Pharmaceutical R&D Ethics Policy

Introduction

Developing and providing safe and efficacious medicinal products is based on high quality science in the discovery and research for new innovations, as well as in the further development of treatments already being in clinical use. Commitment to the practices and high ethical standards concerning our industry means that Orion follows all relevant laws, regulations, guidelines and codes concerning pharmaceutical research.

In our R&D activities our commitment to building well-being means that we develop efficacious and safe medicinal treatments for unmet medical needs, representing innovation and the highest quality standards. Our purpose is to deliver the best for the patient and the care-giving professionals. We take every step of our research and development process in compliance with the internationally adopted regulatory standards and criteria concerning pharmaceutical R&D.

Our mission to build well-being also means that patients taking and doctors prescribing Orion's products can rely on that our products are manufactured using authorised methods and that their materials and components are sourced from trusted and monitored suppliers. Importantly, they can trust that our products become available to the patients through screens of multiphase quality assurance, via legal and controlled distribution channels only, in genuine packages originating from Orion and containing all the relevant and required product information for the patient.

The working society engaged in the years long process of developing a completely new medicine into a commercial product is characterised by highly academic scientific curiosity, discipline, patience and target-orientation, joy of new findings, achievement and never ending learning. Work in our R&D is intensive search for, collection and verification, reporting on and filing information of the compounds studied, the primary purpose being to show sufficient evidence of the investigational drug's approvability for clinical use, i.e. for use in real patients suffering from the target disease and needing efficient and safe relief of symptoms or treatment slowing down the progress of the disease. An equally important purpose of our investment in R&D is to discover products upon which Orion can build its future existence. The facts of business as well as economic risks and possible disappointments are also present in the work: if a research project at some point indicates that this goal is all too difficult to reach, we choose another compound and route to study.

Before we start a research program, we explore a lot of available facts for the basis of decision-making. The following criteria are among the key ones:

- The idea and the target disease relates to our core therapy areas
- There is a real need for new and better approaches to treat the disease
- Clear health economic benefit can be expected for patients and society
- The idea is scientifically feasible to study using the latest knowledge and findings
- The risks and benefits of the idea have been assessed
- We have sufficient competence, knowledge and the necessary resources
- There is commercial potential for a new treatment approach

Health being among the most important values for most people, pharmaceuticals and their R&D have a most intimate human touch. Unfortunate events in the early history of modern pharmaceutical industry have led to strict and comprehensive regulation and control of the entire life cycle of a medicine, as well as to extremely high transparency requirements. Pharmaceutical companies operate globally, and accordingly, also the required standards are valid globally. Healthcare authorities are not the only source of compelling requirements and good practices — also pharmaceutical industry associations have agreed and issued a number of self-regulatory and obligatory codes, compliance with which is efficiently monitored. The key standards concerning R&D are determined in the Good Laboratory Practice (GLP), Good Clinical Practice (GCP) and Good Manufacturing Practice (GMP) guidelines.

Orion appreciates and follows the requirements, standards and ethical codes, understanding that by compromising them we would also compromise our good reputation and our purpose to show the best operational R&D.

The managerial responsibilities follow our operational management and reporting structure, according to which the Senior Vice President heading our pharmaceutical R&D and the Vice Presidents heading our nonclinical and clinical research carry the operational responsibility for our commitment to both regulatory and ethical conduct in our pharmaceutical research.

Orion's Chief Medical Officer, Professor Reijo Salonen puts our intention into the following words:

> *"Patient safety is Orion's core value and our absolute first priority. We are committed to collecting information on safety before our molecules enter human clinical trials, during the clinical development phase, to the product's approval by regulators for use by patients, through its manufacture and distribution chain, and for as long as it is available and in use anywhere in the world."*

In the following chapters we highlight our practices and approaches applied in the sequence of phases through which a pharmaceutical development project advances. The scheme presented in the R&D section of our corporate website at gives an overall view of the road which usually takes at least ten years to go.

Bioethics and Animal Welfare

Animal studies continue to play a vital role in the search for new and improved medicines, and are an essential and unavoidable part of the nonclinical phase of the research process. Without animal testing, there would be no new medicines.

As a requirement, certain results from animal studies must be reported before the medicinal authority can grant a permission to forward a new investigational medicine to tests in humans, i.e., into clinical study phases. Animal studies are even required when the investigational substance is being developed for a treatment of animals.

Orion is committed to the responsible use of animals. The welfare of the research animals is our top priority. We only use animals when it is necessary and unavoidable: to help scientists bridge the gap between the theories developed in

the test tube and the research results required for introducing a new treatment to the patient.

The European Federation of Pharmaceutical Industries and Associations, EFPIA, is actively devoted to promoting animal welfare issues in all of its actions. Orion is a member of EFPIA, and we support and facilitate the same goals throughout our research activities.

In all our nonclinical work we apply the 3Rs principles – Replacement, Reduction, Refinement. The purpose of these principles is to minimise the use of research animals and promote the development of alternative methods, thereby contributing to ethically better science.

> Replacement means methods, strategies or approaches which do not involve the use of live animals. Tests in animals can be replaced through e.g. in vitro techniques using cells or tissues, or by using computerised models and "omics" technologies such as transcriptomics (gene expression analyses) or metabolomics (analyses on biochemical metabolites).
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> Reduction covers approaches with which fewer animals can be used instead of traditional methods without compromising the reliability of the results. It includes better use of the information obtained from a single animal, thus limiting the use of additional animals.
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> Refinement means modifications of procedures, husbandry and care practices of animals during the whole life of a single animal. Pain, suffering and distress are minimised to enhance an animal's well-being. The overall good condition and well-being of the animals improve the quality of the data obtained from studies.

The 3Rs principle was introduced into animal testing years ago, and is now adopted in both Finnish and EU legislation. The conditions of obtaining a licence to conduct animal studies, including the required qualifications of companies carrying out animal studies and scientists involved in them, are also covered by the legislation. Every study has to be approved by the National Project Authorization Board, which acts under the Regional State Administrative Agency.

All Orion's research using animals is carefully considered and justified. Every study shall be scientifically necessary and designed so that the minimum possible number of animals of an appropriate species can be used to achieve the scientific objectives. We pay special attention to causing minimum necessary harm and pain.

Orion has adopted practices that exceed the requirements of the EU and Finnish authorities concerning training and education of the personnel involved in animal

research. Our research personnel is continuously trained to plan and execute studies using animals and to take the best possible care of the animals and their well-being.

Our animal facilities are built to give enough space to move and allowing natural behaving and inspiring activity for each animal species. The animals are sourced from specialised animal breeders, which are highly controlled, and on ethically solid ground. The EHS (environmental, health and safety) and cleanliness aspects have been implemented with very high ambition.

Part of our animal studies is carried out by specialist contract research organisations. Before the assignment we make sure that their animal welfare issues are at the same high level as in Orion. We regularly visit and audit all research partners to make sure that their operations are in compliance with regulatory requirements and our own policies and that the 3Rs are applied in animal research.

In our core therapy areas of R&D, i.e. neurodegenerative diseases and cancer, we need studies using animals to explore physiological phenomena, hormonal background and interactions of different cells and tissues, which can only provide relevant information when studied in whole animals. Only a whole, living animal can give us an answer to questions like whether an investigational new drug molecule relieves symptoms of a disease, or how a molecule is absorbed and metabolised in the body.

In vitro techniques are used for evaluating the molecular mechanism behind a drug molecule, but this has to be confirmed using suitable animal models.

The regulatory methods have to be approved by the authorities. In animal and in vitro testing, we follow Good Laboratory Practice (GLP) guidelines and our internal Standard Operating Procedures. All methods used must give the most reliable information on the investigational drug molecule.

Regular audits of animal testing practices are performed in-house by our veterinarians and also by the Animal Welfare body (AWB); they also give advice in the refinement and development. Inspectors from regulatory agencies, such as the Regional State Administrative Agency and the National Supervisory Authority for Welfare and Health, audit regularly the facilities and animal welfare and experimentation procedures.

All exceptional issues in animal experiments are reported to the AWB, which in turn decides on the actions to be taken. These issues are also reported to the National Projects Authorisation Board.

The results of nonclinical research covering both in vitro and animal research are evaluated by our experts for the basis of taking the research project into clinical phases, i.e. studies in humans or target animal species. In the evaluation, the usefulness of the results in predicting what happens in humans is carefully considered. If the signs of efficacy and safety are promising enough and predict that benefit for patients will overweight the risks, the molecule can proceed to the clinical phase.

As a rule applicable to any point of a research project, studies are discontinued as early as possible, if the molecule shows lack of safety or efficacy.

References

EFPIA website: www.efpia.eu

Act on the Protection of Animals Used for Scientific or Educational Purposes (Laki tieteellisiin tai opetustarkoituksiin käytettävien eläinten suojelusta) 497/2013: www.finlex.fi/fi/laki/alkup/2013/20130497. Unofficial translation into English: pdf

Government Decree on the Protection of Animals Used for Scientific or Educational Purposes (Valtioneuvoston asetus tieteellisiin tai opetustarkoituksiin käytettävien eläinten suojelusta) 564/2013, in Finnish: www.finlex.fi/fi/laki/alkup/2013/20130564. Unofficial translation into English: pdf

Using Human Tissues, GMO and Stem Cells

Tissue samples of human origin are utilised by Orion in various in vitro studies in the drug discovery and development work. The human material is sourced from high standard, reliable and ethically solid suppliers which use controlled and traceable sources and provide documentation for the material.

Human material enables prediction of metabolism routes, for example, or drug-drug interactions without exposure of human subjects to new chemical substances. Human material is also a basis for the selection of relevant animal species for toxicologic evaluation thus reducing animal studies. With these studies some of the clinical studies may even be replaced. Studies based on tissues obtained from humans and animal species are well established and are very widely used within the

scientific community. Therefore, the pros and cons are well understood, thus increasing the prediction value of these systems.

Genetically modified organisms (GMO), genetically engineered whole cell systems or transgenic animals, are increasingly used for research purposes in the pharmaceutical industry. Such models are used in strictly controlled laboratory environment for efficacy and safety evaluations of drug molecules as well as for mechanistic studies to understand human disease, thereby increasing the prediction value of nonclinical research. Predictive cell models are key methods in reducing laboratory animal use. Gene technologies also represent sustainable chemistry. We believe that integration of bio-processes with conventional chemistry is a key towards sustainable production of complex molecules.

Stem cell technologies are an emerging part in the toolbox for nonclinical studies. Earlier these approaches have been based on human embryonic stem cells. However, the recent development towards human induced pluripotent stem (iPS) cells have shown potential to be a future source of stem cells for research purposes avoiding the ethical issues associated with the use of the stem cells of embryonic origin.

The techniques described above are mechanistic models mainly helping to understand complex biological processes and disease as well as to study the effects of drug molecules in relevant human models. Orion's highly educated experts keep on following the latest developments in these fields. Understanding the mechanisms of diseases and the behavior of new chemical entities in biological systems, the most effective and safe candidates can be selected to be forwarded to clinical trials without unnecessary exposure of laboratory animals and, eventually, human subjects to the compound.

Ethics in the Clinical Research Phases

At Orion, we design and conduct all our clinical studies in accordance with high-level ethical principles as well as international and national regulatory requirements. Ethical guidelines such as the Declaration of Helsinki and the International Conference on Harmonisation (ICH) guidelines for Good Clinical Practice (GCP) and Good Manufacturing Practice (GMP) are always followed in our clinical studies, in addition to a number of other international ethical and scientific guidancies, such as those issued by the EU European Medicinal Authority EMA and

the US Food and Drug Administration FDA. These guidelines are integrated into our internal Standard Operating Procedures, SOPs.

We take very seriously our responsibilities towards the persons participating in our clinical studies as study subjects or site personnel, always ensuring their rights, safety, integrity, confidentiality and well-being, wherever the trials take place.

The first clinical study in humans can be conducted with a new molecule only after nonclinical research has confirmed that it is sufficiently safe for testing in humans. All our clinical study plans (study protocol and amendments) are first reviewed and approved by Orion's own highly educated R&D specialists, after which they are reviewed and approved by applicable external experts, ethics committees and relevant healthcare regulatory bodies, depending on the location of the study conduct.

Throughout all the clinical study phases of the program, the safety and the behaviour of the new drug candidate in the human body is explored with rigorous monitoring. We assess all signals of potential safety concerns carefully. Independent external specialists are consulted widely and the project's independent Data and Safety Monitoring Board oversees the study.

Investigators are medical doctors carrying out a determined part of the clinical study under a service contract with Orion or our possible partner. Investigators in our studies are always highly educated specialists in their therapy areas. They are responsible for all necessary activities at the site of the study. The investigators are well familiar with the purpose and protocol of the study, having a detailed understanding about the investigational medicine and its risk-benefit aspects. With their high level medical competence and deep knowledge about the study they can ensure the best possible safety and well-being of the study participants.

A personal informed consent from every clinical study participant (healthy volunteer or patient) shall be obtained in writing before a trial begins. In the informed consent the study is introduced and explained to the participants profoundly so that they understand potential benefits and possible risks in the clinical study. The responsibilities, commitments, roles and rights of the participant, the investigator, the study nurse and the study sponsor are described carefully. We take enough time for the introduction, and we encourage the study participants to ask instant questions or whenever additional information is needed.

Participation in our studies is always voluntary. In certain cases, the authorised caregiver can make the participation decision on behalf of the participant. During the study the participant is free to withdraw from the study at any time without explanation. In the clinical studies sponsored by Orion, we pay particular attention

to the patient's privacy, as well as the confidentiality of the data collected during the study. Individual patient data is protected by using secure data management systems and by following the principles determined in regulatory requirements and the informed consent.

Patients participating in clinical study programs are treated and followed up for free during the study phase. Each patient also contributes to developing better medicines.

Orion registers all clinical trials in credible and publicly available databases as per requirements – typically ClinicalTrials.gov. In accordance with the EMA guidance, clinical trial summary results shall be published in the European Clinical Trials Database (EudraCT). Trial data can be registered in other databases, if there are specific local requirements.

As a research-based company member of the European Federation of Pharmaceutical Industries and Associations, EFPIA, Orion is committed to sharing study-level and patient-level clinical study data on its medicines and indications according to the principles described in the EMA Policy on Publication of Clinical Data and in the EFPIA Commitment. Information about the scientific publications and abstracts presented by Orion in scientific conferences is shared on Orion's corporate website. By providing access to study-level and patient-level data on our clinical studies we show transparency and willingness to contribute to improved knowledge of new medicines and indications. After a marketing authorisation has been granted to our new drug, we allow access to our patient-level data based on a scientific review of the request and the proposal from the external research group consisting of qualified scientific and medical researchers. Before sharing, any patient-level data will be anonymised to protect identifiable information.

In addition to drugs for humans, Orion also develops medicines for animals, mainly for pets like dogs and cats, and for livestock. The clinical studies in the target animals are very similar to human clinical trials and also here we follow the similar internal Standard Operating Procedures. Veterinary clinical studies are conducted according to the principles of VICH (Veterinary International Conference on Harmonization) and Good Clinical Practice guidelines, and permissions from local healthcare authorities are needed before starting a study.

Participation in a veterinary clinical trial sponsored by Orion is voluntary and requires an informed consent from the owner before an animal patient can be enrolled in a study. Investigators in our veterinary clinical trials are veterinary specialists or general practitioners, and they are responsible for the treatment and welfare of the animals participating in the study. Animal patients are suffering from the disease concerned, needing proper treatment. By participating in a

clinical study program they are treated and followed up for free and, together with their owner they contribute to developing better medicines for animals.

Ethics in the Marketing Phase

Although a new medicinal product has been approved for marketing and for clinical use in patients on the basis of the results of a years long, thorough and strictly controlled R&D process, no instance can guarantee its absolute safety or efficacy. One of the many responsibilities of the marketing authorisation holder is to systematically collect experience from the product's benefits and causes of concern immediately after the first launch, and this responsibility continues until the product is no longer available.

Orion is committed to continuously monitoring and assessing the benefits and risks of its products to ensure and secure patient safety using purposeful procedures and methods. This includes, for example, product specific risk management plans, detection of signals of safety concern, periodic reviews of the product's benefit-risk balance, timely and appropriate risk minimisation actions, such as e.g. amendment of the summary of product characteristics with new information concerning safety, communication of safety issues to patients and healthcare professionals, and educational materials. Safety studies can also be conducted after the launch of a product.

We further report adverse events and quality deviations to the healthcare authorities and the relevant healthcare professionals using officially adopted systems and channels, and when there is a reason, we take the necessary actions without undue delay.

Orion is committed to maintaining efficient pharmacovigilance systems and continuously monitoring their applicability, compliance and performance. Pharmacovigilance means the comprehensive and complex process and science of monitoring the safety of medicines and taking action to reduce the risks and increase the benefits of medicines.

As a responsible company, it is also in Orion's interest to fight by all applicable means against the increasing availability of fake drugs. All our employees are anticipated to take rapid initiative for action if alerted by any signal of counterfeit versions of Orion's products.

Pharmaceutical companies have a legal responsibility to share information on their medicinal products to healthcare professionals and patients to ensure their safe

and proper use. Communication concerning prescription medicines is subject to strict regulation, which emphasises that the arguments and information must be in accordance with the product information leaflet confirmed for the product. Orion's sales and marketing organisations for pharmaceuticals follow a broad range of instruction and guidelines. These comprise the locally valid legislation and other requirements concerning medicinal products, marketing and communication, consumers and competition and the International Code on Advertising and Marketing Communication Practice. Equally important are also our internal guidelines which correspond to the EFPIA Codes of Practice, as well as the Orion Group's Code of Conduct and corporate policies.

We arrange regular and continued training and testing to ensure that the persons engaged in our sales and marketing operations have adopted and follow the required principles and guidelines and that they possess the needed knowledge and skills to provide the right information on Orion's products.

References

EFPIA website, www.efpia.eu:

EFPIA HCP Code (Code on the promotion of prescription-only medicines to, and interactions with, healthcare professionals)

EFPIA PO Code (Practice on relationships between the pharmaceutical industry and patient organisations)

EFPIA Disclosure Code (Code on disclosure of transfers of value from pharmaceutical companies to healthcare professionals and healthcare organisations)

EU Commission's website ec.europa.eu/health/human-use: Medicinal Products for Human use