



## Drug development in an era of molecular medicine

**Dr Wolf S Richter** explains how the importance of imaging in clinical trials will only increase as progress in molecular science continues to change our understanding of disease

**S**ignificant progress has been achieved during recent years in the understanding of molecular disease processes, in the identification of disease-specific targets and in the development of target-specific pharmaceuticals. The consequences of this development for clinical medicine and the drug development process are not yet fully obvious.

Information about molecular targets is already used in clinical medicine for the classification of disease and is about to change current paradigms of disease understanding and treatment decisions. This situation is most obvious in cancer. Cancer has been traditionally classified on the basis of the origin of the tumour tissue and the anatomical extent of tumour spread. However, this two-dimensional classification system is not able to fully characterise disease. Already additional information about the molecular signature of disease is required and guides treatment decisions (eg, the determination of HER2 expression in breast cancer is a prerequisite for starting – or not starting – herceptin therapy).

Further advances in our understanding of the molecular basis of disease will help sub-classify disease entities currently treated as one single disease. It is now thought no two cancers are identical

at the molecular level. Even metastases from the same primary tumour can have a different molecular expression pattern. Identifying these disease sub-types and selecting the appropriate target-specific treatment has significant potential to increase treatment efficacy over current standards.

The challenges for drug development in this era of molecular targeting are at least twofold. Firstly, it is obvious that the potential prospects of target-specific compounds are intimately linked to diagnostic procedures which allow the molecular signatures of diseases and subjects to be identified. The development programme of a target-specific therapeutic drug will therefore need to consider how appropriate patients for clinical studies, and later for the target market, can be identified. In most cases, the respective diagnostic tools will either not be available or not be sufficiently validated. As a consequence, a programme to develop (or validate) the associated diagnostic tool must be incorporated. In 2005 the FDA provided preliminary thoughts about the co-development of a therapeutic drug with a companion diagnostic.

Secondly, the overall value for a pharmaceutical company of developing a target-specific drug is difficult to

assess with conventional methods.

At first glance, the market for a drug with efficacy in a patient subgroup will usually be smaller than for an unspecific compound that is taken by almost all patients with a given disease. We have calculated in a cancer model that the potential turnover can be reduced by 20-40%, even considering that higher prices can be obtained with target-specific compounds. However, this calculation is in many cases not sufficient. Careful design of a clinical development programme that integrates diagnostic tools for responders will be able to significantly reduce development costs and the time to market. In our simulations, the required patient numbers for pivotal Phase III trials could be reduced by more than 60% resulting in significant savings in cost and time. In addition, the overall value of a development programme needs to consider the probability of achieving the desired reimbursement level. It is probably fair to assume that the value of a diagnostic-therapeutic combination for a defined patient subgroup can be more easily shown and reimbursement more readily obtained than for larger patient groups without a pre-selection tool.

### Changing paradigms

Current clinical development concepts with clear borders between Phases I, II, and III will need to be adapted to the necessities of target-specific compounds. In most cases, considerations about the development programme will

take the molecular target as the starting point. Based on data from immunohistochemistry, a list of potential target indications can be compiled. The difficulty, however, lies in the lack of transferability of animal and tissue data to the human patient. Several questions need to be answered, such as:

- Does the lead compound reach the target in the human patient?
- Which of the lead compounds should be the development candidate?
- What is the appropriate dosing?
- Which of the potential target patient groups responds best?
- What is the desired target profile?

In recent years, the regulatory authorities have opened the door for new concepts in drug development. The micro-dosing concept, adopted by the FDA and EMEA, allows exploratory clinical trials (Phase 0, pre-Phase I) with a single test substance or a number of closely related candidates. The concept explicitly includes diagnostic imaging with positron emission tomography (PET) which allows one to directly assess if a compound reaches its molecular target in patients, and gives relevant information for appropriate dosing. It also regards certain deviations from existing safety standards to be scientifically justified in order to support pre-Phase I trials, thereby lowering the barriers faced by investigators when seeking early confirmation in humans.

Important further steps include the selection of an appropriate patient group for development, and the confirmation of the therapeutic potential. The selection of appropriate patient groups for development is supported by the integration of diagnostic tests (*in vitro* tests and *in vivo* imaging) into the development programme. The best combination of diagnostic test, patient group treated, and trial endpoint will need to be defined in Phase II proof-of-concept trials before starting Phase III.

Clinical development in the era of molecular medicine will include innovative approaches for identifying lead compounds and early confirmation of a drug's potential. A key part of clinical development will be Phase II studies,

in which therapeutic efficacy will be tested in differently selected patient (sub) groups. Diagnostic imaging bears particular potential in this context. The (preliminary) confirmation of therapeutic potential will often depend on diagnostic imaging as a surrogate for the true clinical endpoint. The results from Phase II will allow a focused and streamlined Phase III programme.

### Value of diagnostic imaging

Diagnostic imaging has gained increasing value in drug development in recent years. This is reflected by increased efforts of the respective scientific societies like RSNA, ESR, SNM, EANM to standardise imaging procedures and educate physicians. For the purposes of clinical development, imaging includes all modalities available in clinical practice like x-ray, ultrasound, CT, and MRI as well as functional MRI/MRS and the nuclear medicine procedures, PET and SPECT (single-photon emission computed tomography), with traditional and customised radiotracers.

Imaging with PET and SPECT bears significant potential during the transition from pre-clinical to clinical development as it allows the same methodology to be employed in animal experiments and human trials. Using PET, basic concepts validated in animals can be transferred to humans, potentially serving as imaging biomarkers for efficacy and/or safety in later phases of the clinical development programme.

In later development, diagnostic imaging enhances knowledge about a drug's potential in different patient groups and disease states (clinical proof-of-concept, Phase II). Imaging methods in later phases preferentially include modalities which are available for routine patient care (MRI, CT, x-ray, ultrasound, PET). The information obtained at this stage is mainly important for designing subsequent clinical trials, to define the target indication, and for internal decision making to identify promising drug candidates early. In pivotal Phase III, imaging may serve as a surrogate endpoint for regulatory approval.

The value of diagnostic imaging within

a drug development programme is intimately linked to the validation of the imaging procedure in the context of its use. The reliability of the data obtained in diagnostic imaging will depend on factors related (1) to the imaging system and the imaging parameters used, (2) to patient-specific characteristics which are independent of the disease process (like weight, patient movement during image acquisition), (3) to the disease process of interest, and (4) to the individual expert(s) reading the images. A careful validation is required to understand the influence of each of these factors on the overall imaging result. This is of particular importance in case of multi-centre clinical trials in which imaging systems from different manufacturers are used. The cross-calibration of scanners and other equipment will assure the results from different centres are indeed comparable. Regular checks of the constancy of the imaging parameters including acquisition, storage and handling conditions will assure the consistency of the results during the trial.

### Conclusion

Progress in molecular science will continue to change our understanding of disease and of appropriate patient management strategies. Drug development concepts will need to be adapted to the evolving new paradigms in clinical medicine. It is foreseeable that clinical proof-of-concept studies for the early confirmation of a drug's risk-benefit ratio and an appropriate selection of patient subgroups will be increasingly important. Imaging is already an indispensable tool in drug development; its importance will increase further. Expert knowledge is required to explore the full potential of imaging in clinical trials.

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