is intended to substitute for a clinical end-point and is expected to predict clinical benefit (or harm or lack of clinical benefit) based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence'.[1] According to Fleming et al., 'Any changes induced in the surrogate end-point by a treatment must accurately reflect changes in the true end-point'.[2] Prentice et al. clarify that a surrogate end-point is 'a response variable for which a test of the null hypothesis of no relationship to the treatment groups under comparison is also a valid test of the corresponding null hypothesis based on the true end-point'.[3]

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Surrogate markers are quantitatively related to tumour burden in all sites. Ideally, they should not be affected by subclonal heterogeneity, and they should be assessable even at low tumour burdens. When selecting possible surrogate markers as clinical trial end-points, investigators should weigh several important criteria in order to collect data that will be relevant and sufficient for subsequent licensure or registration of the anticancer agent. First, is the potential surrogate biologically associated with the true end-point? Second, is the treatment somehow associated with the potential surrogate end-point? Third, does the potential surrogate mediate the treatment's effect on the true end-point and is the potential surrogate biologically associated with the true end-point?[4]

Under some circumstances the use of a surrogate end-point might be misleading. For example, even with known perfect correlation within randomized groups, one cannot rely on the potential surrogate end-point for valid inference about the true end-point, because even the direction of their effects could be opposite.[5] Thus, even in preliminary trials, investigators should not base conclusions on potential surrogate end-points if the validation is based solely on high correlation with the true end-point.

In conclusion, we must agree on new rules that will allow us to accept biomarkers at early stages of new drug investigations. These biomarkers must correspond with some clinically relevant measure, and their use must comply with the usual statistical tools acceptable for new drug registration or licensure. The best sort of trial to select and validate surrogate end-points is a comparative prospective trial that (1) determines the mean difference and variance in the surrogate when the experimental and reference groups are compared, and (2) predicts the mean difference and variance in the ideal true end-point when the experimental and reference groups are compared. Such a trial might not save time or spare patients, however, compared with a trial based on conventional end-points.

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BIOMARKERS: TRANSLATION INTO LABELLING LANGUAGE

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Drug development has progressed to the age of individualisation. Therefore opportunities exist for applying biomarkers in this new paradigm. Several definitions of relevant terms have been proposed by the Biomarkers Definitions Working Group of the National Institutes of Health (NIH) and the U.S. Food and Drug Administration (FDA):

- A biological marker (biomarker) 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'.[3]
- A clinical end-point is 'a characteristic or variable that reflects how a patient feels, functions or survives'.[3]
- A surrogate end-point[4] is 'a biomarker that is intended to substitute for a clinical end-point. A surrogate end-point is expected to predict clinical benefit or harm (or lack of benefit or harm) based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence . . .Although all surrogate end-points can be considered biomarkers, it is likely that only a few biomarkers will achieve surrogate end-point status'.[3]

Pharmaceutical manufacturers, clinical investigators, and regulators rely on different types of biomarkers in the context of drug development. *Diagnostic biomarkers* provide the means to define a population with a specific disease. *Prognostic biomarkers* correlate with outcomes. For example, over expression of her-2/neu in breast cancer or epidermal growth factor receptor (EGFR) expression in colorectal cancer indicates poor prognoses. In addition, tumour size, often assessed with radiographic tools, is a prognostic marker because it correlates with outcome. Such prognostic markers are frequently the basis for establishing inclusion criteria for a clinical trial or for defining a patient population. Predictive biomarkers define populations that might respond more favourably to a particular intervention from an efficacy or safety perspective. They can be used to stratify patients for subgroup analyses. *Surrogates* are biomarkers that correlate with clinical benefit and changes in the marker correlate with alterations in

outcome. Examples include response rate or progression-free survival in oncology or bone mineral density in osteoporosis prevention and treatment. If validated, a surrogate may serve as a primary end-point in a pivotal registration study and could support conditional (European Union) or accelerated (United States) approval of an anticancer agent. In general, pharmaceutical firms should routinely engage in discussions with regulators early in the drug development process.

The critical path initiative (Fig. 1) of the FDA aims to stimulate and facilitate a national effort to modernise the scientific process through which a potential human drug, biological product, or medical device is transformed from the discovery or proof-of-concept stage into a standard therapeutic or diagnostic product. The focus of this initiative is to update the evaluative tools currently used to assess the safety and efficacy of new medical products, including the validation and use of biomarkers in clinical trial patient selection and as surrogate end-points.[4]

CHALLENGES OF USING BIOMARKERS: Regarding the use of biomarkers many questions remain, among them: How good must the validation be before a biomarker can serve as a basis for clinical decisions? Is it necessary to validate the technology used to determine the biomarker and its medical relevance? The FDA is presently analysing a co-development model by which a drug could be approved along with the relevant biologic assay. Will greater market segmentation be the end of the blockbuster business model? Cytotoxic oncology agents are used in broad patient populations, but molecularly targeted therapies would be effective only for particular subpopulations. How much will validation cost? Early discussion of biomarkers seemed to indicate that their use might allow cost savings in clinical trials, but now it appears that early drug development phase costs might be increased (Fig. 1).

Several key questions must be answered to exploit the full potential of biomarkers in drug development from a labelling perspective: to what extent do the primary or secondary objectives of a protocol determine or limit the indicated patient population? How much influence does the protocol design and analysis have on the decision to include biomarker information in either section 'Indication' or section 'Pharmacodynamics? Answers to these questions impinge on stratification and *pre-specified* subgroup analyses and could affect labelling language.

EXAMPLES OF SUCCESSFUL BIOMARKER DEVELOPMENT: Targeted therapy has an effect on the size of clinical studies and safety databases. Trastuzumab (Herceptin®), which binds Her-2/neu and blocks its function, is an example of an efficacy target. Validating the target-biomarker-antibody relationship involved a great deal of effort because the initial diagnostic test was somewhat ineffective. Once the marker was validated, however, only patients whose tumours over expressed Her2/neu (about 20–25% of invasive breast cancers) were enrolled in the phase III trial. Consequently, only 470 patients were required; if subjects had been accrued from the general patient population, an estimated 2200 subjects would have been necessary. Significant benefit was demonstrated in 1.6 years of follow-up instead of about 10 years. The response rate in this subpopulation was 50% compared with about 10% in the overall patient population.[1]

Also an example of a biomarker used as a safety target exists. Irinotecan (Campto®), which is approved for treating metastatic colorectal cancer, was found to cause grade 4 neutropenia in about 8% of the general patient population. Subsequent data have shown that uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1) affects the drug's metabolism and, therefore, its toxicity profile.[2] The *UGT1A1*28* polymorphism, characterised by an additional TA repeat in the TATA sequence of the *UGT1A1* promoter, was associated with greater toxicity.[2] Consequently, the drug's label was modified to reduce the starting dose for patients homozygous for the polymorphism.

In summary, a biomarker and its corresponding assay must be validated before phase III to be useful in reducing trial size. Efficacy targets might allow patient accrual numbers to be decreased, but safety targets will not. Safety targets might require additional subpopulation analyses. The value of interim analysis should not be overlooked. Although usually conducted when 80% of events have occurred, carrying out the interim analysis when only 60% or 70% of events are completed may be of great value. Proper interim analyses could confer benefit by allowing trials to be concluded earlier, thereby speeding the drug to market and reducing costs associated with clinical trials.

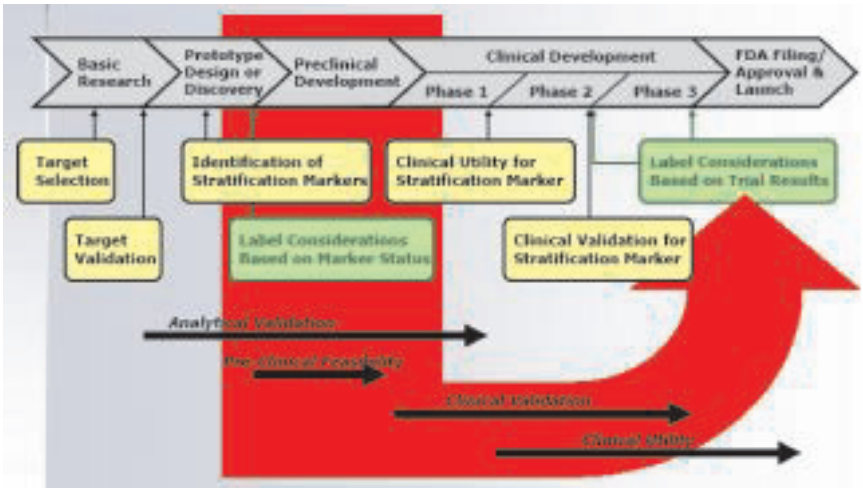

Fig. 1 – Role of biomarkers in the US FDA's critical path initiative for drug development.

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