nature medicine

A taste of new medicine

In 2004, the US spent a whopping $100 billion on basic research and drug development. The number of drugs actually approved: 22, a 20-year low.

Clearly there's a problem here.

There are changes at the US Food and Drug Administration (FDA), however, that are cause for some optimism.

In 2004, the FDA launched the Critical Path Initiative, intended to promote research into ways to help drugs clear the hurdles of demonstrating efficacy and safety more quickly and cheaply. The initiative's latest report, released in March, includes projects to speed drug development, such as developing better disease models and developing surrogate markers to measure drug efficacy more quickly. But the most far-reaching and revolutionary aspect of the report is the FDA's embrace of the idea that the way to get more drugs approved is by tailoring therapy to each patient.

There are probably many reasons for the dearth of new drugs. But a big one appears to be the increasingly stringent regulatory requirements. These are even more stringent for chronic diseases, for which therapy must be given over long periods of time. In the current climate of public distrust of pharmaceutical companies, regulatory agencies such as the FDA have very little tolerance for any adverse effects.

But the biological reality is that absolute safety cannot be achieved. Human beings are genetically highly diverse and have widely differing responses to drugs.

Tailored therapy proposes to overcome these obstacles by developing biomarkers to predict drug efficacy and safety in each patient. This approach has obvious appeal from a scientific point of view and has been trumpeted over the past several years, but turning the pipe dream into reality has been far from easy. To be sure, there are already some examples of tailored therapies, particularly in cancer treatment—such as testing the estrogen receptor status of women with breast cancer to determine whether they should receive tamoxifen. But the FDA's leadership can make a big difference in accelerating the development of tailored medicine, not least because any predictive tests used will ultimately need to be approved by the FDA.

The Critical Path Initiative endorses research to develop biomarkers for tailored therapy, for example, using imaging, genomics, proteomics or metabolomics technologies. Some concrete steps have already been taken. The initiative's first project will develop and clinically validate genetic markers for the correct dosing of the anticoagulant warfarin. In March, the FDA announced that it would work with a consortium of five large pharmaceutical companies and the Critical Path Institute—a privately funded organization launched in part to support the initiative—to develop biomarkers for predicting safety in preclinical tests, and to recommend these to the FDA.

Although tailored medicine might increase the number of drugs that make it to market, how it will affect the drug-making business seems unclear. Drug approval might be made faster and cheaper, but the number of patients that can be treated by any particular drug will be smaller. Will this threaten the development of billion-dollar blockbuster drugs, and can big pharma survive without them? Will tailored medicine open up new opportunities, such as in biomarker tests, which can compensate?

The FDA may also be showing new flexibility in approving drugs that have serious safety risks but for which there is a strong medical need. After an outcry from patients, an FDA advisory panel recommended that Tysabri, which has been linked to two deaths, be approved with some restrictions (*Nat. Med.* **12**, 373; 2006).

The availability of tailored therapies or drugs with serious safety risks, such as Tysabri, means that some responsibility for weighing the risks and benefits of drugs will shift from the FDA to patients and their doctors. The FDA will need to make serious efforts to communicate the risks and benefits of drugs. Even when the risk-benefit ratio is extremely clear-cut, this can pose problems. For instance, in the case of Accutane, prescribed for disfiguring acne, the FDA continues to struggle with effectively preventing its use by pregnant women, as it can cause miscarriages and severe birth defects.

The adoption of a more scientific approach to drug development will not happen overnight, but we welcome the FDA's leadership in moving toward this goal.