Resourcing Drug Development Commensurate With its Public Health Importance

The Road Ahead*

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Cardiovascular (CV) disease remains the leading cause of death in the United States and worldwide, and remains an enormous disease burden (1). Despite this fact, the investment in CV drug development has decreased over the past 2 decades relative to other therapeutic areas such as oncology (2). These trends are concerning and raise the question of whether regulators, other government entities, industry, and academic investigators should rethink the approach to the science we need to reduce disease burden in this enormous cause of global death and disability.

In this issue of JACC: Basic to Translational Science, Hwang et al. (3) demonstrate that the volume of new drugs entered into cardiovascular clinical trials has diminished over the past decade relative to many other fields. However, the number of novel drugs entering Phase 3 trials increased over time. Discontinuation of drug development programs was primarily due to inadequate efficacy, and only 24% of development programs that were discontinued were stopped due to safety concerns. They use data from a large commercial database that tracks the pipeline of pharmaceutical research and development, examining products entering Phase 1 trials from January 1990 to December 2012, with 4,715 products meeting this criterion. The most common CV products being developed were antihypertensive agents, followed by lipid-lowering agents and anticoagulant agents. They found the rate of new CV products entering Phase I trials diminished from 16% of all products in development in 1990 to 1995 to just 5% of all products in development in 2005 to 2012. The number of actual new starts declined, too, from 18 products/year to 13 products/year over that time frame. Interestingly, one-half of the drugs entering Phase 3 were targeting a novel biological pathway, which is a trend that increased over time (p = 0.004 for linear trend). This is encouraging because it indicates a priority for truly novel targets in drug development.

This trend towards less relative investment in CV drug development has been previously reported, and a number of issues were addressed in a meeting of experts convened in 2015 (2). As described in the summary paper, the issues are multifactorial including rising drug development costs and perceptions about the concept of “regulatory uncertainty.” The challenge is finding a balance between the imperative to generate evidence to ensure that new drugs entering the market meet a reasonable standard for safety and effectiveness, yet weighing the burden of cost and efficiency that may push investment in innovation into other therapeutic areas. There was a viewpoint that given the large number of beneficial therapies in CV disease, the stringent requirements for demonstration of benefit in clinical outcomes, although justified, may be pushing drug developers to areas in which smaller trials with less stringent clinical outcome measurements are required.

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It has been suggested that we can “reduce regulatory uncertainty” (4). But what does this actually mean? Because the FDA’s mission includes promoting and protecting the public health by assuring the safety, efficacy, and security of human drugs, and the agency is held to a certain evidentiary standard in approving drugs, simply reducing the sample size or using unvalidated biomarkers for regulatory decision making when determining the balance of benefit and risk has not been a feasible approach for diseases in which so many effective therapies are already available. For the large CV diseases and their proximal risks, there is much to lose if unvalidated putative surrogates are used, only to be proven invalid after marketing to millions of patients and their providers. Indeed, many of the large, failed Phase 3 programs in CV drug development were supported by substantial evidence of favorable effect on key biomarkers that in general have been accepted surrogates, such as blood pressure, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol and hemoglobin A₁C (5–7). Unfortunately, in these cases, the benefit predicted by the improvement in the surrogate was not achieved, either because of lack of efficacy or severe off-target toxicity when the larger trials have been conducted. Perhaps we should focus on improving our evidence generation system so that we can generate reliable evidence in a more efficient fashion. In this age of dramatic advances in information technology, there will be a number of opportunities for generating evidence using integrated health systems and networks of information (8).

It may also be worthwhile to consider the relevant differences between the development of drugs in oncology versus cardiovascular therapies. Advances in cancer biology have led to the dissection of cancer into many small diseases, and many types of cancer either have no effective treatment, or initial effective therapies are just now being discovered. This dissection leads to some fairly cause-specific therapies and molecular targets. Because of the paucity of effective therapies, as targeted therapies are discovered with promise of a very large treatment effect size, we accept more biomarker-based approval, less confidence in the evidence of benefit, and higher uncertainties about safety. We also generally accept higher demonstrated safety risks, including, ironically, cardiotoxicity. Thus, development programs in oncology are generally smaller and less expensive, and the value placed on targeted therapies has allowed sponsors to recoup the costs by charging a lot to a few, although this pricing approach is increasingly under scrutiny.

Importantly, the focus of this paper is on cardiovascular development in the “big problems” like “essential” (idiopathic) hypertension and primary (NOS) hyperlipidemia, and final-common-pathway heart failure—w ith big populations and multiple effective therapies already on the market, many of which are now generic. Currently marketed therapies are well-described with highly acceptable toxicity profiles, so new therapies must compete with these well-established therapies, making safety databases large (routinely about 100-fold as large as it takes to work up the dose-response on blood pressure). So, even though treatments for hypertension and lipids have garnered initial approval based on biomarkers, the programs have been substantial in order to prove clinical outcomes (2). It is worth noting that the regulatory approach to targeted therapy within CV disease has been similar to other diseases as witnessed by the rapid approval of PCSK-9 inhibitors for familial hypercholesterolemia. Within the cardiorenal portfolio where there is clearly an unmet need or where available therapy carries risks, biomarkers have been accepted—for example, electrolyte disturbances or glomerular filtration rate—with less qualifying evidence than we have for blood pressure and LDL, and very large trial sizes for individual drug development programs have not been required.

For post-myocardial infarction/heart failure development, the clinical outcomes are tangible with clear evidence of life-saving effects from a number of available therapies, and the landscape is littered with bones of development programs whose effects on biomarkers turned out much better than did effects on those clinical outcomes (9,10). In addition, it is generally the case that a new therapy must be studied on top of “standard medical therapy,” typically guideline-directed therapy which has proven very effective (11–16). These factors also contribute to large development programs being required. It is worth noting that for epidemic diseases, a modest treatment effect spread across millions of patients can have a profound benefit for the public health, but this same concept means that a modest detrimental effect can cause significant harm to individuals and overall population health.

The empirical findings of this study raise interesting issues about the future of drug development. The steady attrition of molecules in each of the main phases of development reminds us of the need to understand better how to predict likely efficacy and toxicity. The continuing attrition in Phase 3 raises the issue of whether Phase 2 trials could be better designed to inform Phase 3 studies, ensuring that the mechanism and dosing are well defined, as well as
specific subgroups identified which may derive the most benefit from treatment to ensure the highest chance of success in Phase 3—or how often unwar-
ranted optimism drives development following nominally failed Phase 2 studies. One interesting point is that the failure rate in CV disease does not appear to be higher than in other diseases, so perhaps it is not the “uncertainty” that is an issue, but rather the fact that the evidentiary standard requires large, global trials that is holding back investment. Several other recent papers have found that CV drugs are no more likely to fail during or after Phase I than other disease areas (17).

Another challenge is the complex clinical management of comorbid conditions. It is difficult to separate new CV targets without the overlap of existing therapies on those pathways, or to distinguish specific CV targets from comorbid influences. In this regard, it is encouraging to see an increase in developing therapies with novel biological pathways. Oncology is beginning to enter a similar phase in which the combination of multiple targeted therapies and immunotherapy raises concern that stand-alone therapy is not a good approach to either practice and that clinical trials of stand-alone therapies may not provide information needed to appropriately label drugs for use in an increasingly complex clinical environment.

Recent regulatory science publications have pointed out that drug development typically follows new science that unveils molecular targets, so that continued deep basic research in CV disease is critical. On the clinical research front, research should continue to focus on clinically meaningful endpoints and development of methods to measure them in a scalable, less expensive fashion so that the evidentiary standard can be met with a reasonable investment. As our ability to access information continues to evolve, we can improve efficiency when large sample sizes are needed by using information already collected in electronic medical records, registries, and medical billing claims to generate evidence which may lead to the validation of such endpoints.

The combination of deeper molecular science and enhanced, more efficient, evidence generation may make it possible to discover markers that correlate with clinically meaningful improvements and novel targets, and more importantly, fulfill criteria for sur-
rogacy—a change in the marker reliably predicting a difference in clinically meaningful outcomes. These advances may also allow use of multiple data elements to support a systems biology approach to treating patients, so that perhaps more targeted patient cohorts may be recognized for targeted therapy rather than casting a broad net for a therapy that may work in a smaller subset.

The clinical, scientific, and economic foci of drug development for targeted therapies for diseases affecting smaller populations have led to more relative investment in these areas than in CV disease drug development. We have several options to consider if more investment is considered to be an important goal in CV disease because of its enormous global toll. Because drug development follows science, continued investment in the basic biology of CV disease is needed, and because large populations are impacted, attention to improved efficiency of the evidence generation system will be needed to generate needed sample sizes for definitive trials at a lower cost. Finally, involving the full community including industry, the National Institutes of Health, academic experts, funding agencies, regulators, practitioners, and patients will be an important step in strengthening the science and advancing the field.

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