simplifying the procedure for collection, storage, shipment and processing of samples, has been developed in our lab and made available, in order to facilitate large scale studies. The procedure has been applied to assess the FA status in population groups, also in relation to dietary habits and lifestyles, and from different geographical areas, including remote countries, in age groups from pregnancy and neonates to aged subjects, in patients with metabolic disorders, and to evaluate the bioavailability of omega 3 FA formulations. This analytical approach is of help in order to establish relationships with

physiological and pathological conditions, and in defining requirements and recommendations for selected FA, e.g. the Long Chain Omega 3 FA.

INV-86

Biomarkers of oxidative stress - present and future
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Oxidative processes in the circulation and in the arterial wall have been suggested as causal risk factors of cardiovascular disease. However, antioxidants have been proven ineffective in most clinical trials. One of the major limitations of such trials is the lack of appropriate biomarkers to evaluate oxidative stress in vivo. In a way, the current situation approximates that of a statin trial without the possibility to measure cholesterolemia. Though some molecules, e.g. isoprostanes for lipids, carbonyls for proteins, and damaged DNA strands for DNA, have been investigated, a quantitative link between such markers and progression of disease is still missing. This lecture will review the current biomarkers of oxidative stress and their advantages and limitations. Future, potential biomarkers will also be discussed.

INV-87

Formulation of innovative biotech and biosimilar products: Quality, efficacy and safety issues
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Patents on the first generation of recombinant therapeutics have expired or will do so in the coming years. In principle, this will open the possibility for the introduction of generic versions of the out-of-patent products: biosimilars.
Generic versions of *low molecular weight* pharmaceutical products will obtain marketing approval by showing chemical and physicochemical similarity and bioequivalence in studies in healthy volunteers. Recombinant protein based therapeutics, are *high molecular weight* molecules. Here the issue of generic versions is more complicated. Biopharmaceuticals have a complex three-dimensional structure and their biological activity strongly depends on their structural integrity. For the larger proteins, and more in particular the sugar chain(s) bearing glycoproteins, structure characterization is not a trivial task. In fact our arsenal of analytical techniques cannot fully characterize the conformation of these complex proteins. Moreover, the structure and impurity profile depends on a complex manufacturing process including production, the downstream processing protocol and the selection of the formulation and of packaging conditions.
In this presentation examples of the challenges offered by the formulation and use of biologicals will be discussed in the light of the ongoing discussions on the introduction and acceptance of biosimilars.

INV-88

Molecular targeted therapies in cancer medicine
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In recent years, there has been a significant progress in cancer cell biology and molecular oncology such as carcinogenesis, growth, invasion and metastasis. These advances in the field of molecular oncology over the past decade have led to a new phase of cancer therapeutics and several strategies directed to well- designed selective molecular targets and these novel class of agents have been named as "molecular targeted therapies". These new structures target specific cellular and molecular abnormalities. There have been significant progress in the targeted molecules including signalling pathway inhibitors such as tyrosine kinase inhibitors (TKIs), angiogenesis inhibitors, modulators of cell matrix interactions, agents that interact with the cell cycle, apoptosis and protein trafficking. Several of these new therapeutic agents are

quite promising in the clinic and many more are being discovered. m-TOR inhibitors and angiogenesis inhibitors are new class of drugs.
Trastuzumab, Rituximab, Alemtuzumab, Cetuximab, Gefinitib and Bevacizumab are approved for treatment of various cancers. Coupled antibodies to radionuclides have been accomplished for increasing their antitumour activity. Two well known anti-CD20 radioimmunoconjugates are Bexxar (tositumomab; 131 Iodine) and Zevalin (Ibritumomab tituxetan; 90-Yttrium).

INV-89

A case study: An approved biosimilar product
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The first biosimilar medicines developed according to the new EMEA biosimilar guidelines have been approved in the European Union. Examples are the Somatropin products approved in 2006, followed by Epoetin in 2007 and most recently Filgrastim in 2008. The EMEA has approved 13 biosimilar products by now.
The presentation gives an overview of the pivotal concepts of the biosimilar product development starting from the choice of the reference biological product followed by the development of manufacturing processes according to the target directed approach and the subsequent comparability exercise with the biological reference product.
The comparability exercise is the heart piece of the Biosimilar development. The comparability exercise is a thorough and comprehensive comparison between the reference biological product and the biosmilar product on all stages of the development.
The five levels in proving biosimilarity/comparability are:

- Level 1 Physico-chemical comparability
- Level 2 Comparability in biological activity → establishing biosimilarity
- Level 3 Preclinical comparability
- Level 4 Comparability in clinical phase I
- Level 5 Comparability in clinical phase III → confirming biosimilarity

The size and scope of level 4 and 5 depend on molecule characteristics and have to comply with the current EMEA guidelines.
A biosimilar product is designed to meet the criteria of the reference product with regards to quality, safety and efficacy.
This rigorous comparability exercise qualifies Biosimilars for therapeutic interchange.
These concepts reflect state-of-the-art science and are based on the increasing clinical experience and the ongoing significant improvements in analytical and process technology. The tools, which are required for the development and the assessment of the comparability are already available and will be discussed.
The current situation in Europe demonstrate that biosimilar products are competitive in the market place and help to reduce the costs of the health care systems. However, just as innovator medicines are increasingly developed on a global basis, with analytical, preclinical and clinical data developed anywhere in the world acceptable for regulatory submission in any jurisdiction, the data supporting the dossiers of biosimilar products should also be globally acceptable. This would enable broader access to biosimilar products and also enable greater competition and cost savings. This requires that a biosimilar be able to be developed globally to an essentially single comparator biodrug of one of these jurisdictions. Points to consider are the evaluation of the global status of the comparator biodrug, based on public information and physicochemical and biological characterization, and the principles of ICH 5E (Ethnic Factors on the Acceptability of Foreign Clinical Data). Under these aspects, it should not be required to duplicate preclinical and clinical studies for each country/region. The regulatory systems should allow such a global development of biosimilar products based on scientific rationale. This would allow meeting the objectives of access and economy that biosimilar products offer to be made available to the health care systems and patients that need them on a global basis.

INV-90

Biosimilars from the regulator's point of view: Presence and future
Schneider, Christian K.
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Biological medicinal products have a successful record in treating many serious and chronic diseases, and their market is growing faster than that of total pharmaceuticals. Several patents have expired, or soon will expire, resulting in efforts to produce biomedicines "similar" to the originals and relying in part for their licensing on data from these originator products. Biological medicinal products are usually large and highly complex molecular entities which are often difficult to characterize, and whose physicochemical properties are largely defined by their manufacturing process. The Committee for Medicinal Products for Human Use (CHMP) at the European Medicines Agency (EMEA) has issued guidelines that set forth a regulatory framework for the scientific requirements for such "biosimilars". The CHMP Working Party on Similar Biological (Biosimilar) Medicinal Products Working Party (BMWP) has been in charge of drafting these guidelines. The talk will start from a brief description of the current activities of the BMWP, and expand to the recent debate if more complex molecules like monoclonal antibodies could be developed as biosimilars.

INV-92

High throughput bioanalysis using SPME sampling/sample preparation techniques
Janusz, Pawliszyn
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Two high thoughput analytical systems based on solid phase microextaction (SPME) will be discussed. One approach is designed for GC-MS determinations based on SPME syringe supplied with coated metal fibres operated by autosampler and the other for LC-MS automation with a extraction phase coated brush operated by 96 well robot.
In recent years, there has been a lot of interest in monitoring levels of biologically active compounds in living systems in their natural environments. These efforts are a significant departure from conventional 'sampling' techniques, where a portion of the system under study is removed from its natural environment, and the compounds of interest extracted and analyzed in a laboratory environment. The use of solid-phase microextraction (SPME) for in vivo sampling of drugs and metabolites in the bloodstream of freely moving animals eliminates the need for blood withdrawal in order to generate pharmacokinetic profiles in support of pharmaceutical drug discovery studies. The pharmacokinetic results compare well to the traditional methods relying on blood withdrawal but in vivo SPME offers the advantages of speed, decreased animal use, and improved accuracy of data due to the elimination of inter-animal variation from the profile, and the ability to obtain both free and total drug concentration from the same experiment.

INV-93

Quantitative analysis of low molecular weight compounds in biological matrices by mass spectrometry: past, present and future
Hopfgartner, Gérard; Wagner, Michel; Lesur, Antoine; Grivet, Chantal; Varesio, Emmanuel
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Quantitative analysis of low molecular weight compounds in biological matrices such as plasma and urine is mainly performed by liquid chromatography coupled to atmospheric pressure tandem mass spectrometry (LC-MS/MS). LC-MS/MS analysis times are typically in the range up to 5 minutes allowing the analysis of several hundred samples on a daily basis. While in the past for drug discovery and drug development, mostly single analyte assays where developed nowadays one see the need to develop multi-compounds assays and drugs and their metabolites as well as biomarkers. With the improvement of the mass spectrometer sensitivity, sample preparation can be simplified in many cases. New hardware development such as MS3 quantitation and accurate mass allows to explore new more selective approaches for bioanalysis with or without chromatography. While atmospheric pressure ionization remains the most used ionization technique for polar and thermolabile analytes matrix-laser desorption ionization (MALDI) has become an attractive alternative for quantitative analysis in a high-throughput

fashion. Also with MALDI direct analysis of pharmaceutical compounds and their metabolites in tissues has been successfully demonstrated. Finally, LC-MS/MS can also be applied to the quantification of therapeutic proteins and peptides using similar analytical strategies as for low molecular weight compounds.

INV-94

Selective extraction of a target analyte from complex samples by solid-phase extraction sorbents based on aptamers – Comparison with immunosorbents and molecularly imprinted polymer

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The analysis of traces of organic compounds from complex samples needs a sample clean-up before LC/MS analysis to limit matrix effects. Selective materials based on a molecular recognition mechanism can be used for this sample clean-up. Immunosorbents (ISs) based on immobilized antibodies and molecularly imprinted polymers (MIPs) possessing specific cavities have already shown a high potential for the selective extraction of target analytes from complex matrices. Selective extraction can also be obtained using aptamers immobilized onto a solid support. Aptamers are able to bind a specific molecule with a high affinity as antibodies. They are less expensive to produce and present a higher stability than antibodies. They also appear as a good alternative to MIPs for expensive analytes. The potential of immobilized aptamers selected against cocaine was studied. Aptamers were immobilized on various solid supports. The criteria used to evaluate the resulting oligosorbents (OSs) were the binding efficiency, the capacity, the specific and non specific retention. The best OS was applied to the extraction of cocaine from a biological fluid: the analysis of a human plasma led to a very clean chromatogram thus illustrating the high selectivity of the oligoextraction procedure. The potential of the OS in terms of capacity and selectivity was also compared to those of ISs and MIPs.

INV-95

New strategies to perform automated phase I drug metabolism studies

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One of the main reasons for new chemical entities (NCEs) failure in drug discovery is related to inadequate pharmacokinetic properties. Concerning phase I drug metabolism, cytochromes P450 (CYP450) enzymes are responsible for the oxidative metabolism of approximately 90 % of drugs in clinical use and thus, play a decisive role in determining drugs safety and efficacy. Therefore, the assessment of the metabolic fate of NCEs, the identification of CYP450 isozymes responsible for their biotransformation and the determination of drug-drug interactions are important processes to be investigated in drug discovery. These studies are generally performed in vitro incubating NCEs with microsomes or recombinant enzymes and require large amount of materials. This lecture will present two innovative approaches to perform CYP450-based drug metabolism studies with particular attention to cost reduction and automation of the procedure. 1) The development of CYP450-based monolithic immobilized enzyme reactors (IMERs) integrated in a fully automated IMER-LC-ESI-MS system through a column switching set-up; 2) the use of capillaries to perform assays with very low amount of CYP450 solution (ca. 30 nL) off-line coupled to UHPLC-MS.

INV-96

Practical implementation of total error for the validation of chromatographic and ligand binding assays

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Despite the various good practices regulations (GxP) and other normative guidelines (ICH, FDA, ISO) the question of how to define an assay as valid remains incompletely determined. Regardless of the type of assay, the decision methodology to declare a method valid should be the same. Indeed, the objective of any quantitative analytical method is to quantify as accurately as possible each of the unknown quantities that the laboratory will have to determine. What is expected for any assay is that the difference between each result (x) and the unknown "true value" (μT) of the sample must be smaller than an acceptance limit (λ): abs(x - μT) < λ. This acceptance limit depends on the final aim of the analytical method (e.g. 5% for API in drug products, 30% for bioanalysis). A universal strategy is thus proposed to decide about methods' validity that controls the risk of accepting an unsuitable assay. It uses accuracy profiles based on total error and prediction intervals as statistical methodology. This approach allows the analysts as well as the regulatory bodies to know the risk to obtain future results out of the specified acceptance limits and thus the probability of Out Of Specification results. Several examples of application of this validation methodology to chromatographic and Lingand Binding assays will be presented.

INV-97

Target identification for protection against Chlamydia

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As obligate intracellular pathogens the Chlamydiae strictly depend on a variety of host cell pathways and signalling cascades necessary to confer optimal growth conditions inside the host environment. In order to obtain a comprehensive view on the processes governing chlamydial replication and maturation we decided to perform a functional loss-of-function screen of host cell determinants using high-throughput RNA interference (RNAi). As a read-out we chose to test for the completion of the whole chlamydial cycle. With this approach we identified numerous host cell genes, influencing the infection rate, interfering with the growth of chlamydial inclusions, or leading to changes in the number of infectious progeny. Interestingly, we have also identified host cell factors that apparently suppress intracellular chlamydial growth, including factors associated with the structure and the function of the Golgi apparatus. Moreover, we hypothesize the involvement of two targetable proteases in Chlamydia-associated Golgi fragmentation, which turns out to be a prerequisite for lipid acquisition by these intracellular pathogens.

INV-98

What did Chlamydia genomics teach us regarding host pathogen interactions?

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Bacteria of the family of Chlamydiaceae are obligate intracellular pathogens of humans and animals. The different species infect a variety of hosts, with a wide tissue tropism and varied disease pathologies. In particular, species pathogenic for humans are C. trachomatis, an agent of chronic genital and occular infections, C. pneumoniae, a prevalent cause of community-acquired pneumonia, bronchitis and pharyngitis, and C. psittaci, which is common in avian species and can cause rare but severe pneumonia in humans. All Chlamydia species share a unique developmental cycle, during which bacteria multiplication only occurs within a eukaryotic host cell. As a consequence, no cell-free growth system for this organism, and no gene manipulation technique have been developed. Under these circumstances, publication in the last 10 years of the sequences of 12 strains of Chlamydia, representing 6 different species, were particularly welcomed, as they opened several new areas of research. Analyses of each genome, as well as comparison of the genomes of different strains, have allowed to formulate new hypotheses and to consider new scientific approaches. As a consequence, our view of the interactions between the pathogen and the host cell has considerably changed over the past ten years. We will review some of the major new findings prompted by Chlamydia genomic data.

INV-99

Chlamydia adhesins – from identification to function
Hegemann, Johannes H.
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Chlamydiae are obligate intracellular bacterial pathogens which cause a variety of important human diseases in animals and humans. All chlamydial species possess a unique biphasic developmental cycle which is characterized by the extracellular infectious Elementary Body (EB) and the intracellular replicating Reticulate Body (RB). Bacterial infection is a multifactorial process and pathogen adherence to host cell surfaces is the first step in the establishment of an infection. The specificity of this pathogen–host cell interaction is determined by bacterial surface proteins (adhesins) and receptors on the host cell surface. We established a novel yeast adhesion system in which the binding of living adhesin-presenting yeast cells to human cells could be studied. In my talk I will show that the conserved chlamydial OmcB protein mediates adhesion to human epithelial HEp-2 and endothelial HUVE cells. The OmcB adhesin binds Glycosaminoglycan (GAG) structures on the human cell surface and this is essential for infection. Furthermore our system allowed us to characterize Pmp21 as a second chlamydial adhesin. In *C. pneumoniae* Pmp21 belongs to a group of 21 polymorphic membrane proteins, bioinformatically designated as autotransporters, suggesting that these proteins might represent an adhesin repertoire relevant for cell and tissue tropism of the bacteria and/or for immune escape.

INV-100

Drug treatment in chlamydial infection
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Chlamydia are gram-negative bacteria and drugs of choice have regarded as antibiotics and chemotherapeutics and in acute chlamydial infections macrolides, tetracyclines, and fluorochinolones have been preferred. The situation is quite different in chronic chlamydial infections. Prolonged courses up to one year antibiotics seem to have no effect on chronic infection. This has recently misintepreted as the lack of chlamydia in the development of atherosclerosis. There are, however, drugs not used in acute chlamydial infections. Their list is intriguing, since they are ofen used in chronic inflammatory conditions in which chlamydia have been associated. Although we have several models for chronic chlamydial infections, no one has tested the effect treatments in chronic setting. Classic example is statins, which antiinflammatory actions has recently aroused interest. Statins are effective in acute chlamydial infections, but their effect in chronic infections has remained unstudied. The list of drugs commonly used in cardiovascular diseases and which at the same time have antichlamydial effects contain, e.g., aspirin and verapamil. The use of antioxidative vitamins has been a great disappointmen but reports on antioxidative plant flavonoids are successful. Besides antioxidative properties, many of these are shown to be effective against clamydia and this could be an explanation.

INV-101

How predictable is oral drug absorption
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Reliable prediction of oral drug absorption would be helpful in drug discovery. Drug absorption into systemic plasma is affected by drug dissolution, permeability in the gut wall and pre-systemic metabolism. In vivo predictions can be carried out by in silica and in vitro methods. Drug dissolution may be a limiting factor in drug absorption if the drug has low solubility (BCS 2, BCS 4 drugs). In silica prediction of solubility is not reliable at the moment, but obviously solubility can be measured in vitro. In vivo relevance of the in vitro solubility and the risks associated with erroneous predictions are the key factors in this case. The risks are related to the relative contribution of solubility/dissolution and absorption rate in the overall process. The rate of passive drug absorption in humans can be predicted computationally, and in fact these predictions are at least as reliable as more tedious experiments with cell and animals. However, the rate and extent of transporter mediated absorption is much more difficult to predict due to

the sparse information on relative extent of transporter expression and function. Finally, bioavailability is affected by the pre-systemic metabolism. In silica and in vitro tools for oral absorption are discussed, and the role of integrative PK models is demonstrated.

INV-102

How predictable is drug distribution?

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The basic processes governing pharmacokinetic behaviour of compounds are absorption, elimination and tissue distribution, although these processes are often highly interrelated. Against enormous efforts made in understanding mechanisms controlling the first two processes, efforts to understand and predict tissue distribution have been puny. Yet, tissue distribution plays a critical part in controlling the concentration-time course of drugs, with events in plasma reflecting rather than determining the temporal profile. Previously, and still largely today, tissue distribution in human has been inferred from animal studies. Recently, considerable success has been made in moving in a more mechanistic direction through realisation that distribution reflects the interaction between compound and specific tissue constituents, such as neutral lipids, neutral and acidic phospholipids and plasma proteins. Advantages of this approach are many. One is the potential to predict likely distribution in specific tissues, and throughout the body, based on structural and physicochemical properties of the compound. Another is predicting likely changes in the extent of tissue distribution and altered pharmacokinetics, both across species and among categories of subjects, as a function of age, obesity and so forth. Still, there is much yet to learn such as membrane permeability and transporters.

INV-103

How predictable is drug elimination?

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Human pharmacokinetic prediction is a key component of the compound optimization and selection process in drug research.
A key prediction parameter is human clearance as this is implicated in determination of oral bioavailability and elimination half life. It is probably the most difficult to predict accurately as there are many ways for a molecule to be cleared from the body, including metabolic, renal and biliary elimination. There is an array of enzymes and transporters that can clear molecules from the body with species differences in expression and structure activity relationships.
A variety of human clearance prediction methods have been published including scaling of in vitro metabolism data, in vivo allometric scaling and a combination of both approaches. Each method has shown value, especially for carefully chosen compound sets. However, it is very important to understand the disposition of a series of compounds in order to apply the correct prediction method.
Most methods successfully predict within +/- 2-fold of actual human clearance for a majority of compounds. However, all have the potential for large mis-predictions leading to poor outcomes in the clinic. Therefore, although clearance prediction methods have a role to play, they should not be substituted for careful progression of key compounds to human pharmacokinetic experiments.

INV-104

Predicting variability in specific patient populations

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Comparison of varying populations via parallel studies and, more recently, population pharmacokinetics (POPPK) have been the classical tools to assess interindividual variability in pharmacokinetics (PK). Since the introduction of the POPPK in the early 80s, knowledge on biology and impact of pathophysiology on various elements of human "system", that influence the fate of the drugs and it PK, has grown substantially. However, this has not translated into more mechanistic covariate recognition. Quantitative translation of the in vitro information, combined with the appropriate understanding of the link between these systems and the human body, is a relatively young science. The advent of powerful computers capable of handling numerous complicated non-linear models, and the realisation that there is no end to the number of possible clinical scenarios in real life, have contributed to the increased prominence of in vitro-in vivo extrapolation (IVIVE) and "bottom-up" modelling and simulation. This presentation will outline a framework for assessing inter-individual variability PK using virtual human populations which integrates the general knowledge of physical chemistry, biology, anatomy, physiology and genetics to recognize the relevant covariates [1].

[1] Jamei M, Dickinson GL, and Rostami-Hodjegan A, Drug Meatb Pharmacokin, 24: 53-75 (2009)

INV-105

Formulation of biopharmaceuticals

Mahler, Hanns-Christian
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Therapeutic proteins pose specific challenges for the pharmaceutical scientist in order to come up with a sufficiently stable, manufacturable and usable formulation. For example, this may include tackling degradation pathways such as aggregation and precipitation or specific properties such as viscosity.
This talk will address various challenges and also approaches how to come up with adequate formulations for therapeutic proteins.

INV-106

Characterisation of biopharmaceuticals

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Although most marketed biotech products are simple protein solutions or freeze-dried forms thereof, a complete characterisation of these products is extremely difficult. This is due to the structural complexity and heterogeneity of proteins, and their inherent instability. In this presentation analytical tools needed to guide the development of stable protein therapeutics will be discussed. Both state-of-the-art methods and emerging analytical techniques will be presented. In particular, the comprehensive characterisation of protein aggregates, in conjunction with their immunogenicity risk, will be highlighted.

INV-107

In situ forming hydrogels for the controlled release of proteins

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Hydrogels are an important class of materials that have been studied extensively in the last decades for the controlled release of pharmaceutical proteins. In recent years there is a growing interest in physically crosslinked systems based on non-permanent/reversible bonds between the polymer chains forming the hydrogel network. We designed a self-assembling poly(ethylene glycol) hydrogel system based on inclusion complexes between beta-cyclodextrin (beta-CD) and cholesterol. Hydrogels are formed after hydration of a mixture of star-shaped 8-arm poly(ethylene glycol) (PEG) end-modified with beta-CD groups and the same star-shaped PEG end-modified with cholesterol moieties. Rheological analysis as well as 2D-NMR spectroscopy

demonstrated that the obtained gels are due to formation of beta-CD/cholesterol inclusion complexes. Hydrogel properties were dependent on polymer concentration, the beta-CD/cholesterol stoichiometry, and the molecular weight of the starshaped PEG. Release studies with model proteins showed an almost zero-order release for a period up to 10 days. It was shown that the proteins were essentially immobile in the hydrogel matrix and were released due to surface erosion of the gels. The system described above hold promise as injectable gel, suitable for controlled delivery of pharmaceutically active proteins and tissue engineering applications.

INV-108

Challanges in the design of polyplexes for nucleic acid delivery
Breunig, Miriam; Goepferich, Achim
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The key to the delivery of nucleic acids to cells to date has been to compensate their negative charge. This is also the principle of polycationic materials that aggregate nucleic acids to polyplexes, sub-micrometer sized particles taken up by mechanisms of pinocytosis.
Even though this strategy works quite well, there are a number of challenges that still have to be met: cationic materials are toxic to cells and polyplexes may not possess a high efficacy. Furthermore, these particles are subject to intracellular trafficking and distribution that is decisive for their activity but which is poorly understood.
Although there are many problems associated with the use of polyplexes there has also been some progress towards a better understanding of how they function and how they can be optimized. Degradable polycationic materials can decrease the cell toxicity of polycations significantly if they are made of appropriate degradable bonds and microscopic techniques shed light on the intracellular fate of the materials [1]. Despite this progress, we will need to revisit individual cell physiological processes involved in polyplex trafficking in more detail in order to come up with more efficient carriers in the future. The talk will review the progress in this field as well as the challenges ahead of us.
[1] Breunig M. et al., PNAS, 104 (2007) 14454-14459

INV-115

Differential network-based drug targeting: where Systems Biology makes a difference
Westerhoff, Hans V
MCISB and NISB, Manchester and Amsterdam, United Kingdom

We now know what Systems Biology is. Hence, it may be worthwhile to examine the difference it will make. In particular it may be useful to examine where such a difference is needed and how it may be brought about by those who are interested.
There are diseases that can be related to a single faulty gene product and or a single invading microorganism. Structural molecular biology then is the method of choice, designing an inhibitor binding to the target. This paradigm has become mainstream. It is consistent with the block-buster drug desired by the pharmaceutical industry.
However, there is a more substantial number of diseases for which a vast amount of biomedical research has been mounted, and that cannot be cured. The research has led to substantial scientific success and biochemical understanding, and to some, but little, progress in defining cures. The examples are on the long list of 'multifactorial diseases' and include type-2 diabetes, obesity, heart disease, cancer and arthritis, but also parasitemias.
I shall argue that the approach that has been successful for monofactorial diseases is not optimal against these diseases and that finding cures for these diseases, may require a shift in strategy. These diseases are 'network' or 'Systems Biology diseases' and to cure them one needs to address faults in the network rather than in just a molecule.

INV-116

Kinetic modeling in systems biology. Applications
Goryanin, Igor[1]; Lebedeva, Galina[2]

[1]*University of Edinburgh, School of Informatics, Edinburgh, United Kingdom;* [2]*University of Edinburgh, CSBE, Edinburgh, United Kingdom*

Kinetic modeling approach and it's applications for drug R&D are discussed. The presentation describes the process for the reconstruction of a high quality metabolic networks from the genome information, the existing problems in the reconstruction. While usefull these networks can not integrate all available experimental data on different biological levels, time dependences in particular. Only kinetic models (1) provided a unified platform to integrate biological and medical information on genes, proteins, metabolites, disease, drugs and drug targets for a system level mechanistic study of the relationship of cellular processe and disease. Furthermore, the complex organization of cellular networks structure requires us to develop a system-oriented drug design strategy. Practical applications in cancer and inflammation therapeutic areas will be addressed.
(1) Goryanin I and Demin O Kinetic Modelling in Systems Biology Chapman & Hall/CRC, 2008

INV-117

Top-down systems biology approaches to understanding disease and drug action
Nicholson, Jeremy K
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Systems biology tools are now being applied at the individual and population level utilizing analytical and statistical methods that report non-invasively on integrated biological functions. NMR spectroscopy and chromatography linked MS methods have been widely applied to characterize and quantify a wide range of metabolites in biological fluids and tissues to explore the biochemical consequences of drug-induced toxicity and human disease (1). Humans and other animals are symbiotic superorganisms in which there is transgenomic control of metabolism which generates the ultimate challenge in metabolic modelling analysis. In disease or toxicity states metabolic profiles and spectroscopic signatures are changed characteristically in different toxicity or disease conditions according to the exact site and mechanism of the lesion (2). UPLC-MS approaches can deliver information on thousands of metabolites that describe the physiological state of a complex system but also pose new challenges in metabolite structure elucidation. Such techniques are greatly enhanced by Statistical Heterospectroscopy experiments where hybrid NMR/MS spectra can be reconstructed (3). The use of chemometrics allows interrogation of spectroscopic data and can give direct diagnostic information and aid the detection of novel biomarkers of disease and the integration of metabolic data with other omics sets including direct genome-metabolome mapping (4). Such diagnostics can be extremely sensitive for the detection of low level damage in a variety of organ systems and is potentially a powerful new adjunct to conventional procedures for toxicity and disease assessment and can help explain environment-gene interactions that give rise to idiosyncratic toxicity of drugs in man. Examples of the application of metabonomics to system level information recovery from tissues and biofuids will be given with special reference to personalised healthcare and pharmaco-metabonomic profiling (5) and human population screening using novel spectroscopy driven quantitative metabolome-wide association study approaches (6).

1. Nicholson JK Connelly J Lindon J Holmes E (2002) Nature, Rev. Drug Disc. 1 (2) 153-161.
2. Nicholson JK Holmes E Lindon JC Wilson ID (2004) Nature, Biotech. 22 (10) 1268-74.
3. Crockford, D.J. et al and Nicholson, J.K. (2006) Analytical Chemistry 78 363-371.
4. Dumas, M.E. Nicholson, J.K. et al (2007) Nature, Genetics 39 (5) 666-672.
5. Clayton, T.A. Nicholson, J.K. et al (2006) Nature 440 (20) 1073-1077.
6. Holmes, E. Nicholson, J.K. et al (2008) Nature 453 396-400.

INV-118

Correlating PKPD: application in drug development
Danhof, Meindert
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A major challenge in drug discovery and development is the prediction, in a strictly quantitative manner, of drug effects in man on the basis information from in vitro bioassays and/or in vivo

animal studies. Not surprisingly current research in PKPD modelling focuses on the development of mechanism-based PK-PD models, with much improved properties for extrapolation and prediction. Mechanism-based PK-PD models are based on principles from systems biology and contain specific expressions to characterise processes on the causal path between drug administration and response. This includes a) the biophase distribution, b) the target interaction/activation and c) the homeostatic control mechanisms, which may be operative. Ultimately also the effects on d) disease processes and disease progression are considered. The utilisation of these models relies on novel biomarkers characterising, in a quantitative manner, specific processes on the causal path. An important feature of mechanism-based PKPD models is the strict distinction between 1) drug-specific and 2) system-specific parameters to describe in vivo drug effects [1].

1. M. Danhof, J. DeJongh, E.C. DeLange, O.E. DellaPasqua, B.A. Ploeger and R.A. Voskuyl (2007) Mechanism-based pharmacokinetic-pharmacodynamic modeling: biophase distribution, receptor theory, and dynamical systems analysis. Annu. Rev. Pharmacol. 47:357-400.

INV-119

Controlling particle formation processes

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The control of the physical properties of ingredients in particulate formulations is key to efficient progression through the development process. Historically, batches of active pharmaceutical ingredient (API) have been optimised on parameters such as purity and yield with little attention to physical properties e.g. size and shape. Due to the variability of physical properties the formulation scientists has had to develop an extremely robust formulation capable of accommodating wide variations in these API parameters. Recent advances in the understanding of particle production processes have permitted a level of control of physical properties from quite an early stage. This, in combination with the recent introduction of "Quality by Design" principles, can allow the production of material with controlled physical properties with minimal variation batch-to batch ensuring a reproducibility of a formulation is improved and scale-up effects can be minimised. This presentation will demonstrate some recent developments that have been made in the control of particle size during production techniques and how this is reflected on their physical properties and demonstrates the importance of understanding of physical properties in development.

INV-121

Understanding API manufacture - application of QbD thinking to established products

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With the advent of the FDA's Quality by Design initiative[1] new pharmaceutical applications will be supported by focussed manufacturing science - resulting in better process understanding and control definition to mitigate quality risk. Thus pharmaceutical quality should become "built-in" to manufacturing processes by design rather than being "tested in" the product prior to release. In a typical pharmaceutical manufacturing site the age of products and processes can vary greatly, as can the inherent process robustness, understanding, control and therefore quality risk.
How does GSK use QbD principles to generate greater process understanding, capability and control? The purpose of this study was to apply guidance for design of NCEs to established products facing planned change.
Using 2 APIs as case studies the paper will show how by application of manufacturing science and process understanding can be applied to ensuring quality risk is minimised.
In case study 1, a "simple" technology transfer between manufacturing sites of a robust, problem free API process. What could possibly go wrong?
In case study 2, design of a new reprocessing method for an established product.
In both cases the use of QbD principles reduced the likelihood of failure, resulting in design elements that support a quality established product.

Ref 1. For example. http://www.fda.gov/cder/OPS/PharmQual.pdf

INV-122

From particles to product

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There is constant aim for deeper understanding of material properties in solid dosage form design. Only through maximizing understanding of materials and the relative importance of the phenomena and interactions on all levels, i.e. molecular>particle>powder>product, we can control the manufacturing of our dosage forms that meet target specifications for mechanical durability, stability, biopharmaceutical performance and ultimately bring safe medicines and therapies to the patient.
This presentation will discuss the path from particles to product using examples of how we can link particle size and shape distributions to behaviour in down-stream processability such as particle flow and packing characteristics by mechanistic modeling and dynamic particle size measurement. Moreover, the use of 3D-imaging will be demonstrated in monitoring and gaining understanding of a granulation process. Finally a study on how API variability can influence different phases of typical solid dosage form manufacture is shown. The examples of the presentation are also considered from risk management perspective.

INV-123

The potential benefits of FDC's: a view from pharmacology and therapeutic practice

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The use of fixed dose combinations (FDC's) has become increasingly important from a therapeutic and public health perspective. Such combinations are being used in the treatment of a wide range of diseases and proved to be particularly useful in e.g. hypertension, HIV/AIDS, infectious diseases etc. FDC's have advantages when they are shown to be safe and effective and/or exhibit reduced incidence of adverse effects. Very recently it has been shown that FDC's containing a number of active substances with different modes of action may be beneficial in the treatment (prevention) of cardiovascular disease, i.e. the "polypill" containing 3 blood-pressure lowering drugs, a statin, folic acid and aspirin (1).
The scientific rationale behind the increasing interest of FDC's is based on the principles of "systems pharmacology", i.e. a number of different key targets of a disease being addressed simultaneously. In order to quantitatively assess the contribution of each of the active substances to the ultimate effect, PK/PD modelling is the tool to be used (2). "Systems therapeutics" will thereby become an increasingly important component of therapeutic practice.

1. The Indian Polycap Study (TIPS). Lancet (2009) DOI:10.1016/60611-5.
2. D.D. Breimer: PK/PD Modelling and beyond: impact on drug development Pharmaceutical Research (2008) 25: 2720 - 2722.

INV-125

Specific aspects of FDC: Change of usual dosing schedule of one component; different food effects of each component

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During the development process of fixed dose combinations of two or more drugs several more or less serious problems of different origin have to be addressed. Problems having a biopharmaceutic background are mainly caused by the situation that sometimes the combined drug substances are usually taken under different dosing schedules. This may either concern the

frequency of intake or the intake condition relative to meals. As a result it may become necessary to alter the intake conditions for the new fixed dose combination product in comparison to the previously existing schemes and even in comparison to the established testing scheme used in bioequivalence studies. The formulation of modified release products containing fixed dose combiantion may even intensify this problem but may also serve as an alternative in order to overcome such difficulties. A well known example for the problems associated with differing intake conditions caused by different stabilities of drug substances under physiological conditions, different food effects and specific absorption sites are fixed combinations of antibiotics like the combination of amoxicillin and clavulanic acid.

INV-126

Problems with BE testing: FDC versus loose combination or versus individual components

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Combining treatments into one tablet has become an increasingly popular strategy. While a fixed combination is regarded standard for first line treatment of some of the foremost infectious diseases like tuberculosis or HIV, regulatory agencies are more restrained in other therapeutic areas like hypertension. It is important to know that FDCs are generally regarded as NDAs and not generic versions of their single entities.
Single components of a later FDC are mostly used to prove therapeutic efficacy and safety in phase II/III studies and later pivotal BE trials are required to demonstrate equivalence of the FDC to the loose combination.
In exceptional cases where the FDC is merely aimed to replace a well established combination of two cardiovascular drugs which are administered at the same dose interval and timing no further pharmacodynamic studies are required. However, in that case formal BE needs to be proven against each monotherapy. The latter may be an insurmountable obstacle taking into consideration the multitude of possible interactions between the two active components and/or excipients in ultimate vicinity and taken at exactly the same time.
In any case, BE studies are pivotal parts in most FDC development programs and possible pitfalls should be taken into consideration in the very beginning of the development.

INV-128

Candidate selection process: overview, opportunities and challenges

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Attrition of drugs during development is high and very cost-intensive for the Pharma industry. With the aim to reduce the risk of failure and increase the quality of candidates that enter the development phase the selection process has undergone some serious changes over the last few years. As most drugs fail due to either lack of efficacy or safety concerns, some may increase the risk by comprising of poor ADME properties, or cause serious delays and enhance costs as a result of unfavourable physicochemical properties. But also, modifications in marketing or portfolio strategies as well as changes in the direct competitor situation may have a significant impact on the decision of taking a drug to the next stage. As a result, the pharmaceutical industry has responded by strengthening the interface between R&D with more closely involving development experts in the decision making of the candidate selection process. Also, many more data are nowadays generated at a very early stage in discovery that allow the most effective evaluation of the present lead compound regarding all aspects of developability and risk assessment and finally lead to the selection of the best possible candidate. The presentation gives an overview of the candidate selection process and convey how this process is supported by development functions in general and pharmaceutical technology in particular.

INV-129

Integrative risk assessment in ADME(T)
Faller, Bernard
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Inappropriate pharmacokinetics represent a major cause of attrition from lead to clinical candidate selection and a well designed pharmacokinetic profile plays an important role in the successful clinical use of a new molecular entity. Insufficient exposure can be the cause of a lack of efficacy and insufficient exposure multiples makes the assessment of the therapeutic safety margin difficult. In order to manage this risk a number of in-vitro assays of various complexity and throughput have been set-up, tackling the main components of drug absorption, distribution metabolism and excretion. This new approach created a broad scale, largely automated drug discovery environment, which involves in silico and in vitro technologies. The next challenge at this stage is often to extract relevant information from a pool of metadata of different dimensions and possibly partially inter-correlated and convert it into Medicinal Chemistry actions. This lecture will illustrate what it takes to an assay to bring value for decision making, how to extract information from complex data matrices including assays that are potentially inter-correlated and inter-linked and what are the current limitations of these approaches.

INV-130

Drug candidate design from an ADME perspective
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ADME parameters describe the fate of a drug in the body, which is important both for its activity and potential adverse effects, like side effects, toxicity and drug-drug interactions. Thus, the success of a drug candidate is very much linked to its ADME properties. During a drug discovery program both in vivo and in vitro studies are performed to enable a good estimation of the human in vivo situation. Early identification of important ADME parameters for a given drug discovery program enables targeted investigation of structure-ADME property-relationships and thereby design of drug candidates with improved ADME characteristics. Important ADME parameters and ways to investigate structure property relationships will be discussed. The selected drug candidate needs optimal ADME properties with regard to its activity.

INV-131

Addressing specific regulatory excipient requirements in the marketing authorization: Heavy metals, genotoxic impurities, etc...
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In the past decade, stakeholders in the pharmaceutical industry had to face strongly elevated levels of regulatory and quality standards. These could be either internationally harmonized or valid at regional level, furthermore they may be guidelines/ recommendations or even directly enforceable law. As a matter of fact, till this day there is a lack of binding regulation on excipients. Consequently, when it comes to evaluation of a specific functional, new or novel excipient in conjunction with a MAA (marketing authorisation application), both applicants and authorities face a multitude of additional challenges during such assessments.
IPEC as an association of manufacturers and users of pharmaceutical excipients elaborates common excipient standards which are essentially needed to assure an appropriate assessment of the safety and quality of innovative medicines.
For BASF as manufacturer of innovative pharmaceutical substances, in order to overcome regulatory obstacles and be able to launch new and novel excipients at global level, it is crucial to consider and anticipate such regulatory standards. In doing so, BASF gained some experience in responding to a multitude of requests from authorities all over the world which is presented in this publication.

INV-132

Co-processed excipients: Regulatory challenges

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A co-processed excipient can be defined as a combination of two or more compendial or non-compendial excipients designed to physically modify their properties in a manner not achievable by simple physical mixing and without significant chemical change.
In other words the development of a co-processed excipient is a means to obtain a material with specific characteristics and functionality without having to develop a new chemical entity and having to invest in the process of bringing a novel material to market.
This presentation will discuss various processes used to manufacture co-processed excipients and how these materials differ from simple blends. In EU guidance on the regulatory status of excipients there is no direct reference to co-processed materials which generates some confusion on how they should be described in a marketing application and what data the manufacturer needs to provide to support its use. Discussion will focus on whether a co-processed material needs to be considered as a 'novel' material or whether a more simplified qualification can be achieved.

INV-133

Excipient certification – value and strategy

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In February 2008 the EU Commission published the report from Europe Economics which concluded that there was a negative cost-benefit balance for changing the status quo with regard to the application of GMP to "certain" excipients. Of the proposed alternatives that the commission requested feedback upon, a risk based approach was the least costly, followed by self regulation. Legislation by the EC was seen by all parties as the most expensive option.
Picking up on self regulation, the European Fine Chemicals Group and IPEC Europe established an Excipient Certification Project. Now in collaboration with IPEC-Americas, the UK Pharmaceutical Quality Group and the European Association of Chemical Distributors (FECC), this project will deliver a 3rd party audit scheme in which certification of excipient suppliers to the IPEC-PQG GMP Guide and the IPEC GDP Guide.
The details of the 3rd party certification scheme will be described, including the development of an excipient classification system based on risk to the end user which leads to more advanced GMP controls as the risks heighten. Overall the scheme's benefits to suppliers, users and the regulatory bodies will be illustrated.

INV-135

Age-appropriate drug formulations for children

Breitkreutz, J
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An age-appropriate drug formulation is a prerequisite for the successful drug treatment of children [1]. However, paediatric drug formulations are a challenge in drug development as the human body undergoes fundamental changes from birth to adulthood.
In 2007 the new regulation of the European Union on medicinal products for paediatric use came into force. For all drugs with new chemical entities a Paediatric Investigation Plan (PIP) has to be submitted to the Paediatric Committee (PDCO) at the European Drug Regulatory Office (EMEA) at an early stage of drug development [2]. Pharmaceutical companies urgently need guidance for the rational and economically acceptable galenical development, but various key issues are still unsolved:
- When does a child may accept a solid dosage form for peroral use? Which size may be acceptable at which age?
- How is efficient taste-masking achieved? How to predict the taste sensation of children and how can this be confirmed by clinical studies [3]?
- Which medical devices are appropriate and how can we improve them for use in children?

- How can industry ensure safe preparation of extemporaneous formulations prepared by parents or pharmacies?

[1] J. Breitkreutz & J. Boos, Exp. Opin. Drug Deliv. 4: 37-45 (2007)
[2] J. Breitkreutz, Clin. Ther. 30: 2146-2154 (2008)
[3] A. Cram, J. Breitkreutz, S. Desset-Brèthes et al., Int. J. Pharm. 365: 1-3 (2009)

INV-136

Paediatric medicines: A clinical point of view
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The lack of availability of medicines for children is global. It concerns all children of the world, both in the developing and in the developed world. The physiological changes related to growth and development and paediatric diseases or forms of diseases influence use of medicines in children. Medicines for children should be available in age appropriate formulations, and should fulfil criteria of quality, safety and efficacy. Paediatric formulations should allow flexible dosing and be easy to administer. Around 80% of drugs approved for adults do not containing dosage recommendations for children. The result is widespread unlicensed and off-label use of medicines in children with all its consequences. This does not imply that these medicines have no been studied in children at all. Much of existing data on the safety and efficacy of paediatric medicines comes from academic research, has not been submitted for regulatory assessment, is not reflected in labelling, and often difficult for the prescriber to find. To provide children with better medicines, new formulations, more and better clinical trials and pharmacovigilance data are needed in all relevant paediatric age groups. This requires collaboration of paediatricians, paediatric pharmacologists, paediatric pharmacists, pharmaceutical industry, regulators, and especially children and their parents.

INV-137

Therapeutic antibodies: trends and future developments
van de Winkel, Jan G.J.
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Monoclonal antibodies currently represent the largest group of therapeutic proteins in development. More than 25 percent of all drugs in development are presently based on antibodies, and 22 monoclonal antibodies (mAb) have been approved by the United States FDA for a wide range of diseases. Technologies to generate therapeutic antibodies have matured from mouse to entirely human molecules. Especially the development of human Ig-transgenic mice facilitates the rapid development of human therapeutic antibodies. Such antibodies can be used long-term for treating human disease. The development of novel antibody therapeutics centers around three main players: the target, the antibody and the patient. To successfully design new therapies all three need to be considered in an integrated manner. Better insights into antibody biology catalyzes the development of novel therapeutic approaches. This presentation addresses important developments and new trends in the therapeutic antibody field. These include modification of antibody effector function and development of novel antibody formats, optimally tuned to improve the therapeutic potential.

Reference: Parren P.W.H.I., and J.G.J. van de Winkel. An integrated science-based approach to drug development. Curr. Opin. Immunol. 2008; 20: 426-430.

INV-138

CMC requirements for first-in-human studies with biopharmaceuticals
Sonnega, Carina E.A.
Drs. Carina E.A. Sonnega, Biotechnology Consultant, La Garde Freinet, France

First-in-human studies are small, time-lagged dose-escalation studies evaluating safety and tolerability in healthy volunteers or patients, depending on the indication and ethical considerations. Safety of the subjects in such studies is paramount. Quality aspects are in principle the same for all investigational medicinal products (IMPs), whether they are of a small molecule- or biopharmaceutical nature, and should, in themselves, not be a source of risk for first-in –human trials. Nevertheless, due to the specificity of the quality attributes of biopharmaceutical products, particularly where it concerns complex molecules, they should be taken into account in the risk assessment performed before entering a first-in-human trial. This presentation aims at providing an overview of the current global regulatory climate for first-in-human studies, focusing on the particular quality aspects and CMC requirements for biopharmaceutical products derived from biotechnological processes. The overview will be accompanied by some practical tips for first-in-human regulatory submissions based on hands-on experience, and illustrated with a case study.

Key reference: EMEA/CHMP/SWP/28367/07 - Guideline on Strategies to Identify and Mitigate Risks for First-In-Human Clinical Trials with Investigational Medicinal Products, 19 July 2007.

INV-139

Formulation and process development for first-in-human biological products

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Preclinical studies in animals can evaluate risks deriving from biological drugs like monoclonal antibodies only to a limited extent e.g. immunogenicity. For small molecules predictability is generally better than for biologics.
Nevertheless the immediate start of phase I studies in humans is often required for economical and ethical reasons.
Therefore an effective strategy for the development of First-in-Human (FIH) formulations is valuable.
Additionally, often a couple of drug candidates for the same target are assessed in parallel before the start of first human studies so that feasibility for further development has to be predicted or should be predictable via in-silico and high throughput screening methods also from a drug product CM-perspective using tools such as automated Differential Scanning Colorimetry (DSC) or Right Angle Light Scattering (RALS).
Since formulation development runs in parallel to the analytic method development, standard characterisation methods must be available e.g. for the description of the aggregation or fragmentation behaviour.
A further development risk which can be reduced concerns the cleaning of process equipment from active drug substance and its respective analytics even at a timepoint when the potency of the molecule is still unknown.
For this purpose the use of disposables in the manufacture of FIH products is a reliable strategy.

INV-140

Beyond personalized medicine – from hype to reality

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Although we have had great expectations for pharmacogenomics, very few of them have been met to date. The reasons are many and complex, spanning a range of scientific, political and economic problems. Perhaps the most important realization is that the complex character of most diseases and the attendant complexity of pharmacotherapeutic management and treatment often make it difficult to achieve an optimal therapeutic outcome using a classic pharmacogenomics approach, because individual and situational factors play an equally important role. Pharmacogenomics has often been positioned as synonymous with individualized medicine. This presentation argues for expanding the meaning of individualized medicine to encompass individualized diagnosis, prescribing, monitoring, compliance, information and marketing as well as classic pharmacogenetics. We will never have either the research or the

economic resources to individualize all aspects of treatment from molecule to man. Therefore we need to clarify which factors will provide the most individualized medicine for our resources; or put in socioeconomic terms, how do we get the most individualized medicine for the money?

INV-141

The future research strategies in personalised medicine
Vreugdenhil, Erno; de Rijk, Roel
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A central clinical question is why a drug is highly effective in one patient while that same drug is less effective and even without efficacy in other patients. According the National Institute of Health, adverse drug reactions is believed to account for more than 2.2 million serious cases and 1000,000 deaths in the US. Presently, there is no way to predict whether a person responds well, moderate or not at all and consequently the pharmaceutical industries develop drugs with a 'one size fits them all' strategy.
Genomic research has shown that a large part of the individual human genetic variability can be contributed to the so-called 'single nucleotide polymorphisms' (SNP's). Clear evidence exist that these SNP's are crucial factors for drug efficacy. Presently, numerous pharmacogenomic efforts are dedicated to identify disease-associated SNPs in order to refine diagnosis and pharmacological therapy. In this seminar, I will discuss different strategies that link genetic variation to biological function and future therapy aiming to restore this genetic variation with a specific emphasis on nucleic-acid-based drugs. As an example, I will highlight the consequences for psychiatric diseases of genetic variations in genes affecting glucocorticoid signalling in the brain, in particular glucocorticoid receptors.

INV-142

Application of pharmacogenomics to clinical problems in depression
Oestergaard, Svetlana; Møldrup, Claus
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The aims of this study are to review the literature for evidence supporting an association between genotyping and clinical outcomes for treating depression and to discuss perspectives on genotyping in antidepressant therapy.
Studies were searched in PubMed, EMBASE, International Pharmaceutical Abstracts (IPA), Web of Science and Cochrane Library.
Ninety-nine articles were identified. All except three articles were retrospective cohort studies. The other three articles were two meta-analyses and a decision-analytic model. These three studies looked for the polymorphic site in the serotonin transporter gene promoter, 5-HTTLPR. The main finding from these meta-analyses was that the l-variant was associated with a better response to SSRIs. The main conclusion from the decision-analytic model study was that performing genetic testing before prescribing antidepressant treatment may lead to greater numbers of patients experiencing remission early in treatment.
There is a lack of evidence justifying the use of genotyping serotonin transporter polymorphism as a guide to treating depression. Clinical outcomes of genotyping this polymorphism are evaluated by improvement of depression score, odds ratio, and number needed to treat.

INV-143

No code of codes for life style changes – a challenge for personalised medicine
Hansson, Mats G.
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The human genome was believed to be the code that defined our possibilities and limitations as human beings. The Nobel laureate Walter Gilbert once called it the "grail of human genetics". Other similar epithets were "the blueprint of life", "a future diary", "the biological grail". As knowledge increased about epigenetics and the complex role of the biochemical environment of

the cell for the transcript of genes, the claims by the geneticists became more modest. However, it is still a fact that a new avenue is opened for personalised medicine based on the rapidly increased knowledge about the genes. Developments in research about gene-environment interaction points in the same direction. Rheumatoid arthritis is today one of the few diseases where the magnitude of gene-environment interaction has been demonstrated. It should therefore be amenable to preventive efforts, including change in health-related behaviours. However, even if both the genetic and the environmental risk factors are known it is also well known that change of behaviour is not directly correlated to information about health risks. The real challenge for personalised medicine that I will discuss in this presentation is to understand the implications of gene-environment interactions at the individual level and also master the ethical problems of assigning personal responsibilities for individual health risks.

INV-145

Past, present and future of drug development
Holzgrabe, Ulrike
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Even though the techniques for drug discovery became more diverse for the last 20 years starting with high-throughput screening, combinatorial chemistry, virtual screening, fragment-based design, and "omics", the number of approved drugs is continuously decreasing. A series of Nature papers attributes the problem to the lack of translational science, indicating the problem to translate a drug candidate from bench to bedside. Thus, the session will deal with entire process of drug development.
This talk will demonstrate the first steps of lead optimization in an academic environment using the so-called piggy-back approach. Mono- and bisnaphthalimides, e.g. elinafide, have been developed as cancerostatic drugs. Recently, naphthalimides could be profiled as potent agonists of the muscarinic receptor. Within the frame of a broad screening program the naphthalimides were tested for their activity against Trypanosoma brucei, Leishmania major, Staphylococcus aureus, Plasmodium falciparum and toxicity against macrophages. Depending on the substitution pattern the naphthalimides were active against either microorganism in the low micro- and nanomolar range of concentration combined with almost no cytotoxicity. The structure-activity relationships were different for each purpose indicating that the piggy-back approach can be considered as a worthwhile method for drug development.

INV-146

PK/PD modeling: Streamlining drug development
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The cost of drug development has exploded in recent years and risen to a level that soon will no longer be affordable to society. The public expectation of drug safety and guaranteed therapeutic success has become unrealistic. As a result, the number of new drug approvals can be expected to go down in the near future, a trend that is already noticeable in drug classes with low market potential due to short term therapeutic use, e.g. antibiotics. One reason for the high cost of drug development are many unnecessary studies where the results could have been predicted with reasonable certainty. PK/PD modeling is a tool that can be used to collect and integrate all the available information about a drug candidate and its class in order to make rational decisions on studies that will decrease the uncertainty of the compound. It is based on quantitative data on drug exposure and response and particularly well suited to adress the question of dose finding and optimization. In the drug development process, it bridges the complete cycle from discovery a to clinical use. The advantage of this approach is to define objective go/no-go decision criteria for the development process rather than relying on subjective empirical decisions. There is no way that today all developing questions can be answered by experimental evidence, and modeling and simulation is a powerful alternative approach.

INV-147

Drug metabolism pathways to improve oral bioavailability of amidines and guanidines
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Orally available amidoximes (N-hydroxyamidines) like ximelagatran and N-hydroxyguanidines allow the maintenance of the amidine and guanidine function and thus the interaction of amidinium – ions with carboxylates of target proteins. The wide application of this prodrug principle to increase the oral availability of amidines requires the identification of amidoxime reducing enzyme systems. For 40 years, it was believed that only three molybdenum containing enzymes are present in the human body. With the purification, cloning, expression and characterisation of human mARC it became clear that a fourth molybdenum containing enzyme exists and that the human genome codes for two mARC-proteins.Upon reconstitution with cytochrome b5 and b5 reductase, mARC1 and mARC2 are capable of reducing amidoxime prodrugs. This successfully reconstituted system can serve as a model in order to predict the in vivo situation of newly developed amidoxime prodrugs and also to explain known reductions observed in vivo. Our studies also demonstrate that the prodrug principle is not dependent on P450 enzymes. Thus, P450-dependent interactions are avoided, which also explains why those have not been observed for amidoximes tested in the clinic. mARC proteins are also involved in the reduction of xenobiotics leading to detoxification and have to be added to the list of enzymes involved in drug metabolism.

INV-148

Pharmacometrics: Improving dose selection in early clinical development
Schaefer, Hans Guenter; Lehr, Thorsten; Duval, Vincent; Dittberner, Silke; Dansirikul, Chantaratsamon; Freiwald, Matthias; Staab, Alexander
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Early clinical trials (Phase I/IIa) provide the key information to decide whether a drug development candidate is suitable for full development (Phase IIb/III) or not. Due to the nature of these trials the dose-exposure-response relationship can be obtained for biomarker endpoints, but not for the final clinical endpoint . Therefore, an integrated data analysis approach including compound specific pharmacokinetic and biomarker data in conjunction with published and/or internal data is key. Here, pharmacometrics has an important role to play. Pharmacometrics applies mathematical and statistical models to describe in quantitative terms the dose-exposure-response relationship including disease (progression) and models correlating biomarker data with clincial endpoints based on competitor information. Thereby, pharmacometrics enables the decision makers to evaluate in "what-if scenarios" the key characteristics of the compound in a quantitative manner, with the goal of providing explicit, reproducible, and predictive evidence for moving the compound into full development. Three case studies are presented to illustrate how the early application of pharmacometrics can a) provide a good dose estimate based on first in man and biomarker data b) select a safe dosing regimen for an oncology compound and c) help with translating early biomarker data with clinically meaningful endpoints.

INV-149

The science behind a granule: 'A life story'
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Wet Granulation is a size enlargement process where powder particles are bonded together using a liquid, which can be poured, sprayed or melted into the powder mass. Granulation is an important processing step in many industries, perhaps most notably in the, pharmaceutical and food industries. Historically, process and product development has taken place on a case by case basis, with significant costly trial and error required.
There is now a move forward to take this 'black art' approach towards a more science based engineering design methodology, with a view to develop a 'granulation theory' and a

comprehensive multi-scale model. In order to do this it is necessary to employ various experimental techniques across all the length scales; micro-, meso-, and macro-. Some of the techniques being further developed; such as particle image velocimetry (PIV), High Speed Imaging, Thermal Imaging, X-Ray Tomography, Visual On-line sizing (VOS) and DEM modelling, and their application from drop-powder and drop-granule interaction and evolution of granule structure at the micro-scale, to intra-granulator powder motion and collision rates, binder distribution at the macro-scale, will be introduced.

INV-150

QbD formulation design

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QbD formulation design is not a new concept, in its simplest form it can be described as good scientific practice. Pharmaceutical formulation scientists have applied good scientific practice to formulation development for decades with much success. The approach to formulation development in this current QbD development climate requires a shift in focus for the formulator. The formulator now needs to consider what the CQAs will be and what formulation and process variable could effect the CQAs. The formulator will now conduct small scale DOEs to understand the critical variables effects on the CQAs and develop the necessary scientific rationales to focus the large scale DOE experimentation and develop the control strategy. The aim is now to produce formulations and processes which are robust and suitable for scale-up and a QbD submission.
The formulation scientist has a myriad of analytical and science of scale tools that can be applied in formulation development that will aid the production of a QbD formulation and manufacturing process. Examples of how these tools are applied to formulation design will be presented.

INV-151

QbD for inhalation products

Thalberg, Kyrre
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DPI products require a very small particle size of the API, which makes it difficult to obtain high-performing formulations which are at the same time robust and well-controlled. Furthermore, the combination of the dry powder formulation with the inhaler device imposes additional challenges which have to be overcome in the development work.
Delivered dose and fine particle dose are two critical quality attributes of a DPI product. Both require specialised analytical methodology. Delivered dose measures total exposure to the patient, while fine particle dose relates to the dose reaching the lungs, and hence to pharmaceutical effect for a locally acting drug. IVIVC studies may thus serve to bridge in vitro product behavior to pharmaceutical profile.
The next step is to link API and excipient attributes and processing parameters to the critical product quality attributes to establish a design space for manufacturing. Here, challenges with regard to raw materials and powder processing will be discussed.
It is also important to assess the robustness of a DPI product in the hands of the patient. The device should be as fool-proof as possible and in-use studies as well as mis-use studies of the drug product will be needed during product development.

INV-152

The factory of the future

Kraunsoe, James; Dakin, Jon
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The Pharmaceutical Industry is experiencing multiple challenges as a result of market and regulatory changes together with scientific and technology advances.

Novel approaches to product design and manufacturing are being used in response to these challenges. The presentation describes how a better understanding of science and the application of technology strategies enhance technology transfer, scaling and commercial competitive advantage. The 'Factory of the Future' will benefit from increased manufacturing flexibility, robust processes with real-time feedback, easier process change control, resulting in improved value contribution to the business.

INV-154

Drugs mainly taken by the elderly: Are sufficient efficacy and safety data provided? - A regulatory view

Thirstrup, Steffen
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The impact on drug development of the new EU peadiatric legislation cannot be overemphasized. This regulatory change will hopefully result in a significant number of drugs being developed to better target his patient population. Despite the fact that the elderly population is growing in all western countries the same attention in terms of regulatory requirements have not yet been introduced. Development of new therapies - whether they are intended for conditions mainly occuring in the elderly or in the general population - should be undertaken in accordance with the ICH E7 guideline developed 15 years ago. Although this guideance document put much emphasis on the requirement to included a sufficient number of patients over 65 years of age, the regulatory experience is that many new drugs have only been given to a limited number of elderly and especially to patients above 75-80 years of age. Therapeutic advances in a number of clinical areas (e.g. cardiology and oncology) have resulted in an increasing number of elderly and older subjects beeing the potential target for new therapies despite the fact that only limited experience exist with regard to possible interaction with co-medications as well as co-morbidities. Such ogbservations calls for an increased regulatory awareness of the elderly population

INV-156

The elderly as the target population: Necessity to determine the PK of a NCE in the elderly patient in more detail?

Mueck, Wolfgang
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Following recent regulatory initiatives (i.e. 'pediatric investigational plan'), drug use and drug development in children attracts considerable attention of many PK and PK/PD scientists. However, at the 'other end of the age scale', the elderly are by far of no less importance, similarly representing a special group of patients at risk. Our increasingly aging societies lead to more and more elderly patients, at even higher ages, being treated with a lot of different drugs at a time (poly-pharmacy). This presentation will provide an overview of approaches in pharmaceutical drug development to collect adequate PK data in elderly subjects/patients, and will outline general concepts to gain all the information necessary to best guide dosing and labeling recommendations for the elderly.

INV-157

Should the regulatory environment change to reflect population demographics? Role of population PK

Rowland, Malcolm
University of Manchester, School of Pharmacy and Pharmaceutical Sciences, Manchester, United Kingdom

Assessment of both absolute bioavailability (BA) and bioequivalence (BE), to meet regulatory requirements, tends to be performed in a relatively small, tightly controlled, group of young healthy adults. It is tacitly assumed that such information applies directly to the target patient population, which, for many conditions, is increasingly the elderly, in whom gastrointestinal

function is known to differ from the young. Much of these differences in function are sufficiently well understood to allow reasonable prediction of likely BA in the elderly based on young adult data. However, there are many subtleties that can influence formulation performance in vivo, so that BE of drug products demonstrated in the young may not guarantee BE in the elderly for certain drugs. If a concern exists BE assessment could be performed in elderly subjects but an alternative, and arguably better, approach is to undertake assessment in the target population. A formal BE study in patients may be problematic but a population PK approach may offer a solution, and indeed may obviate the need for a formal BE study. Regulatory agencies should be sensitive to this, and related possibilities.

INV-158

Novel galenic approaches to formulations tailored for the elderly

Bar-Shalom, Daniel
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At a workshop held in connection with the Controlled Release Society Annual meeting in New York, 2009 , problems associated with the oral administration of medicine to the elderly were reviewed. From a technological point of view, the main challenges appeared to be the prevalence of polypharmacy and swallowing difficulties. Interviews with elderly patients and observations of actual drug administration to the elderly in the nursing home scenario were conducted. The assumption that conventional pills and capsules are not the optimal dosage forms for this patient group was confirmed. A review of the literature revealed some useful approaches but unfortunately some potentially dangerous ones as well. An attempt is made to outline approaches as to how to improve existing solid oral dosage forms in terms of size, shape, surface structure, mouth feel and others and some – potentially – novel alternatives to the conventional solid and liquid oral dosage forms are presented.

INV-159

Toxicologic profiling of compounds at the candidate selection stage: tools, advantages and limitations

Blomme, Eric
Abbott Laboratories, Abbott Park, United States

Toxicity represents an important cause of failure in drug discovery and development. Therefore, better identification of the toxic liabilities of experimental compounds represents one of the most promising alternatives to decrease overall R&D costs and increase probability of success. In this presentation, we will review several profiling methodologies for toxicology that can be used for candidate selection. Using specific examples, we will illustrate how these methodologies can be successfully implemented in a discovery or preclinical organization.

INV-161

Prediction of adverse reactions through data mining

Jenkins, JL[1]; Mikhailov, D[1]; Whitebread, S[1]; Hamon, J[2]; Urban, L[1]; Davies, JW[1]; Scheiber, J[2]
[1]Novartis Institutes for Biomedical Research, Cambridge, United States; [2]Novartis Pharma AG, Basel, Switzerland

This talk will first describe a method that can be used to predict adverse drug reactions from the chemical structure only[1]. Then related problems will be discussed and further development of the method towards an understanding of pathway-related mechanisms will be introduced[2]. This focusses on compounds that, although different in chemical structure, exhibit the same adverse drug reaction. An analysis of common "off-pathways" based on data mining and modelling techniques is elaborated. In addition, a recently published method to analyze the chemical space of adverse drug reactions will be described[3]. In summary, this talk aims to deliver a comprehensive overview of what can(not) be currently achieved in the area of in silico prediction of adverse drug reactions.
[1] Analysis of pharmacology data and the prediction of adverse drug reactions and off-target

effects from chemical structure. Bender A, et al. ChemMedChem. 2007 Jun;2(6):861-73.
[2] Gaining Insight into Off-Target Mediated Effects of Drug Candidates with a Comprehensive Systems Chemical Biology Analysis. Scheiber J, et al. J Chem Inf Model. 2009 Jan 13. [Epub ahead of print]
[3] Mapping adverse drug reactions in chemical Space. Scheiber J, et al. J Med Chem [in press]

INV-162

ADME Techniques – What's new in our World?
Mackie, Claire
J&JPRD, EU Discovery ADME/tox, Beerse, Belgium

Todays Discovery experts have identified the importance of understanding a compounds ADME properties in parallel with the pharmacodynamic relationship as a crucial step in the Discovery process. Utilising a wide toolbox of assays, the critical aspects and properties of the compounds can be studied and revealed. Through understanding these properties more clearly, the pre-clinical and clinical pharmacokinetics can be predicted more successfully, or can they? With this in mind, and looking at the current tool boxes we have available, what are the current questions and challenges we face? The presentation will briefly look at the current tool box, discuss in more detail the current questions and challenges and explore some new approaches and technologies to further explore the A, the D the M and the E.

INV-164

From lead to drug candidate, from animal to man
Locher, Mathias
Merck Serono, DMPK, Grafing, Germany

In the case of NCEs a labor intensive and sophisticated early-ADME screening is established, testing the compounds in a series of in vitro assays and in in vivo models to understand the PK characteristics of the new molecules. Also the prediction of a safe starting dose for FiM studies, the estimation of an efficacious dose or the simulation of PK in humans is done using established tools. Can these processes and tools simply be applied to biopharmaceuticals? This presentation will mainly focus on the early development of biopharmaceuticals until FiM and describe the differences between NCEs and NBEs as well as some hurdles that have to be taken until patients can be treated. Topics like pharmacokinetics, immunogenicity, immunogenicity risk assessment, safe starting dose in man, as well as high risk proteins will be adessed.

INV-165

Pharmaceutical development and manufacturing: trends in processing of solid oral dose forms
Moreton, Chris
FinnBrit Consulting, Waltham, MA, United States

Pharmaceutical development and manufacturing is changing. The introduction of ICH Q8 (Quality by Design – QbD) encourages the development of better formulations; better products with less risk of failure. The potential benefits of QbD for manufacturing will be discussed. Continuous processing is a logical extension of the combination of QbD and Process Analytical Technologies (PAT) and its potential will also be reviewed. A fundamental basis of both QbD and continuous processing is an understanding of product variability, how it arises, what contributes to it, and how we can work with it. This will be reviewed as it relates to both QbD and continuous processing.

INV-166

Continuous process and life cycle management; the factory of the future
Roche, Frank
Glaxo SmithKline, Brentford, United Kingdom

There has been considerable discussion from regulators, equipment manufacturers, and operating companies around the technical and commercial benefits of continuous manufacturing. In reality, the benefits only become realisable given robust on line measurement technology allowing precise controllability and potentially real time release.
This paper describes Glaxo SmithKline activities to realise the benefits of integrating emerging continuous manufacturing technologies with emerging on or at line analytical technology and information management systems. Commercial and technical drivers, and experience of practical project execution will be shared. A view of a future manufacturing platform based on continuous flow principles and continuous unit opeations will be given.

INV-167

Challenges in measurement system development for continuous processes
Suhonen, J.; Marbach, R.; Paaso, J.
VTT, Optical Instruments Center, Oulu, Finland

The concept of continuous pharmaceutical manufacturing creates new demands for the measurement technologies, due to some inherent differences between batch and continuous processes. Novel measurement technologies will be needed in order to monitor critical quality attributes in the future pharmaceutical production concepts. Based on this information, the process could be controlled and the variation of end products quality will be minimised. New requirements of quality assurance systems lead to the use of time-resolved and spatially resolved measurement technologies, i.e. to fast imaging and multipoint techniques with real-time data analysis and interfacing.
VTT has long experience of developing on-line monitoring and detection systems for continuous processes in pulp&paper and steel industry. Some examples of fast multipoint spectroscopy and imaging techniques utilised in other manufacturing processes will be illustrated in this presentation. Some ideas on how these measurement technologies could be used in the pharma industry will be addressed, as well. Measurement speed, robustness of instruments, easy calibration, price sensitivity, cleanliness of process interfaces among others are critical requirements, which should be taken into account in the development of new PAT tools of continuous pharmaceutical processes.

INV-168

Continuous wet granulation process for solid oral dosage forms
Boppert, Alexander Boppert
Lödige, Life Science Technology, Paderborn, Germany

The wet granulation process – mixing, granulating, drying – for the production of oral solid dosage forms can be carried out in continuously operating. As proven in other industries continuous processes offer a number of advantages like smaller equipment, less manpower, less product handling and exposure and overall reduced production cost. Lödige is a provider of the complete continuous production train from the raw material to the dried granulate.

INV-171

Well known European Herbal Medicinal Products – still a pharmaceutical treasure trove?
Heinrich, Michael
The School of Pharmacy, University of London, Centre for Pharmacognosy and Phytotherapy, London, United Kingdom

The list of compounds ultimately derived from traditional knowledge, for example in Europe, is very long indeed and includes morphine, codeine, and aspirin to name just a few but also drugs licensed relatively recently like galanthamine and - a very recent example -peplin. Here I review this link and - using examples of new drugs currently under development preclinically or in clinical trials - discuss how such new drugs have been 'discovered', or more precisely developed into a clinically used medication. Field-based ethnopharmacological studies are the most

essential basis for such drug development efforts. Such studies have a multitude of theoretical and applied goals and in fact only very few are in any way directly linked with projects in the area of drug discovery. One of the core tasks of ethnopharmacologists is to ascertain that such traditional knowledge is safe-guarded and remains an integral and appreciated part of a culture and that - if commercial products are developed from of such knowledge - both the material and immaterial benefits are distributed equitably.
Preclinical (i.e. pharmacological and phytochemical) research has been conducted on numerous plants using a multitude of pharmacological targets. Such knowledge not only is an element of drug development, but contributes to our understanding of the effects such local and traditional medicines.
Some recent examples of clinical developments of drug leads into new medicines highlight the potential of such knowledge-based drug development programmes. Many new drug leads are 'poster children' of ethnopharmacology driven drug developments programmes. Lastly, some extracts, which are complex mixtures of active and inactive constituents, have been developed and are used now clinically. Ethnopharmacology and drug development can only be understood if a truly multidisciplinary approach is taken and this is one of the most exciting and promising challenges of the field - it requires a dialogue not only between disciplines but also between cultures.
Preparations derived from *Cannabis sativa* have been used as medicines throughout Europe and Asia since the earliest written records, especially in the treatment of pain and inflammation. This species has yielded important commercial phytopharmaceuticals, but despite of the great resurgence of interest in the medicinal applications of cannabis, current research and development activities still do not use properly standardized extracts of the plant. As part of its EU's sixth Framework Programme a consortium of European SME's and research organisations currently develops standardised extracts of cannabis for the treatment of rheumatoid arthritis and migraine. The emphasis of the consortium's work is on defining the chemical and pharmacological requirements of a final medical product derived from cannabis and ensuring that they are available in the resulting standardised extract and pharmaceutical formulations.

INV-172

Discovery of new pharmaceutical leads from TCM drugs
Hamburger, Matthias
University of Basel, Pharmaceutical Sciences, Basel, Switzerland

In the history of drug discovery and development, natural products have been the most prolific source for drug leads. With the globalization of traditional Chinese medicine (TCM) and success stories such as the antimalarial artemisinin, lead discovery efforts from TCM herbs have been intensified.
Identification of bioactive natural products in extracts remains a major challenge. To accelerate and facilitate the discovery process, we have implemented a technology platform for miniaturized activity-based natural products discovery. The platform includes 2D-barcoded liquid extract libraries, HPLC-based micro-fractionation in 96-well format for bioassays and simultaneous on-line spectroscopy (PDA, TOFMS, and MS/MS), and off-line microprobe NMR spectroscopy.
The platform is successfully used for ongoing projects on TCM-based lead finding. A screening for GABAA receptor modulators was carried out with an automated two-microelectrode voltage-clamp assay with transiently transfected Xenopus oocytes. Identification of GABAA receptor ligands with scaffolds new for the target will be presented. Compounds with antiplasmodial and angiogenesis-inhibitory properties were also identified from TCM herbal drugs using the profiling approach and will be discussed.

INV-173

Medicinal plants and systems biology: a perfect holistic match
Verpoorte, Robert; Choi, YH
Leiden University, Pharmacognosy, Leiden, Netherlands

Only about 20 novel drugs were developed in 2005. The withdrawal of two novel drugs shortly after their introduction, makes the future of drug development even more uncertain. There are

several reasons for this. The paradigm of drug development is: single compound, single target. For the ca. 450 known targets good drugs exist. However, for many diseases our knowledge is insufficient (e.g. cancer), or the market too small to invest about 1 billion € for developing a drug. Going back to a more holistic approach for drug discovery could be an interesting approach. The well established Asian medical systems seem interesting for inspiration for drug discovery. To proof the value of the medicines the more holistic approach of systems biology is required instead of the reductionist approach of high throughput screening. System biology is based on an unbiased measurement of as many parameters as possible under different conditions (e.g. control and treated patients) and use mathematics to find possible correlations between compounds present in the botanicals and the effects observed. This would detect synergy and pro-drugs, something missed in the reductionist approach. The methods in systems biology include metabolomics, proteomics and transcriptomics, as well as physiological measurements. Such a systems biology approach might revolutionize drug development in the coming years.

INV-174

Molecular targets of natural drug substances

Imming, Peter
Martin-Luther-Universitaet, Institut fuer Pharmazie, Halle, Germany

All creatures have many building blocks in common, down to biochemical structures. That is why natural substances seem to be predestined to bind to drug targets in man. A principal component analysis of a large number of combinatorial and natural products and drugs revealed the greater chemical similarity of the latter two [1]. How about target preferences of natural products in comparison to synthetic drugs?
The talk will categorise targets chemically and analyse the nature of drug targets, based on a comprehensive compilation and analysis of molecular targets of drug substances [2]. The focus will be on targets of natural compounds that are or were in use as therapeutic agents, and compare this with targets of drugs in general. Differences will be traced to historic, chemical, pharmacological, and social reasons. The prevalence of natural products, e.g., among antibacterial agents seems to be derived from first, the necessity to have several hydrophilic binding sites for strong and lasting attachment to vital targets of bacteria. Synthetic drug candidates tend to be more hydrophobic than natural compounds. Second, other microorganisms are well equipped with compounds with defensive or symbiotic function that may be used as antibacterials.
1. Feher M.. Schmidt J.M. (2003) J. Chem. Inf. Comput. Sci. 43, 218-227.
2. Imming P. et al. (2006) Nature Rev. Drug Discov. 5, 821-834.

INV-176

Pharmacy education in Europe: Vision for the future

Krzysztof, Nesterowicz
Jagiellonian University, Medical College, Toxicology, Krakow, Poland

The European Pharmaceutical Students' Association, EPSA is focused on the ways and methods of studying Pharmacy in European faculties at the time of Bologna Process implementation. EPSA takes an active role among European students in promoting the need of the life long learnig process. The Association rewards Pharmacy students all around Europe with a Life Long Learning Certificate for their participation in extra-curricula activities related to their development as future pharmacists. During EPSA events there are educational workshops and lectures for participants.
Is our curricula updated enough with proper knowledge which we need in our profession?
Are European students familiar enough with modern methods of studying like e-learning, blended learning, Problem Based Learning or Task Based Learning?
Where can new methods of studying be more effective than traditional ones, and where can they not?
What are changes in the role of a teacher?

INV-204

Information to patients, students' position

Piaggio, Tomaso
EPSA VP of EU Affairs, Malta

With the Pharmaceutical Package finally released on 10 December 2008 the European Commission adopted a legislative for a Directive and a Regulation on information to the general public on medicinal products subject to medical prescription. The aim of this directive would to establish harmonised rules taking account of developments in society (empowered patients seeking more information) and technology (increased use of the internet).
EPSA welcomes the fact that the Commission has pulled back from some of the more extreme ideas floated in the original consultation on this issue. And in particular applaud the emphasis on quality criteria and the recognition of the key role of health professionals such as pharmacists in this area that this proposal shows. Moreover the recognition that there cannot be an information 'free for all' and that a degree of supervision of information, prior to dissemination, is necessary if the public is to be effectively protected is another Commission's policy that EPSA appreciated.
In conclusion the Commission seems to have accepted that there are genuine dangers in a radical liberalisation of the current regime. However, there are still some aspects of the Directive Proposal that need serious consideration. In order to raising awareness on this issues among students and young pharmacists and to find other critical expects that the commission didn't undertake in his proposal, EPSA, during his Annual Congress, launch a questionnaire on that topic.
The EPSA Annual Questionnaire 2009 *'Information to Patients'* aims to assess students' point of view with regards to education related to the topic, thereby identifying needs for improvements in the pharmaceutical curricula across Europe. The questions examine the role of the patients, health professionals and the industries.

INV-177

E-learning in Pharmacy education

Nesterowicz, Krzysztof
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Introduction: e-Learning is an approach to facilitate and enhance learning through, and based on, both computer and communications technology. e-Learning may be used to suit distance learning through Wide Area Networks, and may also be considered to be a form of flexible learning where just-in-time learning is possible. [1]
Nowadays e-education is often connected with traditional learning. In this way, the first direction of development in Europe-blended learning comes into existence. [2]
The European Community is aware of the importance of these developments and supports them in many ways. At first it is necessary to acknowledge an important growth of blended and collaborative learning applications. Many institutions try to make universal learning modules which promote cooperative methods of work. Other initiatives focus on the idea of building a common e-learning system. [2]
Aim: The new methods are useful in teaching and studying Pharmacy in the modern, mobile society. The aim of the presentation is to introduce teachers and students with new methods of studying.
Approached issues: Is there a real need for new methods of studying like e-learning?
Are students aware about modern ways of studying?

References:

1. http://www.dublin.ie/learning/e-learning.htm
2. Meger Z., E-EUROPE, International Conference on e-learing in education, E-Learning - European Trends, 9, Warsaw 2006.

INV-179

EPSA Individual Mobility Project: Bringing research, working oportunities, pharmacy students and recent gradauates together

Ceh, Boštjan
EPSA Central IMP Coordinator, Ljubljana, Slovenia

The EPSA Individual Mobility Project is a long term project that gives the opportunity to students of phar-macy, particularly those in their late years of studies, and recent-graduates of pharmacy or pharmaceutical sciences from all European countries (members of EPSA) to gain an additional real-time work or research experience in any field of pharmaceutical profession. Consequently, the IMP represents a unique opportu-nity for students and recent graduates to also gain valuable knowledge of other European countries, cus-toms, cultures as well as learning and getting to know the European diversity, which are the experiences encouraged also by the European Commission.
IMP was created with four main objectives:

- To make research and practice abroad (IMP Training) attainable for all European students and gradu-ates of pharmacy
- To give European pharmacy students a chance to learn how to work in a foreign, challenging environ-ment and gain familiarity of foreign working customs in order to promote development of their future ca-reers.
- To offer companies the most competent students with the profile best fitting their requirements, who might also become their future employees
- To interconnect research, work and procedures in the companies with the theoretical-knowledge of stu-dents, who have a chance to implement their knowledge in companies.

The Individual Mobility Project is a great programme which has the potential to break down the European barriers and unify all European countries, especially when referring to exchange of pharmacy students or recent graduates from pharmacy.
The EPSA IMP offers an excellent opportunity for networking between our IMP Partners and therefore con-nects the companies and other institutions (such as hospitals, research institutes, faculties of pharmacy and other institutions) on all levels.
EPSA aims to spread the IMP network among all EPSA member countries (currently 29 European countries) and establish new IMP partnerships in order to offer a veriety of mobility oportunities for European students of pharmacy. **In order to persue our aims and offer the benefits of the IMP to pharmacy students, recent graduates and to our IMP Partners, we are inviting all representatives from different pharmaceutical fields of the pharmaceutical profession to get to know the concept and idea behind this project and take active part in it.**
Only with contribution of our IMP Partners (pharmaceutical companies, pharmaceutical industry, pri-vate/public research and galenic laboratories, regulatory bodies, pharmaceutical associations, pri-vate/public hospitals, clinics and community pharmacies, faculties of pharmacy, research institutes, etc.) Individual Mobility Project (IMP) will gradually help to establish a new profile of pharmacy professionals, who will have all the new abilities and experience to work in different environment, and above all improve the working habits and working knowledge, especially when speaking of employability and new working experience.

INV-180

Introduction to the PQLI initiative, background and current status
Potter, Chris
ISPE, Tampa, United States

In this session important, relevant and current science underpinning ISPE's Product Quality Lifecycle Implementation (PQLI) programme will be presented. PQLI is a multi-disciplinary, global programme for practical realisation of the ICH quality vision, and the Introduction will place in context how good scientific understanding is linked to other disciplines in process understanding and control to assure efficient manufacture. PQLI is designed to give practical 'how to' guidance on different approaches to implementing ICH guidelines supporting the quality vision, specifically, Q8 and Q8 (R1), Pharmaceutical Development, and its Revision, Q9, Quality Risk Management, and Q10, Pharmaceutical Quality System, and other related guidelines, for example Q11, Drug Substance Manufacturing Process.

INV-184

Applications of QbD and PAT in the development of cellulose ether polymers for oral controlled release formulations

Hughes, Kevin, W; Bain, David
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Quality by Design (QbD) principles have received considerable attention in the pharmaceutical media driven by recent regulatory directives. The development of design space, which defines the lack of product and process performance insensitivity, can minimize the requirement for further clinical justification when post-approval changes are required. One key area of variability is for functional excipients, particularly those of natural or semi-synthetic origin such as METHOCEL™ Premium grades. This presentation will examine the impact of key HPMC variables on drug release from these systems. Proposals for robust product design and supplier partnership will be presented.

INV-185

A quality by design approach to the understanding and predicting excipient properties and functionality

Basu, Prabir
NIPTE, West Lafayette, United States

Successful development of pharmaceutical dosage forms and the resultant manufacturing effectiveness depend on the physical, chemical, and mechanical properties of both the active and excipient components. Pharmaceutical materials are extremely challenging because pharmaceutical excipients, typically organic solids including proteins, are more complex and less well characterized than inorganic solids, and typically consist of multi-component particle systems. As a result of this lack of information and understanding, today's formulation scientist faces a knowledge gap when attempting to design pharmaceutical products and manufacturing processes. Despite awareness of the importance of physical and mechanical properties, little progress has been made in developing the following:
1. Standard methods of measurement for material properties
2. Reliable and publicly accessible information systems of properties for common components and
3. Models that relate fundamental measurements across scales of investigation to product quality.
The National Institute for Pharmaceutical Technology and Education (NIPTE) wishes to establish an information system that is used to maintain values of fundamental pharmaceutical excipient material properties, and which contains models, best practices, and methods for using this data in the systematic design of pharmaceutical products and processes.

INV-186

Excipients make the difference

Guth, F.
BASF SE, Pharma Ingredients & Services, Limburgerhof, Germany

With the recent advancements in pharmaceutical technology, drug formulations have evolved from traditional medicinal products into drug delivery systems. This progress was brought forward with the use of new technologies in the pharmaceutical industry as well as by the introduction of new or novel excipients. This context is illustrated with the example of two polymeric excipients with different physico-chemical properties and different functionalities: Copovidone which has traditionally been used as a binder is now being used increasingly in melt-extrusion processes for the manufacture of solid dispersions or solid solutions in order to enhance the bioavailability of poorly soluble drugs [1]. Polyethylene glycol and polyvinyl alcohol graft copolymer was developed as an innovative instant release film coating agent that dissolves extremely fast and does not require the addition of a plasticizer. Because of its high flexibility it is also very suitable as hydrophilic pore former in polyvinyl acetate or ethylcellulose based sustained release dosage forms [2].

[1] Bühler, V.: Polyvinylpyrrolidone Excipients for Pharmaceuticals. Springer Verlag Berlin, Heidelberg, 2005
[2] Bühler, V.: Kollicoat® Grades. Functional Polymers for the Pharmaceutical Industry. 2007

INV-187

The benefits of novel materials in pharmaceutical development and barriers to innovation

Denton, K A
Novozymes Biopharma UK Ltd, Regulatory Affairs, Nottingham, United Kingdom

Novel materials such as biological and biotechnological excipients play a crucial role in bringing new, improved and potentially safer medicines to the market. The use of highly pure, consistent and, ideally, animal-free pharmaceutical components can be critical in ensuring final drug product quality, safety and efficacy, especially in the rapidly growing field of advanced therapy medicinal products. However, the lack of globally aligned regulatory mechanisms for reviewing novel excipients is currently creating significant barriers to the development of innovative pharmaceuticals. The situation is particularly problematic in Europe where the existing master file system is more restricted than in other major world regions (e.g. USA and Japan) where master files can be submitted for a broad range of drug ingredients. This presentation will discuss the regulatory environment for biotech excipients with a focus on the EU situation. It will also summarize IPEC's ongoing initiatives to improve regulatory systems for excipients, including their proposal for the introduction of excipient master files as a crucial factor in creating an EU regulatory framework to encourage innovative product development and accommodate the emerging advanced therapies and technologies.

INV-188

M&S at the interface to clinics: Estimating human dose and safety margins from preclinical information

Lavé, Thierry
Roche, DMPK, Basel, Switzerland

In drug discovery and pre-clinical development clinical drug candidates are characterized for their absorption, metabolism, distribution and excretion (ADME) and physico-chemical properties and their efficacy and safety profile in a variety of animal models and in vitro systems. Thus a large amount of data is available at this stage to contribute to the decision making process.
The use of biologically realistic models allows for the separation of the biological and compound-specific components. These models, by design, are capable of integrating information about various processes, related to pharmacokinetics, pharmacodynamics and formulation. They can be used to predict the complete drug concentration and effect-time course in vivo.
These models are essential to address key questions during drug discovery and development such as (i) what is the expected human PK profile for potential clinical candidate(s) ? (ii) is our candidate suitable for the intended dosing regimen ? (iii) what is the expected variability and uncertainty in the predictions? (iv) do we expect any food effect ? (v) how can M&S guide formulation strategies/options ? and (vi) what is the safe and efficacious dosing schedule? An overview of the PBPK-PD approach will be presented with an emphasis on integrating information from the various functions to support the decision making process.

INV-190

Future needs in selecting clinical candidates

Kansy, Manfred
F. Hoffmann-La Roche Ltd., PRNBS - Structure Property Effect Relationships, Basel, Switzerland

Pharma industry is challenged by an increasing pressure to improve its declining productivity, caused by increasing R & D expenditures at relatively stable numbers of new market introductions (NMEs). Today, major reasons for attrition are related to safety and efficacy issues. Among others, biomarkers and in silico techniques (Modeling & Simulation [M&S]) are discussed to be strategic components which will positively influence Pharma R & D productivity. M & S tools can only exploit its full potential if the sometimes separated phases in R & D merge its joint capabilities. Only thus the selection of appropriate targets and lead series, the optimization of lead compounds by structural modifications can be improved. This will result in more correct

efficacy estimations and related dose selections and a better scaling of potential side effects. Real-time access to high quality internal and external data and information is one major pillar for the success of in silico techniques and the basis for improvements in safety and efficacy predictions, allowing a link from compound structure and its properties to downstream pharmacological and safety relevant effects.
The contribution will give an overview on our recent progress in predicting downstream effects by considering structural features and properties of drug candidates.

INV-191

Introduction to the topic "drugs and the environment" and outline of the legislation to assess the environmental risk of drugs
Halling-Sørensen, Bent
Copenhagen University, Copenhagen, Denmark

Pharmaceuticals are indispensable for a high quality of life. Their use however also has an environmental downside that we as pharmacists must help to handle. In recent year a huge amount of data has been collected demonstrating the widespread of a variety of active drug ingredients in the aquatic environment and sporadically even in drinking water. Being only insufficient eliminated in the conventional sewage treatment plants, there is a growing evidence that the substances and their metabolites have adverse effects on aquatic and in some case terrestrial organisms on both the individual and population level. The question is what can we as pharmacist do to adequately address the question? There are presently only two known cases of pharmaceuticals effecting wildlife on ecosystem level that will be discussed. These cases are the only well documented presently. Several other pharmaceuticals – e.g. antibiotics, antiepileptics, cancer drugs and several others – may have an effect on wildlife but this is not proven. We have quit a lot of laboratory data identifying possible effects – but nothing on ecosystem level. There is a recognition all over Europe that there is a broad variety of pharmaceutical substances in treated waste water and rivers. This talk will try to outline the problem and give an overview of the current legislation of the different EMEA guidelines

INV-193

The use of mathematical models to assess the fate of pharmaceuticals in the environment
Jørgensen, Sven Erik
Copenhagen University, Environmental chemistry, Denmark, Denmark

Environmental Risk Assessment of pharmaceuticals requires that the concentrations in different environmental compartments (for instance soil, stream water, plants, insects, birds etc.) are found or estimated by mathematical models. It is the so-called predicted environmental concentration, PEC, that is compared with the predicted non effect concentration (PNEC). How do we find PEC? It is hardly possible without environmental mathematical models, as the alternative would be a very high number of analytical data. Models are synthesis of what we know about the problem and the system, and they are therefore drawing on our theoretical knowledge about the environmental, our knowledge about the properties of the pharmaceuticals and a (limited) number of analytical data. Models are very powerful environmental management tools that have been used increasingly during the last decades. It is discussed how it is possible to develop a reliable environmental models. Further more the presentation will give the current knowledge of different types of mathematical models that are used in regulation to estimate environmental concentration and give concrete examples of use of models to assess PEC for pharmaceutical.

INV-194

Pharmaceuticals in the Danish environment. An overview of identified pharmaceuticals that may pose a thread to the environment
Halling-Sørensen, Bent
Copenhagen University, Copenhagen, Danmark

The talk will give an overview of the current situation in Denmark giving the level of pharmaceuticals exposure to the environment and a comparison to the environmental effect levels of the exposed drugs.
The occurrence of pharmaceuticals in different water bodies and the findings of effects on aquatic organisms in ecotoxicity tests have raised concerns about environmental risks of pharmaceuticals in receiving waters. This approach was evaluated by applying it to 22 high volume human-used pharmaceuticals using ecotoxicological effect data from laboratory studies, followed by a comparison of predicted risks to monitoring data on the effluents from sewage treatment plants in Europe and pharmaceutical sales quantities. We found that for 19 of the 22 selected pharmaceuticals the existing laboratory data were sufficient for probabilistic risk characterizations. The subsequently modeled ratios between monitored concentrations and risk limits considered to be sufficiently safe, were mostly above a factor of 100, which suggests that the current paradigm for environmental risk assessments in the EU is protective for the aquatic environment. However, similarly calculated ratios for five pharmaceuticals (propranolol, ibuprofen, furosemide, ofloxacin, and ciprofloxacin) were below 100, while ibuprofen and ciprofloxacin are considered to be of high concern due to lack of toxicity studies.

INV-195

Overview of model building for quality by design
Folestad, Staffan
Pharmaceutical and Analytical R&D, AstraZeneca R&D, Mölndal, Sweden

By scientific design and assessment of materials and processes, with respect to quality and clinical relevance, an in-depth understanding of the drug product and the associated process can be established. Such a structured approach to Quality by Design (QbD) also provides new routes for control of quality based on advanced processing with predictable process output.
At the core of QbD is the in-depth product and process understanding where the ultimate verification of understanding is simply a predictable product quality and process output. In technical and scientific terms this translates into establishing Models for Product and Process with predictive capability. This presentation aims at giving an overview of Model building for QbD. The different scientific routes for Model building ranging from First Principles approaches through to Chemometric approaches will be outlined. It is emphasized that irrespective of which alternative route that is taken, successful Model building, and achieving predictive capability, always rests on a truly holistic approach to Pharmaceutical development and manufacturing. Finally, the purpose of this presentation is to serve as an introduction into the subsequent lectures in this session where further details will be shared through case studies and detailed examples on development and application of Models for QbD.

INV-196

Advances in model based approaches for QbD in product development
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As interest grows in QbD and PAT, it is timely to consider the management and value of emerging data. Issues related to the challenges of achieving higher level ambitions of acquiring mechanistic understanding of complex pharmaceutical formulations and their processing need to be reassessed given the goal of establishing sound, scientifically proven rules. From data will come information which can lead to knowledge and eventually we might aspire to wisdom. How far along this cascade have we progressed? A range of techniques and tools have been used to support ambitions in QbD, ranging from computer based simulations and knowledge engineering tools to real time analytical measurements. Specific steps of multi-stage processes have been researched at a fundamental scientific level and equations of state have been defined providing sound knowledge and potential for true control. However, whilst these various individual pieces of work represent progress in the field of material and processing science and product design for pharmaceuticals, it remains necessary to continue to strive for mechanistic understanding and knowledge across this multifaceted spectrum of interest. Even more crucial is the requirement to 'join up' the pieces of knowledge into an integrated format to provide, ultimately, fully predictive formulation design and process control systems for product development.

INV-197

Predicting the product and process: Advances in model building for Quality by Design (QbD)

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Design of experiments was applied to increase the process understanding and process efficiency of a freeze dyring process. Mannitol solutions, some of them containing NaCl, were used as models to freeze dry.
Non-invasive and in-line Raman, NIR, plasma emission spectroscopic and wireless temperature measurements were continuously performed during lyophilization to monitor the mannitol solid state, the endpoints of the different process steps and physical phenomena occurring during the process. The collected spectra during the processes were analyzed using chemometric techniques. A 2-level full factorial design was used as screening design to study the significant influence of process and formulation variables upon freeze drying. Several critical process aspects were used as responses for the design. After screening, a central composite design was applied using the remaining significant variables to optimize process efficiency and to be able to make product and process predictions.
The screening design results helped to increase process understanding and showed that several process and formulation variables significantly influence different lyophilization aspects and that both types of variables are interrelated. The central composite design allowed to determine the optimum combination of process and formulation variables resulting in an as efficient as possible process.

INV-198

Prediction of product and process quality in fluid-bed granulation – A three monitoring method approach

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Fluid-bed granulation is a complex process, difficult to control due to the strong interactions between process variables, such as moisture content and granule size. To control the process via correct pathway, one should be able to monitor the process, i.e. measure the process variables, in-line.
In this study, three PAT techniques, i.e. the acoustic emission (AE), flash topography particle size analyzer and multi-point NIR probes, were instrumented into a lab scale fluidized bed granulator for simultaneous granulation process monitoring. Parallel techniques were used for characterizing granule size distribution and moisture content of granules during fluidization. CelletsR, protease granules and caffeine formulation were used as samples. Granulations were carried out in a custom made modular top-spray granulation chamber [1].
The granule size values obtained with the used PAT techniques were in good agreement with the values measured with off-line reference methods. Multi-point NIR (8 probes) and AE methods were able to detect the three granulation phases, mixing, agglomeration and drying. The most informative data can be obtained when multiple PAT techniques are applied simultaneously for in-line process monitoring.
[1] Matero S. et al., The feasibility of using acoustic emissions for monitoring of fluidized bed granulation, Chemometr. Intell. Lab. , in press.

INV-199

Herbs and spices: Using natural products to investigate pain mechanisms

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The human body receives information about its external and internal environment through special senses and the somatic senses. One important role of the somatic senses is to detect tissue injury or potentially harmful thermal, mechanical and chemical stimuli - generally referred

to as nociception. The discovery of the capsaicin receptor TRPV1 and other Transient Receptor Potential (TRP) ion channels including the mustard/garlic receptor TRPA1 in sensory neurons and epithelial cells has provided novel insight into somatosensation. The role of TRPV1 and TRPA1 as *chemosensors* in nociception is of particular interest. TRPV1 serves as a sensor of the lipid environment in addition to detecting heat and low pH. TRPA1, a proposed noxious cold receptor, is a detector of sulfhydryl reacting environmental chemicals, which may be present as air pollutants or produced by organisms as a defence mechanism during infection. Interestingly, drugs such as paracetamol (acetaminophen) and cyclophosphamide are metabolised to TRPV1/TRPA1 active compounds that are analgesic or noxious. Both TRPV1 and TRPA1 are promising future drug targets for treatment of pain and other symptoms associated with somatosensory dysfunction. The identification of endogenous TRPV1 and TRPA1 agonists and understanding their biochemistry may also offer novel antinociceptive drug therapies.

INV-200

Ion channels and Drug Discovery — TRPV1 channel and pain …Patients with chronic pain — Saved by the bell... *pepper?!*

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TRPV1 (Transient Receptor Potential Vanilloid 1) is a transient receptor potential (TRP) ion channel, that is located in sensory nerves which are involved in pain perception (nociceptors). TRPV1 is sensitive to capsaicin.
Capsaicin can be purified from plants belonging to the genus *Capsicum* which consist of around 25 known species. The fruits of *Capsicum* can vary tremendously in color, shape, and size (e.g. the common bell pepper or the habanero). Most of the capsaicin in a pungent (hot) pepper is concentrated in blisters on the epidermis of the interior ribs (septa) that divide the chambers of the fruit to which the seeds are attached. Capsaicin is a known irritant for mammals, and produces a sensation of burning pain in tissue with which it comes into contact.
A natural product is a chemical substance, produced by a living organism, that has a pharmacological or biological activity that can be utilized in pharmaceutical drug discovery. Here, capsaicin has been used to develop antagonists to TRPV1. Typically, nociceptors were activated by adding capsaicin (*in vitro* & *in vivo*; rats & human), and then TRPV1 activation was prevented by adding chemically synthesized, biologically optimized compounds. In summary, the natural product capsaicin has been instrumental in the drug discovery of a potential new chronic pain relief medication.

INV-201

Preventing pain with nature: How natural products help us discover new drugs

Sabirsh, Alan
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This presentation will describe how natural products, with a focus on ion channels, can contribute to two initial stages of drug discovery: target validation and lead generation. By target validation we mean conclusive identification of a key component in pathological development, that can be observed and modulated using some treatment. By lead generation we mean the development of target-modulating molecules with properties that make them useful as drugs.
For target validation, natural products that activate TRPV1 are very useful because they are unusually potent and very good at creating pain (which is why they exist). They are also readily available, relatively easy to purify and, in some cases, can easily be made into antagonists.
For identifying new molecules that can affect the function of TRPV1 natural products are also useful because they can be used as to activate a target (causing pain) in an assay that is then used to test for molecules that attenuate this activation (alleviating pain). Alternatively, natural extracts can be screened for new molecules that alleviate pain more effectively and with fewer side effects. Sources of natural extracts will be discussed, as well as some of the challenges associated with using them. Methodologies currently used for screening extract libraries will be presented, including a brief review of recent progress in this field.

INV-202

Developing cone snail venom as a treatment for pain

Clark, Richard J[1]; Jensen, Jonas[1]; Nevin, Simon T[2]; Callaghan, Brid P[2]; Reena, Halai[1]; Adams, David J[2]; Craik, David J[1]
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Venoms from marine snails of the Conus genus comprise a myriad of peptides called conotoxins used for the rapid immobilization of prey. These molecules target membrane receptors with exquisite selectivity and potency and have become invaluable neurophysiological probes and drug leads for a range of disease states including the treatment of chronic pain. However, like most peptides, their beneficial activities are partly undermined by susceptibility to proteolysis in vivo and poor oral activity. Our research project seeks to apply the concept of head-to-tail cyclisation of conotoxins, via a linker, to greatly improve their bioavailability and resistance to proteolytic degradation while maintaining their full potency. We have applied this concept to the alpha-conotoxin Vc1.1, which is currently under clinical development as a treatment for neuropathic pain. We have produced a cyclic analogue of Vc1.1 that, unlike the native molecule, exhibits significant analgesia when administered orally in a rat pain model. In addition we will describe our efforts to elucidate the complicated structure/activity relationships of the á-conotoxins to assist in the development of novel drug leads.

INV-205

Trainings for a better future

Winnecke Jensen, Louise
EPSA Vice President of Education, Copenhagen, Denmark

It is becoming more and more acknowledged that informal education is of big importance to the professional as well as personal development of young people. This comes from the fact that a lot of skills, e.g. communication and leadership skills, are required for a person to interact optimally with others. Often the pharmaceutical curriculum does not put much focus on such skills, and EPSA is therefore offering the European students of pharmacy an opportunity to improve their so called "soft skills". Soft skills can be perceived as tools which can be applied in various situations throughout life.
In this presentation EPSA's initiative and ideas will be described, and a thorough insight into EPSA's trainings will be provided. If time allows a brief demonstration of a training session will be given.

INV-203

Pharmine Project

Bonnici, Marisabelle
EPSA President, Attard, Malta

Pharmaceutical Education involves a large number of competencies and quality assurance is required to ensure a unified curriculum producing pharmacists with competencies in all areas. This Project is being run jointly between the European Association of Faculties of Pharmacy and other partners including GENSEC – general and specific competencies, SYNTEC – synergy with industry, EDSOC – pharmacy education and society, continuing education, ePHARM – IT and pharmacy, and INTERNAT – international relations.

INV-207

Physicochemical characterization of nanocarriers: size, charge & surface hydrophobicity

Keck, Cornelia
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The interaction of nanoparticles with the body is essentially determined by their physicochemical properties. These are not only size or charge, but also surface hydrophobicity. Especially regarding the surface hydrophobicity, often too little attention is given to it. Charge and surface hydrophobicity determine the extent and nature of body proteins adsorbing on their surface (protein adsorption pattern). These proteins determine the tolerability of the nanoparticles, but also e.g. their organ distribution after i.v. injection.
With modern laser techniques such as photon correlation spectroscopy (PCS) and laser diffractometry (LD), convenient size measurements seem to be no problem nowadays. In the presentation potential pitfalls are highlighted when applying PCS and LD. Optimized ways of analysis are suggested. Charge determination is also easy with laser technologies, but the crucial point is selecting the correct measuring conditions to obtain really the information required. Optimized measuring conditions are presented. Surface hydrophobicity is often not measured because of the problem of a method really reflecting or quantifying this parameter. A range of characterisation methods will be presented with suitability for different nanocarriers (e.g. non-coated versus coated). These methods are Rose Bengal adsorption, Rose Bengal partitioning, hydrophobic interaction chromatography (HIC) and aqueous two-phase partitioning.

INV-208

Nanocrystals & lipid nanoparticles as industrially feasible nanocarriers – review of state of the art
Müller, Rainer H.
Free University of Berlin, Dept of Pharmaceutics, Biopharmaceutics & NutriCosmetics, Berlin, Germany

Nanoparticulate delivery systems are under investigation since many years, e.g. the polymeric nanoparticles since the 1970ies. However only a few of them made it from the development labs to the market, that means being on the market in a substantial number of products. Obstacles for market entry are e.g. the lack of large scale production methods, or excipients without a regulatorily accepted status. The liposomes are one of these few systems in the market, being introduced first to the cosmetic market in 1986, to the pharmaceutical market around 1990. Since this the first nanocarriers with broader potential – from our point of view - are the nanocrystals (pharma market introduction in 2000) and the lipid nanoparticles (cosmetic market introduction in 2005).
The presentation reviews the state of the art for both delivery systems. They can be considered to be complementary. Nanocrystals are the formulation of first choice for molecules from biotechnology or plants which are poorly soluble in water and in organic media. The first (NanoCrystal) and second generation of nanocrystals (smartCrystal) are briefly reviewed, highlighting different application potentials.
The lipid nanoparticles are suitable for drugs being lipophilic and soluble in lipophilic media, but also for highly potent peptides (dissolved in lipid matrix by solubilisation). A special version is the lipid nanoparticles made from lipid-drug conjugates (LDC) allowing loading of the particle matrix with up to appr. 30% of hydrophilic molecules. The present dermal cosmetic products are very briefly reviewed and the potential of lipid nanoparticles for dermal delivery discussed.

INV-209

Toxicological testing for safety of of nanomaterials
Landsiedel, Robert
BASF, Ludwigshafen, Product Safety - Regulations, Toxicology & Ecology, Ludwigshafen, Germany

Nanotechnology offers great opportunities in developing innovative solutions by selective modifications of material properties. However, new material properties may also alter the effect of these materials on humans. Therefore, nanomaterials need a thorough safety assessment before use and marketing. Testing strategies and appropriate testing methods for nanomaterials are still under discussion. There are, concepts on how toxicological standard testing methods have to be modified to account for nano-specific needs and recently the genotoxicity of nanomaterials has been reviewed and recommendations for appropriate testing have been made [Landsiedel R et al., Mut Res 2009; 681:241]. In general, the importance of test item

preparation and characterization [Schulze C et al. 2008, Nanotox 2:51] has been recognized for nanomaterials toxicity testings as well as the importance of understanding their uptake and distribution in the body [Fabian E et al. 2008, Arch Tox82:151]. Inhalation of aerosols from nanomaterials is the exposure of highest concern. And appropriate testing procedures have been established. For this method, the generation and the characterization of aerosols from nanomaterials have been investigated: Aerosols from nanomaterials are complex mixtures comprising of a large fraction of agglomerated particles and – to a minor extent – of actual ultrafine or nanoparticles.

INV-210

How to successfully market nanotechnology: from the academic idea to the market (part I)

Müller, Rainer H
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There are many different nanoparticulate delivery technologies currently under development and known since many years. However, only a very limited number made it to the market. Classical examples are drug-loaded i.v. nanoemulsions and the liposomes. The presentation reviews major hurdles for market introduction, and presents strategies to enter the market , using as examples solid lipid nanoparticles (SLN), nano lipid carriers and drug nanocrystals. Aspects covered are the transfer from academia to industry, industrial aspects such as status of excipients, large scale production, trade marks, partnering and first product realization. In part II as latest development the enhanced action of the dermal silver nano-complex will be presented as product example.

INV-211

How to successfully market nanotechnology: from the academic idea to the market (part II)

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INV-212

Workshop in Pharmacoepidemiology: The metamizole case

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This session focus on pharmaco-epidemiology as a tool for detection and identification of serious adverse effects of drugs. The example discussed is the metamizole case from a Scandinavian perspective.
Metamizole is one of the most sold analgesic drugs in the world. One of its side effects of was agranulocytosis. In the 1970-ties a high number of cases were reported in Scandinavia. In Sweden early warnings for the side effect were launched from the authorities and further reports finally resulted in a withdrawal of the preparations containing metamizole in the late 1970-ties. However, high worldwide use without excessive prevalence of agranulocitosis called for a re-introduction of the preparation. . Intense epidemiologic studies revealed that the risk of metamizole induced agranulocitosis seemed to be a little exaggerated and the prevalence was lower than suspected. The epidemiologic had not found any direct comparisons of the risk to other similar preparations and concluded that there was no absolute need for re-introduction to the market. Metamizole was anyway again marketed in Sweden though the background of several fatalities in youing people due to blood dyscriasies. However, soon again several new cases of agranulocytosis was reported and the preparation was finally withdrawn.

INV-214

Speaker Sessions • Posters • Careers Forum
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2009 2nd PHARMSCIFAIR
Premier European Platform for Advancing Pharmaceutical Sciences
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What happened therafter?

Beermann, Bjoern
Medical Products Agency, Uppsala, Sverige

The International Agranulocytosis and Aplastic Aneamia study indicated that the risk of agranulocytosis caused by metamizol was as low as 1.1 case per million users. That means that the risk for severe adverse reactions was very much lower than for example by aspirin and other NSAIDs which frequently cause severe gastrointestinal complications. Taking ino account the need for efficient analgesic drugs on the market ,the Medical Products Agency MPA) decided in September 1995, after a hearing with its scientific advisery board, to reintroduce metamizol on the Swedish market. Up to 1999 fourteen (8 in outpatients) new cases of agranulocytosis were reported within the spontaneous reporting system. This corresponds to an incidence of one case per 1439 (95% CI 1:850, 1:4684) prescriptions which is in good agreement with the estimated incidence in the seventies, 1:3000 patients. An important difference was the fatality rate, which was 29% in the seventies and 0% in the nineties. The high risk for agranulocytosis made MPA to withdraw metamizol another and probably final time in 1999.