Controversies

March 23, 2017

Barry Blackwell: Corporate corruption in the psychopharmaceutical industry

Charles M. Beasley's commentary

As someone who has spent his entire medical career in the pharmaceutical industry, I have followed Barry Blackwell's original essay, Corporate Corruption in the Psychopharmaceutical Industry, the Comments, and replies to the Comments with angst. Thanks to an integration of the sequential documents provided to me by Tom Ban, plus the latest Comment as of the time I began writing this Comment (December 13, 2016), by John Nardo on December 8, 2016, I believe there have been 12 submissions extending to more than 120 printed pages (based on printing the file of integrated sequential documents that Tom sent me).

Based on my concern that any Comment that I might make that would reflect favorably on the industry (even if some Comments on my part did not reflect favorably on the industry) could easily be viewed as biased, I quickly decided not to contribute any Comments to the ongoing and lively discussion. In early November, I received an e-mail from Carlos Morra with copies to Tom and Barry inviting me to submit a Comment as a person who had spent his medical career in the pharmaceutical industry. I have had several conversations with Tom about this matter and did agree to submit some Comments.

For a more thorough disclosure, I joined Eli Lilly and Company immediately following completion of my residency in psychiatry and was with Lilly for almost 28 years before retiring at the end of April 2015. The first two-thirds of my time with Lilly was spent in Phase 2-4 development of drugs, primarily with psychiatric indications. The latter third of my career was spent as a special consultant working in drug safety across all therapeutic areas. This work entailed directing the in-depth assessment of a number of complex questions regarding specific safety matters for individual drugs, reviewing safety analyses and interpretation for many of the company's potential new products, and working with my statistical and data science colleagues to develop standardized methods of analyses and presentation for integrated analyses of multiple studies for potential new products. As is probably well known to most, Lilly pleaded guilty to a misdemeanor criminal charge for off-label

promotion of olanzapine (a drug with which I was much involved in its development for the first indication of schizophrenia before being moved on to other duties). Lilly was fined $1.415B.

I will not disagree with the assertion that pharmaceutical companies have engaged in actions that are corrupt as have prominent academic researchers, within psychiatry and other scientific fields, with fake data, sometimes for direct financial gain. The most extreme example is that of one individual who pleaded guilty to 36 criminal counts, including 18 counts of theft by taking, 10 counts of theft of services, seven counts of false statements, and one count of violating his/her state's Racketeer Influenced and Corrupt Organizations (RICO) Act. She/he was sentenced to serve 15 years in prison, followed by 15 years' probation. He/she was also fined $125,000 and ordered to make restitution of $4.26M. Corrupt behavior is inexcusable whether it is on the part of an organization or an individual.

I decided to limit my Comments to four areas, the first two being quite related. First, I will discuss the cost of drug development for a new chemical entity. Second, I will discuss the differences in cost of development for generic small molecule drugs (as opposed to biosimilar biological drugs, the technical term for the conceptual equivalent of a generic biological drug) and an evolving trend in pricing of generic small molecule drugs that has received little attention save for the most extreme examples of the points I will make. Third, I will offer some suggestions pertinent to journal editor consideration of manuscripts describing the results of randomized clinical trials (RTCs), or any clinical trial, that would serve to enhance further and ensure transparency, unbiased, and full disclosure of trial results. These suggestions apply to trials of potential treatments in all areas of medicine, are particularly relevant to Phase 2-4 industry conducted trials, but might well apply to non-industry conducted trials as well. Finally, I will briefly mention how potential investigators in RCTs can contribute to enhancing the objectivity and clinical usefulness of data obtained from RCTs that include active controls.

Barry discusses the cost of development in his essay in a subsection titled "Inflating Cost and Extending Patents." He notes the amount of $802M developed by the Tufts Center for the Study of Drug Development (CSDD). CSDD has periodically conducted this research and published the results in the academic literature. The $802M estimate was from results published in 2003. Barry suggests that the estimate of Marsha Angell of $100M (published 2005)[i] is probably more accurate. He notes that in constructing her estimate, Angell used a variety of sources (data), including that from

the Public Citizens Advisory Group. He indicates that the CSDD methods are not fully described and that data used to construct the estimates are not publicly available. In addition to citing Angel to dispute the high estimated cost of development by CSDD, he notes that the CSDD is " . . . largely supported by the pharmaceutical companies . . . " I have no way of knowing what proportion of the funding of the CSDD funding is provided by the industry or other sources. I would point out that even if pharmaceutical companies are corrupt, the fact that the CSDD is funded by the industry does not offer strong evidence that the estimates of development costs by the CSDD are intentionally or unintentionally biased to favor industry positions. The CSDD estimates should be judged on methods employed, preferably by those with substantial health economic expertise with no personal stake in the results of the computation.

As said above, the CSDD periodically updates these estimates. I believe it is inaccurate to describe the methods used to arrive at the estimates as not well described or hidden in a "black box". The methods are described in an academic manuscript, 34 pages in length (quite long for the specific journal and academic journals in general), in which the $802M estimate was reported.[ii] The methods are also summarized on the CSDD website.[iii] It is true that 1) the R&D cost data were for a select set of compounds and 2) that the pharmaceutical companies provided these R&D costs for the selected compounds. However, it is important to note that the sample of compounds was chosen at random from the CSDD database of investigational compounds. Given this description of compounds, I doubt bias in choice. About R&D costs provided, it is certainly possible that the companies lied about these costs and inflated them. Personally, I doubt such corrupt behavior. Figures could be roughly checked against annual corporate financial statements that are available as public records, adjusting for all compounds in development that could be estimated from public disclosures. Of course, these balance sheets in annual reports could be faked/inflated as well. I will say more about R&D spend costs used in estimating development costs below.

I will not detail the arguments that Angell puts forward to refute the CSDD estimates of drug development costs in Chapter 3 of her 2005 book,[1] nor the counter arguments. As per Blackwell, Angell does favor estimates based on Public Citizen computation. CSDD has developed an extensive critique of the methods of Public Citizen (and the methods of Tuberculosis Alliance)[iv] and as perhaps would be expected claims major faults with these two computations. I cannot affirm who is right and who is wrong. I am not a trained health economist researcher. I happen to give more credence to the CSDD estimates. I do firmly believe that when affirming that Angell and/or Public Citizen estimates

are correct than those of CSDD; the arguments put forward by CSDD in support of their estimates[4] should be acknowledged and fully discussed.

The most recent (for costs as of 2013, results released in 2014, published academic manuscript 2016) CSDD estimate is $2.558B.[v]

In 2012, two Forbes Magazine authors computed an estimate.[vi] These authors used: 1) a count of drug approvals for the "major pharmas" (criteria not defined but included but included data for 12 multi-national companies); 2) R&D spending as reported in annual earnings filings pulled from a Thompson Reuters database using FactSet (InnoThink Center for Research in Biomedical Innovation – Thompson Reuters Fundamentals via FactSet Research Systems) for 15 years (extending back to 1997); 3) adjustment for inflation. The estimated average was "at least" $4.0B with considerable variability across the companies and ranged up to a high of $11.8B for one company (range: $3.7B - $11.8B). While this estimate is not contained in an academic, peer-reviewed publication, the method of computation was quite straightforward. As above, the methodology did rely on cost data supplied by the companies. Did they lie in their annual securities reports? The number of approvals is a straightforward figure. Using total R&D costs would include the R&D costs for Phase 4 studies and other necessary post-approval research activities, so the Forbes work overestimates the cost of bringing a new chemical entity to market for a first indication. Another matter that could confound these estimates is whether the authors considered only first approvals for new chemical entities or also included line extensions of approved drugs such as alternative formulations (e.g., an injectable formulation of an approved oral medication), approvals for new indications, etc. in their count of approvals. The authors do not clarify this matter. Including all approvals would account for funds spent on line extensions (less than cost of first approvals for new formulations but can be variable for new indications relative to first approval for the first indication). With regard to factoring out costs of Phase 4 research and other necessary post-approval research, the CSDD group, in their 2016 manuscript estimated an additional 12.2% average R&D spend on such post-approval R&D activities (pre-approval: $2.558B, total: $2.870B).

Multiple criticisms of the CSDD estimate have generally not appeared in academic, peer-reviewed published manuscripts. The one exception to this statement regarding publication of criticism of CSDD estimates is the critique of Avorn published in the NEW ENGLAND JOURNAL

OF MEDICINE[vii] but this was not a research-based critique, and the concerns raised by Avorn were addressed in response by the CSDD researchers.[viii]

A 2011 academic manuscript[ix] systematically reviewed academic publications estimating the cost of drug development. This work included 13 publications with the earliest period of estimation being 1963-1975 and the latest being 1995-2010. The authors' adjusted estimates from each publication to a 2009 estimate and provided both a cash estimate and a capitalized estimate (capitalized estimates are higher and favored by the CSDD group with the reason for this explained in their publications). Among the 13 publications was the CSDD estimate publication from 2003 described above. These authors reported a range of 2009 capitalized estimates of from $161M to $1.8B (several substantially higher than the 2003 estimate for the CSDD estimate that converted to $993M for 2009 from the reported $802M).

I believe in the high side estimates of the cost of bringing a new chemical entity to the position of being a new drug. All readers will need to draw their conclusions. I do suggest that in drawing conclusions a great deal of complex data and methods must be objectively considered.

Assuming any give estimated the cost of development, what price is justified for a medication that has cost a considerable amount to bring to market, especially when the chances of success in development with an individual molecular entity that makes it out of the synthetic laboratory of the pharmaceutical chemist is quite low? The price that is justified is a question that I cannot answer and one with which society must struggle. I believe that the realities are that given the low probability of individual molecule success, high and progressively escalating costs, drug development within a capitalist economy will likely need stable if not progressive increases in return on investment to stimulate innovation. While altruism can stimulate innovation, I suspect that profit motive is the stronger and more common stimulus, particularly when the innovation requires complex large, complex organizational systems to bring the innovation to the point of being available to the public. While a brilliant individual scientist, or small group, might discover an innovative treatment, the processes and work needed to turn that discovery into an approved drug are multi-faceted within diverse areas of expertise and extremely time-consuming given current regulatory expectations.

Could we reduce drug prices if all development were handed over to a government entity, presumably with no need for profit? I do not know the answer to this question, but I do not believe that such a move would reduce development costs and these costs might actually increase due to the

unwieldy and inefficient processes of bureaucracies. Needless to say, I harbor negative opinions that can be considered as biases regarding the efficiencies of government organizations working in some areas. I outline below some of the factors that I believe contribute to the increasing costs of development.

Factors potentially contributing to rising costs of development based on my personal observations:

1. The conditions requiring first treatments or substantially improved treatments are increasingly resistant to innovative discovery: For whatever reasons it is proving tough to find a treatment that will substantially slow or stop the progressive cognitive and functional decline associated with Alzheimer's Disease compared to substantially but not necessarily completely reducing the positive psychotic symptoms associated with schizophrenia (in only a substantial proportion of patients diagnosed with schizophrenia).
2. The nature of the studies required to demonstrate efficacy of a potential new treatment for those conditions in great need of treatments is growing more complex and lengthy: Assuming a quality study without excess placebo response, the efficacy of a D_2 antagonist in the treatment of positive psychotic symptoms can generally be demonstrated in a study of 4-6 weeks duration with between 50-100 subjects receiving active treatment and a comparable number receiving placebo. To show the efficacy of a compound in slowing or stopping the progression of cognitive decline in Alzheimer's Disease, the required length of the study is likely to be on the order of two years with a substantially larger number of subjects than in studies of positive psychotic symptoms. While this point is not applicable to all conditions in need of treatments, I believe it applies to many both within neuropsychiatric conditions and in conditions within other medical fields. So, for example, in the domain of cardiovascular disease related to atherosclerosis, demonstration of a positive effect on some physiological factor thought to contribute to atherosclerosis (reduction in LDL, increase in HDL, etc. – biomarkers [efficacy surrogates]) is insufficient. A reduction in Major Adverse Cardiovascular Events (MACE) must be demonstrated. Such studies can require multiple thousands of subjects per treatment arm and run for two years per individual subject (three-five or more years if needing to recruit many thousands of patients). While these studies are generally enriched with high risk subjects, if the base rate of events of interest in the placebo-treated group is less than expected in determining sample size and length, a very costly study

can fail, even with an effective treatment, because of too few cases of the adverse outcome of interest in the placebo-treated group. Novel study designs and statistical methods can speed up and reduce the size of such studies but only to a limited extent.

3. Progressively increasing expectations for additional studies related to various aspects of potential drug effects over and above efficacy: These expectations are primarily in the domains of toxicology, drug metabolism, clinical pharmacology, and safety in patients. Two examples of such requirements are:
    a. the need to affirmatively demonstrate that a new hypoglycemic agent is not associated with excess MACE events demonstrate (non-inferiority analysis, generally a meta-analysis of multiple long-term studies);
    b. for all small molecules and some biologics, demonstrate that the drug candidate is not associated with a mean change in QTc that might suggest some risk for induction of Torsade de Pointes (TDP) although on a population basis TDP is an extremely rare event even with drugs that do delay ventricular repolarization – the so-called Thotough QT (TQT) Study.

    Both requirements are expensive, particularly the hypoglycemic agents' study with respect to the number of patients and time of observation needed. Based on personal familiarity, the TQT Study would cost between $6-20M in external spend only (I cannot estimate internal spend) some 5 to 10 years ago. I am not suggesting a debate on the wisdom of such requirements from a public health cost-benefits perspective. Personally, I have always advocated a conservative approach to knowledge acquisition that might keep a small number of patients safe, irrespective of the cost. However, we must be aware that such requirements, in aggregate, do drive up development costs and risk for bringing a product to market.

I want to turn to an important distinction between development costs and risks with new chemical entities and generic versions of these drugs, specifically with respect to small molecules (easily synthesized/copied in comparison to the development of a biosimilar). There is no risk in the development of the generic product, assuming competence in chemical manufacturing, fill-finishing, and quality control along with all the required documentation procedures. We are all aware of the most egregious examples of old generic drugs with little total use in the marketplace and therefore virtually no competition between generic manufacturers being exorbitantly priced, sometimes at prices

exceeding the branded product when released. This exorbitant price practice, from my perspective, is clear price gouging and profiteering. While I tend to be a strong believer in free enterprise and lack of government control of the pricing of anything, such practices cause me to doubt my beliefs. For some companies engaging in this practice, there was no risk or cost of development (rights acquired), and for other companies engaging in the practice, while there were risks and development costs (original branded drug developed by the company), substantial profit has already been acquired through the sale of the branded drug.

The following comments are probably only applicable in countries without pharmaceutical price controls where parties other than a government entity is buying medications from the manufacturers. While readers might be aware of the following, I want to briefly describe what I view as an almost equally disturbing trend in the pricing of generic drugs. It is perhaps more disturbing because it is less obvious than the extreme examples alluded to above but might be more impactful on the cost of health care. I believe that there is a growing trend for at least a substantial number of new generic drugs with only moderate population-based use to be priced at a substantial proportion of the price of the original branded medication. Therefore, there is not the substantial price drop that one might expect.

I am citing a personal example to illustrate the point. I take several medications on a chronic basis. The "retail" price at my pharmacy for one medication that has been generic for many years with multiple generic manufacturers (prevalence of condition under treatment is quite common in the US) is $142.19 for a three-month supply at the maximum approved dose. The "retail" price for another generic medication that I take that has been generic for only about two-three years and where the prevalence of the condition under treatment is in the range of 20-60 per 100,000 (two additional FDA approved indication for this medication and some additional off-label prescribing increase total use) is $5256.19 for a three-month supply at the maximum approved dose. I am providing "retail" prices reported by one large national pharmacy chain. I do not have "retail" prices available to me for the original branded drugs. I cannot compare generic to branded price. However, it is clear that the price of the second medication is substantial in absolute terms and many-fold that of the first medication.

I cannot be certain that the cost of bulk manufacturing of the second drug is not substantially more than that of the first drug, but I doubt that it is 37-fold greater (ratio of "retail" costs). The

chemical structure of the second drug is not complex. In attempting to track down the bulk manufacturing costs of the second drug, I met with problems. US-based chemical supply houses supply only analytical samples of the drug, and therefore these costs provide no basis for estimation of bulk manufacturing costs. While I could find small bulk quantities (the largest amount equivalent to several thousand days of therapy) offered by non-US providers I considered the sources potentially questionable with regard to quality/purity and therefore am uncomfortable with comparing generic drug price to bulk price based on these available prices.

I have prescription insurance and pay approximately 10% of the "retail" price claimed by the pharmacy for both these drugs. What is unknown to me is the price paid by the wholesaler to the manufacturer, the wholesale price paid by the pharmacy chain to the wholesaler, or the amount paid by my insurer after negotiating a large quantity price discount with the pharmacy chain. How much actual profit and which entity might be making that profit is quite unclear. That claimed "retail" price of $5256.19 might have little relationship to the price paid by my insurance provider and sequentially back up the line to the generic manufacturer. Based on the ratio of my out-of-pocket costs to the "retail" price for these two drugs, that "retail" price does appear to have a relatively direct relationship to my out-of-pocket costs.

This might be a growing trend with drugs becoming generic and might remain with little notice if the generic product is at least somewhat below the price of the original branded product paid by major payers (i.e., insurance companies) because these major payors will still reap the benefits of generic entry into the marketplace that can be substantial on a population basis. Individuals who are completely self-pay and individuals who are taking medications where the prices of the branded originals were relatively high will still be faced with substantial cost after the introduction of the generic product under such a scenario. With no development risk, such a potential scenario where the generic product is not inordinately expensive to manufacture in bulk yet is priced relatively close to the price of the original branded product. I would also view as profiteering. Profit is being made without risk in development and based on the innovation of others. If this is a growing trend, one does not have to invoke the notion of overt conspiracy or active collusion on the part of generic manufacturers to understand its development. It takes little thought to conclude that if some reasonable degree of savings is being offered to major payors with a generic product coming into the marketplace, those major payors might not complain too loudly.

Here are some thoughts on how journal editors can further act to ensure high quality and objective reporting of the results of Phase 2-4 RCTs. The virtually universal requirement that for the results of any RCT to be considered for publication, the RCT had to be registered in ClinicalTrial.gov has done much to improve objective and full reporting of results. I believe that editors could further enhance this completeness and objectivity by requiring sponsors/authors to submit two documents along with the draft manuscript reporting results: 1) the full and last (with all amendments) protocol version; and 2) the Statistical Analysis Plan (SAP) that will usually have been developed to accompany the protocol. The protocol will describe the conduct of the study in detail and make explicit all efficacy and safety assessments that were conducted and when they were conducted. A SAP will exist for many if not most RCTs, particularly those supporting regulatory approval. It will usually lay out in detail the basis for the sizing of the RCT (if not detailed in the protocol). It will specify which analyses are considered primary, secondary, and exploratory and the hypotheses evaluated by the analyses (if not detailed in the protocol). Finally, it will detail all the a priori analyses to be conducted and the details of methods for these analyses. Importantly, the SAP will specify any adjustment for multiple comparisons and any "gate-keeper" strategies for the conduct of sequential multiple analyses with or without adjustment. A final SAP might not be completed until after study completion but will almost certainly have been completed before study data have been locked and unblinded to those persons conducting the specified analyses. Review of these documents in parallel with the review of the manuscript describing results can easily help determination of completeness and objectivity of reporting in the manuscript. Review of the SAP and protocol can allow determination of the appropriateness of the analyses and their methods. Such a review would not be a necessarily quick process. Current RCT protocols can exceed 100 pages in length of single space print, and SAPs can be longer. However, critical information pertinent to questions regarding objectivity and completeness can be spotted with some first-pass skimming.

Some individuals have suggested that all RCTs should be subjected to independent analyses by 3rd parties. My view is that this is unnecessary if the analyses and the methods described in the SAP for a study are complete and appropriate for the data and manner of the collection in a study as determined by reviewers, particularly statistical reviewers collaborating with clinical reviewers. While errors can be made in programming analyses that are pre-specified, I doubt that sponsors intentionally "fake" analyses or "make up / alter" data. In this age of complete data sets[x] submitted in a well-defined set of databases for easy confirmatory analyses by FDA along with substantial site

auditing by FDA, intentional malfeasance would be very complicated to orchestrate, and the potential for getting caught would be high. My greater concern would be willful malfeasance on the part of one or a small number of investigators in a large RCT hoping to curry favor with the sponsor or even with other more sinister motives. I could be wrong on both counts of course.

Potential investigators can contribute to objectivity in the conduct of RCTs involving active comparators (with or without a placebo comparator) and thereby the reporting of results of such RCTs by carefully evaluating their willingness to participate in a specific RCT based on the extent to which the investigator believes that the protocol for the RCT does or does not optimize the use of the active comparator (or at least does not use the active comparator in a manner that would likely degrade its efficacy or its safety profile). Failure to optimize the use of an active comparator would most likely involve the dose and/or frequency of administration of the active comparator. Ethical sponsors will generally have an active comparator administered in a manner consistent with approved package labeling at the time the protocol is finalized. Use of an active comparator consistent with the comparator's approved package labeling is entirely consistent with best regulatory practice and, in general, clinical practice. There are however occasions where academic literature would strongly suggest an alternative dose regime would better optimize the effects of the positive comparator. When a potential investigator views the data as quite substantial supporting better outcomes for the active comparator using an alternative approach to the use of the active comparator from that in the protocol, the ethical action would be to decline an invitation to act as an investigator. The strength of such data supporting alternative administration from that contained in the protocol is not always clear cut or overwhelming. Again, sponsors generally should administer the active comparator consistent with approved package labeling. One difficulty for journal editors and reviewers relates to this matter. It might be the case that during the several years between completing a protocol and completing a study and the manuscript reporting results data strongly supporting the alternative use of the active comparator is developed. The question of potential bias in a protocol designed must be judged in the context of the state of high-quality scientific knowledge at the time the protocol was finalized and not at the time of manuscript review. Less than optimal use of an active comparator that was unintentional and became known due to evolving scientific data after study initiation can be addressed as a matter in the manuscript Discussion section. In addition to the way an active comparator is administered, other aspects of a protocol that might contribute to intentional or unintentional bias are the various efficacy and safety assessments that are conducted as well as those not conducted that

would be of clinical importance. The methods of conducting the analyses of efficacy and safety assessments (data) could be less than optimal and create bias but this best addressed during manuscript review and consideration of the SAP as discussed above.

Briefly, I believe that cost of developing new chemical entities and new treatments is both very expensive and very risky business. Therefore, it should be substantially rewarded to foster continued innovation. I believe costs will continue to rise due to both progressively increasing difficulty with finding new treatments where needs exist and increasing regulatory and market expectations. Although others are more optimistic than I am, I doubt that much can be done to rein in this escalation without giving up or altering some of the expectations and requirements. Shifting to the topic of reporting of RCT results, a simple step that could result in more time required for review by journal reviewers could potentially further enhance the quality of the reporting of results. Finally, investigators can also contribute to enhancing objectivity of RCTs, particularly when involving active comparators.

References / Endnotes:

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iii http://csdd.tufts.edu/files/uploads/cost_study_backgrounder.pdf. Accessed December 13, 2016.

iv http://csdd.tufts.edu/files/uploads/assessing_claims.pdf. DiMassi JA, Hansen RW, Grabowski GH. Assessing claims about the cost of new drug development: a critique of the Public Citizen and TB Alliance reports. November 1, 2004. Accessed December 13, 2016.

v DiMasi JA, Grabowski HG, Hansen RW. Innovation in the pharmaceutical industry: new estimates of R&D. J HEALTH ECON 2016; 22:47:20-33.

vi http://www.forbes.com/sites/matthewherper/2012/02/10/the-truly-staggering-cost-of-inventing-new-drugs/#136db1c54477. Accessed December 12, 2016.

vii Avorn J. The $2.6 billion pill – methodologic and policy considerations. NEJM 2015; 372:1877-1879.

viii DiMasi JA, Hansen RW, Grabowski HG. The cost of drug development. NEJM 2015; 372:1972.

ix Morgan S, Grootendorst P, Lexchin J, Cunningham C, Greyson D. The cost of drug development: a systematic review. HEALTH POLICY 2011; 100:4-17.

x Sponsors are required to submit easily analyzable datasets in a standardized format for any drug / biologic application submitted for FDA consideration. The entity CFAST has driven this effort at standardization. CFAST, a joint initiative of Clinical Data Interchange Standards Consortium (CDISC) and the Critical Path Institute (C-Path), was launched to accelerate clinical research and medical product development by facilitating the establishment and maintenance of data standards, tools, and methods for conducting research in therapeutic areas important to public health. CFAST partners include TransCelerate BioPharma Inc. (TCB), the U.S. Food and Drug Administration (FDA), and the National Cancer Institute Enterprise Vocabulary Services (NCI EVS), with participation and input from many other organizations. See http://www.cdisc.org/cfast-0 for a list of CFAST participating organizations. CDISC has been primarily responsible for development/maintenance of these dataset specifications. There are 3 standardized datasets that are defined. These include: 1) the data collection (case report form) dataset (Clinical Data Acquisition Standards Harmonization - CDASH); 2) the tabulation (raw data as collected) dataset (Study Data Tabulation Model SDTM); 3) the analysis (any transformed r computed data based on the SDTM data that were input into analyses programs (e.g., QTc values computed using the QT length and RR value) dataset (Analysis Data Model - ADaM).

Charles M. Beasley

March 23, 2017