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**MINI REVIEW**

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**PRECLINICAL DRUG DEVELOPMENT**TERESA BRODNIOWICZ<sup>1</sup> and GRZEGORZ GRYNKIEWICZ<sup>2\*</sup><sup>1</sup>MTZ Clinical Research, Pawińskiego 5, 02-106 Warszawa, Poland<sup>2</sup>Pharmaceutical Research Institute, Rydygiera 8, 01-793 Warszawa, Poland

**Abstract:** Life sciences provide reasonably sound prognosis for a number and nature of therapeutic targets on which drug design could be based, and search for new chemical entities – future new drugs, is now more than ever based on scientific principles. Nevertheless, current very long and incredibly costly drug discovery and development process is very inefficient, with attrition rate spanning from many thousands of new chemical structures, through a handful of validated drug leads, to single successful new drug launches, achieved in average after 13 years, with compounded cost estimates from hundreds of thousands to over one billion US dollars. Since radical pharmaceutical innovation is critically needed, number of new research projects concerning this area is steeply rising outside of big pharma industry – both in academic environment and in small private companies. Their prospective success will critically depend on project management, which requires combined knowledge of scientific, technical and legal matters, comprising regulations concerning admission of new drug candidates to be subjects of clinical studies. This paper attempts to explain basic rules and requirements of drug development within preclinical study period, in case of new chemical entities of natural or synthetic origin, which belong to low molecular weight category.

**Keywords:** drug design discovery and development, new molecular entities, biological activity testing, pharmacokinetics, quality management, common technical document, preclinical phase

Development of new drugs is perceived as a very complex process, which can be described from many different points of view; science and business story behind a new drug launch do not necessary match. Brisk scientific discovery can end up in clinical study failure or even withdrawal after launch – over 90% drug leads do not make it to the market.

Therefore, general view of the contemporary pharmaceutical industry is, despite of its some spectacular successes, that of certain dissatisfaction – globally, more is spent on drug discovery and development every year and less is delivered, in terms of radical innovation (1–3), which remains in sharp contrast to incredible progress achieved in basic science research and phenomenal involvement of technical potential, spanning from new information technology to sophisticated robotics. Leaving aside overwhelming economical R&D problems of big pharma industry with knowledge management and generating much needed innovation, we would like to discuss this part of drug research and development, which our readers are likely to come across

personally, as project managers, researchers or reviewers and experts. Following European integration, local scientists finally stand a chance to design and submit ambitious research projects in advanced medicinal chemistry, prospectively realized within international cooperation. It is obvious that such development puts considerable load of responsibility on the entire environment of researchers within life sciences. In particular, chemists, pharmacists and biochemists should strive for more effective communication with drug discovery and development (DDD) area, which requires some specific knowledge. We intend to recapitulate essentials of DDD process as practiced under current legal requirements, with some focus on quality assurance systems and safety. In particular, an evolution of a drug candidate will be explained in terms of knowledge accumulation and technical documentation filing. In order to simplify this complex task, we will be concerned only with so called “small molecules” (basically synthetics, roughly below 1000 daltons), as opposed to “biologicals” of either natural or biotechnological origin (4).

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### Origin of new structures for DDD

Although application of foreign substances (xenobiotics) in case of illness had been practiced since the time immemorial, modern pharmacy, operating with defined chemical entities of reasonable chemical purity, is just a little more than a century old. During that time there were two principal sources of medicinal substances: a) natural products, obtained chiefly from plants or microbial sources, and b) chemical synthesis, which basically took over in the second part of the period. Currently, historical view of an individual scientist discovering new drugs in his individual, modest laboratory, gave way to entirely different picture – that of a large organization, in which sophisticated logistics combines an effort of cohorts of various specialists into a pipeline of DDD, involving dozens of laboratories focusing on particular tasks within narrow technical specialties. At the same time a new source of pharmacologically active substances emerged – biotechnology, using biochemical methods on technical scale, providing secondary metabolites and recombinant proteins by mastering natural metabolic pathways and generating new ones. Biologicals and biosimilar products became a large branch of pharmaceutical industry with its own specificity. It is generally agreed, that the first step of the DDD process consist of target identification and validation. While traditionally a disease or pathology was considered a target, today molecular level of perception is employed, and identification of a faulty biochemical process and a macromolecule responsible is regarded obligatory. Typical targets are receptors, enzymes, elements within gene expression systems or particular events of intracellular signaling cascades. Such reductionism is not entirely satisfactory, but even if systems biology approach, with its mul-

tiscale dynamic modeling of physiology takes over, the general idea of starting DDD process with biological descriptors screened against structural representations will stay in force (5, 6). Although genomics as a single line of research did not fulfilled its promise to deliver identified medicinal targets, there are many more “omic” approaches, which significantly increase our knowledge how physiological processes are related and governed on a cellular and organismal levels. The second big step in any DDD project or program is development of an activity assay, in which new compounds can be tested, to eliminate inactive ones. Typically, for a given target two types of tests are made available: high throughput, based on interaction with target proteins or selected cell lines, which allow to check affinity/activity of large libraries of compounds very quickly (within hours), and low throughput, run on tissues, organs or animals, in which preselected compounds are investigated in more detailed procedures, for weeks or months. This system reflects incredible inefficiency of traditional way of pharmaceutical industry screening, characterized by very high drop-out rate, amounting to many thousand failures per one successful drug candidate. Once proper target is defined and bioassays are established and validated, medicinal chemistry enters the field, with a mission to provide a new chemical entity, which can interact with the target on the systemic level in a drug-like manner. Moreover, prospective new drug candidate must demonstrate: specificity (defined mechanism of action), potency (high affinity for selected target), selectivity over other possible biological targets, and above all – safety for patients, which is to be demonstrated at the end of DDD process, in carefully designed clinical trials, starting from early preclinical (Fig. 1). Additionally, the new drug candidate should also

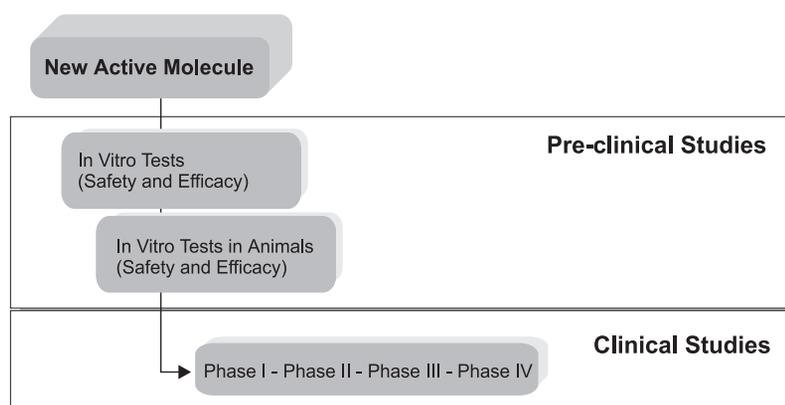


Figure 1. Drug development diagram

fulfill some non medical criteria: 1) intellectual property rights for the active molecule should be clearly defined and well protected; 2) the compound should be available in reasonably priced and technically feasible process, easy to scale up and control, affording consistently the active substance (API, historically referred to as Bulk Drug Substances [BDS]) of high chemical purity and desired physico-chemical properties (7). These rather restrictive requirements concerning the new drug itself and the way in which it is developed, are a matter of pharmaceutical law as well as numerous guidelines issued by agencies regulating main markets of pharmaceutical products. Both: the law and the guidelines are currently a subject of harmonization between the main pharmaceutical markets: the US, Europe and Japan, highlighting safety and quality. International Conference on Harmonization ([www.ich.org](http://www.ich.org)) regularly issues detailed guidances for pharmaceutical industry analogous to these emitted by European ([www.emea.europa.eu](http://www.emea.europa.eu)) and American ([www.fda.cedr.gov](http://www.fda.cedr.gov)) agencies.

#### Quality criteria for a new drug candidate

The authors own experience indicate that large proportion of projects concerning medicinal chemistry, with DDD elements carried out in our country during last decades, treated this ideology purely declaratively without any intention to follow up rules, regulations and to assume responsibility for money spent on rather chaotic studies and unplanned activities. New system of local science funding and in particular participation in international programs will obviously require complete change in such attitude. The peer review system for the grant proposals will surely require professional level of DDD project design and management. The best advice for any project under drug discovery and development banner is: have a plan for entire action leading to complete registration file. In particular, clinical development plan (CDP), anticipating pharmaceutical formulation, dosage and patient population should be treated as a cornerstone document, from which a reasonable plan of preclinical studies can be re-developed. To explain it further, we will assume that hypothetical project starts from a point after principal discovery phase, in which biological target is defined, a new molecule is designed and intellectual property rights for its application are secured. To make it even more simple, let us assume that the compound in question is a low molecular weight synthetic chemical, for which an oral formulation is envisaged. Even in such simplified case, the

question: how to arrange for preclinical verification of selected new chemical entity is by no means simple, as prospective therapeutical indications generate great variety of pathology models, activity tests and other procedures. In general, the nonclinical team, is responsible for regulatory affairs strategy formulation, anticipating questions to be posed by authorities examining future registration application. Secondly, safety assessments are to be undertaken and manufacture of clinical supplies (both: API and pharmaceutical preparation) have to be secured. All these activities should be coordinated and planned to minimize time to the first application to humans, without compromising safety. As all tasks in the preclinical phase require the drug substance, the critical question: "when a new chemical entity studied becomes a drug candidate in sense of analytical specification?", should be answered precisely and as early as possible. Initial *in vitro* biological activity tests can be easily carried out on milligram quantities, while animal toxicity studies and in particular pharmaceutical development, can easily elevate the active substance demand to a kilogram level (3). Chemical synthesis for the purpose of hit identification is usually performed on a fraction of millimolar scale, without any consideration for process development. On the other hand, on the drug lead and drug candidate level, chosen synthetic variant has to be examined in detail, particularly in terms of impurity formation, and then optimized. Drug substance stability in time and under stress has to be determined. This involves development and validation of analytical methods and identification of critical parameters of synthetic process, which can frequently be derived from academic knowledge about a reaction mechanism. Analytical specification for an API can be changed during development, according to the best knowledge available, but it should start at the reasonable level of chemical purity. For a generic drug, there is customary requirement of 99.8% of HPLC purity with no single unknown impurity crossing 0.1% level. For new drug candidates, especially at preclinical study period, more flexible standards are possible e.g., with no individual purity present above 0.5%. At the same time, based on advances in analytical techniques with coupled detection methods, it is reasonable to assume, that no such thing as "unknown impurity" should be included into specification.

The entire process of DDD is summarized for purpose of filling a new drug application, in standardized form of Common Technical Document (CTD), diagrammatically represented in form of a triangle (Fig. 2), containing five modules: 1. region-

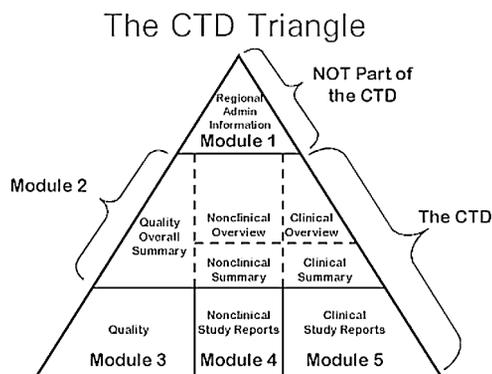


Figure 2. The Common Technical Document Elements (Source: "Implementation of the CTD", FDA ICH Public Meeting, May 8, 2001)

al and administrative information (concerning applying organization), 2. overviews and summaries, 3. quality, 4. nonclinical study reports and 5. clinical study reports. Since one of us (T.B.) has recently characterized formalities and activities involved in clinical trials (8), from CRO perspective, this paper concentrates on the preclinical segment of DDD, comprising CTD modules 3 and 4.

Module 3, dealing with quality of a drug substance and a drug product, is in its first part of particular interest to any project devoted to new drug design, discovery and development. Since final drug active substance (frequently described as API, short for: active pharmaceutical ingredient) has to be exhaustively and meticulously examined and its properties fully characterized, in particular in respect to stability and content of impurities, legitimate question arises, when pharmaceutical quality requirements become critical within a pathway of biological testing. In order to solve this problem, particular points of the module 3 need to be discussed in some detail. Content of the module, in its part devoted to the substance, consists of the following points: 3.2.S.1 General Information, 3.2.S.1.1 Nomenclature, 3.2.S.1.2 Structure, 3.2.S.1.3 General Properties, 3.2.S.2 Manufacture, 3.2.S.2.1 Manufacturer(s), 3.2.S.2.2 Description of Manufacturing Process and Process Controls, 3.2.S.2.3 Control of Materials, 3.2.S.2.4 Controls of Critical Steps and Intermediates, 3.2.S.2.5 Process Validation and/or Evaluation, 3.2.S.2.6 Manufacturing Process Development, 3.2.S.3 Characterization, 3.2.S.3.1 Elucidation of Structure and Other Characteristics, 3.2.S.3.2 Impurities, 3.2.S.4 Control of Drug Substance, 3.2.S.4.1 Specification, 3.2.S.4.2 Analytical Procedures, 3.2.S.4.3 Validation of Ana-

lytical Procedures, 3.2.S.4.4 Batch Analyses, 3.2.S.4.5 Justification of Specification, 3.2.S.5 Reference Standards or Materials, 3.2.S.6 Container Closure System, 3.2.S.7 Stability, 3.2.S.7.1 Stability Summary and Conclusions, 3.2.S.7.2 Post-approval Stability Protocol and Stability Commitment, 3.2.S.7.3 Stability Data. The list is exhaustive and practically self-explanatory, leaving little room for comments. It has to be understood that the format applies for new chemical entities as well as for generic drugs. In the first case situation is more difficult for researchers, because there is no pharmacopoeial information on methods available, which in case of generics greatly assists pharmaceutical analytical services, and no back-up with reference standards, so analytical methods have to be elaborated from scratch. It is obvious from the above, that characteristics of the API covers not only the chemical entity itself, but also the process for its manufacturing, which is potentially confusing, because more often than not, synthetic methods evolve from incidental laboratory preparation, through optimization and scale up, to validated technical process, which sometimes utilize entirely different synthetic strategy, materials and conditions than its small laboratory scale predecessor. It is easy to postulate that all biological tests should be carried out on a substance obtained in a stable, validated technical process, but at the time when test results are needed to guide development decisions, such substance is unavailable and will appear only many months down the pipeline. The question how to overcome this difficulty sounds tough, but the answer for a prospective project leader is easy: perceive DDD pipeline scheme as a learning process and mobilize your best scientific knowledge at every checkpoint. It stands to reason to concentrate on chemical purity of the substance of interest in the early phases of preclinical testing period. It is reasonable to assume that test used for hit search are qualitative in character and 90% purity level can be considered satisfactory for such purpose. It is the toxicity testing platform, which requires pharmaceutical type specification of tested substance, including impurity profile and impurity characteristics, therefore, well developed analytical methods and proven manufacturing process have to be already in place. For an API required chemical purity level is set at 99.8 % and an unknown impurity should not exceed 0.1%. Although these levels can be considered negotiable in the development phase, impurity profile can become a critical factor – if changes in synthetic process scale up or optimization resulted in new impurities, it could jeopardize validity of biological

tests, in particular lengthy and costly toxicology. Thus, importance of finalizing chemical route of synthesis early, with minimal number of steps and elimination of unknown impurities, is evident. Polish Pharmaceutical Law (Dz. U. 2008 Nr 45, poz. 271) and Directive from the Minister of Health dated November 4<sup>th</sup> 2008 (Dz. U. Nr 201, poz. 1247) require, that the form directed to the Clinical Trials Registry (CEBK), contains detailed description of the active substance including physical and chemical characteristics, description of manufacturing process, analytical methods, controls, standards specification, stability etc., in line with the CTD format. These requirements correspond to the Committee for Medicinal Products for Human Use "Guideline on the Requirements to the Chemical and Pharmaceutical Quality Documentation Concerning Investigational Medicinal Products in Clinical Trials" (CHMP/QWP/185401/2004 final; London, March 31<sup>st</sup>, 2006).

It is of great importance to record changes in quality management and regulatory agencies attitude towards applicants, which have taken place in recent years. Traditionally, quality control was carried out off line, after manufacturing process completion, which could lead to rejection of ready made batches of product. Current guidelines require, that process is designed in such a way, that quality is ascertained within, by proper control of critical parameters. Process analytical technology (PAT) is a systemic tool allowing on line control of parameters, which efficiently eliminates generating batches of product below specification requirements. Regulatory agencies not only encourage using best process design for quality risk management but are visibly more inclined to dialog with an applicant, based on sound scientific knowledge, which is a revolutionary change from an early GMP period, in which any modification of DMF (drug manufacturing file) recorded process was out of question on the purely formal grounds.

### Biological activity testing

Dependence of biological activity on molecular structure is the key concept of medicinal chemistry, which has evolved through structure-activity relationship (SAR) methodology into modern bioinformatics allowing for prediction and modeling of biological properties as valuable support for experimental *in vitro* and *in vivo* tests. Contemporary process of new drug discovery and development relies to a high degree on selection of defined drug-like properties, which are considered

prognostic for a lead compound success, provided proper metrics can be introduced. Since the matter is reviewed comprehensively in numerous monographs (9–11), we will only briefly tackle some issues which are considered important for accelerating DDD process. Absorption, distribution, metabolism and excretion (ADME), which are of utmost importance for any xenobiotic characteristics and reasonably well distinguish between drug-like and non drug-like compounds, are believed to be a function of simple physicochemical properties as well as an affinity to various complex functional biopolymers. Lipinski's rule of 5 (RO5) is an example of generalization based on physicochemical descriptors, which gained wide recognition as useful exclusion criterion (12). It has been derived from observation that ca. 90% of orally active drugs has molecular weight below 500 Da, not more than 5 hydrogen bond donors, not more than 10 hydrogen bonds acceptors, and log P value below 5. It needs to be added, however, that this extremely useful rule works much better for synthetic compounds than for natural products. Since ADME refers to a rather broad set of physiological processes, many attempts have been made to secure quantifiable parameters for its measurement. In contemporary DDD aqueous solubility, Caco-2 permeability, volume of distribution, plasma protein binding, blood-brain barrier penetration, oral bioavailability, intestinal absorption, P450 metabolic stability and elimination half life are routinely employed for drug quality assessment. Advances in analytical methods and novel *in vitro* assays greatly facilitated access to ADME data in comparison to historical times when most measurements were carried out using radiolabelled compounds in rodent models. For example Caco-2 cells permeability, which is predictive for absorption of orally administered compounds, became widely accepted test on which permeation based classification system (PCS) of compounds was based (13). Currently expanded model, already adopted by the World Health Organization, called Biopharmaceutics Drug Disposition Classification System (BDDCS) functions, which divides drugs into four classes, according to solubility (low/high) and permeability (low/high) criteria. On such bases, Class one compounds (high solubility and high permeability) were singled out by the FDA for waiver of *in vitro* bioavailability testing of immediate-release solid dosage forms (14, 15). Pharmacodynamic properties of drug leads and drug candidates are as a rule tested on several levels, from molecular (e.g., receptor binding, microarrays) through cell lines, to

selected organ and model (e.g., knock-out) animals. On the lower levels there is increased use of imaging technologies (e.g., fluorescent tags) to enhance specificity and sensitivity of biological test results. There is constant tendency to save animals on ethic principles and validity of animal models as human predictors is often criticized on purely scientific principles.

Preclinical pharmacological analysis of new drug lead covers area from *in vitro* functional assays, through isolated cells and tissue studies, to *in vivo* animal pharmacokinetic (PK) and pharmacodynamic (PD) experiments. Responses to a dose of drug are quantified in terms of efficacy (maximum strength of the effect) and potency (amount of drug required for specific effect to occur; usually expressed as inverse of  $EC_{50}$ ). An issue of pharmacological profiling has been brought up relatively recently. Since any drug candidate is likely to bind to multiple targets, distinct from the intended one, such lack of specificity should be seen as potential source of adverse effects and consequently failure in clinical trials. Efforts to identify as early as possible the candidates with best target selectivity and best safety profile include design of pharmacological testing, with extensive use of bioinformatic methods and target databases, like *in silico* screening of phylogenetic families of functional proteins for possible binding.

Perhaps the most significant initiative for future preclinical testing is called microdosing. This method, based on application of a single sub-pharmacological dose of investigated compound to healthy volunteers, has recently passed proof of concept set of experiments, comparing pharmacokinetic (PK) results of such dosing with regular pharmacological regimen. The power of microdosing, which is also called "clinical trials phase 0" is based on sophisticated detection system with sensitivity in attomole to zeptomole ( $10^{-18}$  –  $10^{-21}$ ) range, provided by accelerator mass spectrometer. Investigated drug sample is first enriched, by specific labeling during synthesis, with  $^{14}\text{C}$  long half-life radioactive isotope. Accelerator mass spectrometry (AMS) allows for detection of heavier carbon isotope and determination of  $^{12}\text{C} : ^{14}\text{C}$  ratio with exquisite precision, thus can provide a wealth of pharmacokinetic and metabolic data from a single experiment. Typically, ca. 100 microgram of a studied compound is administered to a human subject and after preselected time samples of blood, urine and sometime a biopsy samples are collected, analyzed and separated by HPLC, then analytes are converted into graphite in chemical oxidation-reduction sequence and subjected to

AMS measurement. This technique, which can easily secure data for total mass balance of an injected drug sample, can be adopted to other isotopes of biologically important elements (calcium, chlorine, hydrogen) (16).

### Toxicity testing

Regulatory agencies (EMEA, FDA) require substantial evidence of safety and efficacy as the basis for a new drug registration, significant part of which is to be generated at preclinical stage. Traditional term: toxicology for covering entire field of DDD, gradually fell out of fashion and finally was replaced by non-clinical safety assessment (NCSA). All tests in this area must be performed with certificate of appropriate ethical committee in certified laboratories, under GLP conditions. Studies in safety pharmacology constitute continuous action carried out throughout DDD process with tasks like genetic toxicology, toxicokinetics, carcinogenicity and reproductive toxicity possibly overlapping with a clinical support period. Discovery phase is usually connected with multiple administration protocol, lasting usually 4 weeks (occasionally 6 months or even longer), carried out on two animal species, typically rats and non-rodents. Typically, three dose groups are formed, with a low dose close to pharmacologically effective one, with purpose of establishing no observable effect level (NOEL) and minimum toxic dose (MTD). Apart from close CNS (behavior, posture, body weight, temperature etc.), respiratory and cardiovascular monitoring of experimental animals, wide pathological assessment is performed (involving *inter alia*: heart liver, kidneys, spleen, brain, pituitary and adrenal glands, thyroids and parathyroids, CV, GI and reproductive tracts). Considering this, it comes as no surprise that 28-day toxicology experiment takes several months to complete, from preparation to statistical elaboration of the raw data. Reproductive toxicology is of special concern, following well known thalidomide tragedy. Just like in other areas of biological activity, there is a need for constant awareness to remember possible consequences of genetic differences, even within the same species. Available study of clinical and post-marketing adverse drug reactions in recent years indicate that majority were reported in neurological, gastrointestinal, cardiovascular and hepatic areas (17). It can be assumed that although elimination of *in vivo* assays in new drug safety evaluation is unrealistic, the role of computational toxicology will grow systematically (18).

### Issues concerning preparation of clinical batches

As soon as a compound is selected for development, dosage form design should start up. Since a majority of drug candidates are disqualified during clinical testing, care should be taken to optimize design of preclinical studies in order to eliminate compounds which are likely to fail in further evaluation. Besides, efforts should be mobilized, not to spend too much time and expenses on a risky investment in clinical batch preparation. On the other hand, for certain drugs formulation might be absolutely critical for drug efficacy. It seems reasonable to dissect physicochemical properties of a given new chemical entity into two parts: dependent, and independent of a solid state. In the first category are such important properties like dissociation constants, partition coefficients and stability in solutions. In the second are: solubility, polymorphism, solvent affinity and thermal parameters characteristic for phase transitions. Traditionally, both categories were taken into account at the same time during preformulation studies. Presently, it is required that pharmaceutical quality should be achieved by design, through well managed product and process development (19). Although much of physicochemical characteristics mentioned in this paragraph is provided by analysts carrying out chemical development of API, there is no guarantee that a drug substance meeting specification mixed with excipients meeting specification will make a good tablet. It is therefore understandable that provisional formulations, like hard gelatin capsules containing only the active ingredient, are often used for early phases of clinical trials.

### Conclusions

Neither target recognition nor lead identification has attained satisfactory level for successful and productive new drug mining. Current therapy is based upon less than 500 macromolecular targets (ca. 45% G-protein coupled receptors, 28% enzymes, 11% hormones, 5% ion channels, 2% nuclear receptors), while functional genomics indicate an order of magnitude higher number (20). Therefore, many more viable therapeutic targets are waiting to be discovered. Finding their prospective ligands is a matter of formidable complexity. Chemical space, accommodating all possible structures may be infinite, but even its fraction containing only small molecules up to 500 Da molecular weight sums up to at least  $10^{60}$  compounds, unmanageable as a reservoir of structural diversity by any means, except virtual

searches, for which drug-like cluster mapping and other selection rules are already being designed (21). Pending further progress in bioinformatics, there is an acute need for NCEs, which can be qualified as good leads for DDD.

In general, for admission of a new drug candidate to clinical studies, sound non-clinical data obtained under GLP conditions are needed, accompanied by a manufacturing process (comprising both: active pharmaceutical ingredient and pharmaceutical product) executed under proper quality control and documented according to Common Technical Document format (3). There is an increased tendency to design drug-like properties *in silico*, and also to use bioinformatics methods extensively for modeling and predictions, in all segments of biological activity testing. Despite of phenomenal progress in life sciences, including achievements of genomics and systems biology, there has been no major change in the drug discovery and development paradigm and the process of DDD remains painfully slow, exorbitantly expensive and dismally inefficient. DDD requires, more than ever, effective and timely coordination of chemical development, safety assessment and pharmaceutical formulation, as there is no foolproof blueprint when and how the appropriate quality substance should emerge. The use of new pathology models, involving transgenic animals facilitate same stages of preclinical studies, but a lack of proper biomarkers for organ toxicity, particularly myocardial tissue damage, liver toxicity and nephrotoxicity are serious drawbacks of the present system.

Fortunately for those involved in DDD projects, there is a good supply of quality scientific literature covering all details of preclinical development, and recent volumes of *Drugs and the Pharmaceutical Sciences* series provide a good example of it (22–25). Besides, there are topic-specific guidelines issued by EMEA and FDA, applicable to preclinical as well as clinical development, which should be carefully studied beforehand, for every step of a DDD project. It is particularly satisfying, that scientific findings and arguments become sufficient ground for a dialog with regulatory agencies in cases of postulated changes of process development, testing scheme or pharmaceutical quality control. In 2004, FDA launched the Critical Path Initiative as national strategy for development, evaluation and manufacturing not only human drugs but also foods and cosmetics with intention to turn more research into new tools and methodologies which could improve all FDA regulated products (26). This initiative has received appropriate funding

from the US Congress, making hopes for accelerated drug development technologies realistic and setting an example for ICH actions.

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