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Associate Editor's Commentary: In Praise of a BRAT

Peter J. Pitts[1]

The FDA is currently designing a 5-item grid as a management tool to explain its benefit-risk decisions in a more concise format. The grid comprises 5 basic factors that need to be addressed in any decision on the commercial availability of a drug. The top 2 factors are the seriousness of the condition addressed and the need for a new treatment of the condition. Then comes the traditional heart of the New Drug Application (NDA) package: analyses of clinical data on the benefits of the drug and the risks associated with its use. The fundamental factor is explicitly the level of risk management associated with the product. The FDA will be taking this into consideration in every decision; sponsors who ignore or underplay the identification of who should use the product and who might use it will have a gap in their filings. The grid proposal does not call for a fixed mathematical formula behind each approval since the agency has not tried to reduce the judgments in an approval decision to a rigid calculation.

In the words of Dr John Jenkins, director of the Office of New Drugs at the Center for Drug Evaluation and Research, disagreement "happens a lot in the decisions that we have to make. Very few of the decisions that we make on drugs are easy. Very few of the drugs we see have a dramatic overwhelming benefit with relatively no risk. We see that most drugs have marginal to moderate benefits on a population basis and they have general safety but they have the risks of serious toxicities at some low levels."[1] In other words, every decision is very complex. Acknowledgment that decisions are not simple "black and white" ones is a good start here, but there's a better way forward.

A recent paper in *Clinical Pharmacology & Therapeutics*[2] calls for the creation of a Benefit Risk Action Team (BRAT) framework, a set of processes and tools for selecting, organizing, summarizing, and interpreting data that is relevant to decisions based on benefit-risk assessments. The result of a 5-year effort by a team organized and facilitated by the Pharmaceutical Researcher and Manufacturers of America (PhRMA), the BRAT framework is a move toward an assessment that seeks to incorporate all relevant aspects of benefit and risk. The focus is on both qualitative and quantitative analysis. The current framework can incorporate weighting of outcomes but does not focus on calculation of overall benefit-risk scores.

The authors argued that BRAT provides a standardized yet flexible platform for incorporating study outcomes and preference weights as well as for communicating the rationale for decisions. They commented as follows:

> The advantages of developing and adopting such a framework are well recognized. By specifying the essential attributes that both regulators and companies should consider across the life cycle of a drug, the entire process of drug development, review, and approval would be strengthened. In the development and approval stages, the existence of a risk–benefit assessment framework would improve the quality of the discussion between sponsors and regulators and, as a consequence, between providers and patients, particularly with respect to medicines for which the benefit–risk balance is not straightforward (e.g., because of large and complex efficacy and safety data sets or because of inherent uncertainty regarding the available data).[2]

The authors concluded that

> because benefit–risk assessment for a drug is rarely straightforward, the framework or similar tools for elucidating the relevant data can help facilitate discussions between sponsors and regulatory agencies, help communicate complex information to other stakeholders, enhance the transparency of assumptions and decisions, and provide support for difficult regulatory benefit–risk decisions.[3]

This issue of the *Drug Information Journal* contains a report on how the BRAT idea has been put into practice within the pharmaceutical industry.[4] The lessons learned are valuable and are likely informative as the FDA contemplates its own design.

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