ICH revisions for benefit–risk assessment

Author
***Nancy Pire-Smerkanich**, Educational Liaison, International Center for Regulatory Science, University of Southern California, US.*

Keywords
Benefit–risk (B-R); International Conference on Harmonisation (ICH); US FDA; European Medicines Agency (EMA); Structured approach; Safety/efficacy; Innovative Medicines Initiative (IMI); Common technical document (CTD).

Abstract
The assessment of a medicinal product which measures its benefits/efficacy and risks/safety is a core concept of regulatory decision-making both for sponsors and regulators. Benefit–risk assessment has been an important topic in the industry over the past decade. The globally accepted standard for the documentation of benefit–risk that lies within the International Conference on Harmonisation (ICH) common technical document (CTD) was issued in 2002 and has not kept pace with the progress made in this area.

Under current ICH Guideline, M4E (R1), sponsors are expected to include their conclusions on benefits and risks in the Clinical Overview of Module 2 of the CTD (Section 2.5.6). There is general guidance provided in M4E (R1) regarding the expected content of this Section, but no further structure is suggested that could aid industry in structuring their benefit–risk assessment. We do know that the US FDA and European Medicines Agency have developed structured approaches that are currently being implemented within their organisations and although they have adopted different approaches, there are elements that can be harmonised and included in the CTD structure to provide applicants guidance in how to format and present this important information.

Over the past several years an increasing amount of discussion has centred on the benefit–risk (B-R) assessments of new medicines. Some of the current interest in B-R is driven by activities initiated by regulatory authorities as part of their transparency initiatives. These initiatives utilised structured approaches to support regulatory decision-making processes and the communication of these assessments. Although prior discussions were mostly conducted in the academic realm, its practical significance has made the discussions more important to the industry sector. This is not the only change in the discourse. The original rules that governed B-R assessment were largely directed at demonstrating and evaluating B-R in the pre-market or approval phase of product development. In the past decade, however, there have been some highly publicised cases of post-marketing statistical evidence coming to light after drugs have been approved. One example is the cardiovascular problems related to Vioxx, a COX2 inhibitor, which were associated with long-term use and led to its withdrawal from the market. Safety issues such as these are typically detected only after the product had been marketed for several years.[1] These findings were largely responsible for a new wave of concern about B-R evaluation. They spurred regulators in the US and Europe to put new rules in place to increase the effectiveness of post-marketing safety surveillance and continued assessment of B-R in later phases of the product lifecycle.

The initial concerns for regulators were safety issues. These skewed post-market activities to the risk side of the B-R relationship. Here, increasingly systematic and sophisticated tools were being used to identify and estimate risk.[2] Harmonisation efforts in the areas of risk management and pharmacovigilance, led by (R2) working groups from the Council for International Organization of Medical Sciences (CIOMS)[3] and the International Conference on Harmonisation (ICH), have been successful at providing better guidance for industry for these risk assessments, by harmonising tools such as the use of standardised coding for adverse drug reactions (eg, the Medical Dictionary for Regulatory Activities (MedDRA)), and the development of ICH E2E "Pharmacovigilance Planning" as well as the ICH E2C(R2) "Periodic Benefit Risk Evaluation Report (PBRER)". These latter formats are replacing the more traditional periodic safety update reports (PSURs) with modified approaches that assess risk in the context of benefit estimates. However, in order to assess and communicate this relationship in a balanced and comprehensive manner, a more systematic approach appeared to be needed for the benefit side of the equation. Thus, use of the term "risk–benefit" has changed gradually to use of the term "benefit–risk".

The US has been one of the first countries to rethink the way it deals with B-R assessment. In 2006, the Institute of Medicine (IoM) published a report recommending that researchers from both academia and industry investigate new approaches for conceptualising, measuring and applying B-R analysis. They further recommended that the Center for Drug Evaluation and Research (CDER) within the FDA should "develop and continually improve a systematic approach to benefit–risk analysis for use throughout the FDA in the pre- and post-approval settings".[4] This recommendation was followed, in 2009, by an initiative led by CDER to develop a structured approach for the B-R assessment of drugs that could serve as a template for new product reviews and help to clarify the basis for the FDA's regulatory decisions. This new approach was seen to align with another requirement placed on the organisation by the President of the United States in a "Memorandum to the Heads of Agencies on Transparency and Open Government".[5]

Figure 1: FDA benefit–risk framework.

Decision factor	Evidence and uncertainties	Conclusions and reasons
Analysis of condition		
Current treatment options		
Benefit		
Risk		
Risk management		
Benefit–risk summary assessment		

Source: P Frey. 'Benefit Risk Considerations in CDER: Development of a Qualitative Framework'. Paper presented at the DIA Annual Meeting, 2012.

Some of the goals to which the FDA transparency initiative had committed were issues dealing with better communication and a more transparent review process that would provide the public with an understanding of FDA decision-making.

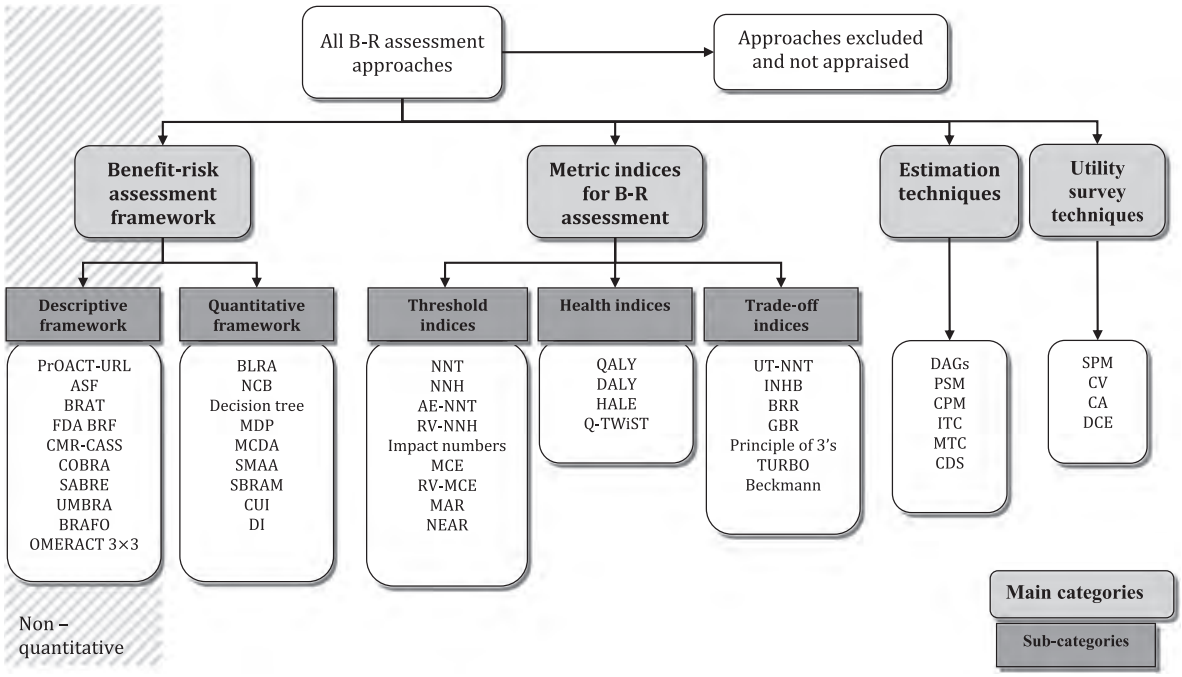
The two separate but related US government imperatives to encourage more open communication with stakeholders were reinforced when the FDA Safety and Innovation Act (FDASIA) was passed in 2012. It reauthorised the Prescription Drug User Fee Act (now called PDUFA V) in which the FDA was allowed to collect fees from industry for the review of new drug approvals, but only by agreeing to specific performance goals. As part of the most recent performance goals accepted as part of the PDUFA V implementation plan, the FDA committed to using a structured approach to assess the benefits and risks in the drug regulatory decision-making process and to communicate this aspect of the assessment process more effectively.[6] The framework and its corresponding template consist of a table that the FDA assessors complete as part of their new drug application (NDA) review process (see Figure 1).

At the same time, European activities related to B-R were also taking place. The European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) recommended that they too use a structured approach for evaluating the relative benefits and risks associated with new medicines as part of their European public assessment reports (EPARs). The committee formed a working group to assess various methods for B-R assessment under development by several academic and government/industry partnerships and established working relationships of their own with cooperative groups such as the Innovative Medicines Initiative (IMI).[7] The IMI has performed an extensive evaluation of the framework and methods for B-R assessment (see Figure 2).[8] The fact that the regulatory agencies of two dominant players in the drug development arena, the US and Europe, were investing substantial resources in the study of B-R frameworks suggested that change could be anticipated in the way that drugs would be reviewed. However, in the past, when separate initiatives have taken place in different constituencies, the resulting approaches have been dissonant and have created different standards. For this reason, in the latter part of 2014 the ICH formed an Expert Working Group (EWG) to evaluate the current multidisciplinary guideline for the Common Technical Document (CTD) Clinical/Efficacy sections – M4E (R2), a section most directly related to benefit assessment. As part of its November 2014 meeting it also published the final concept paper, business plan and work plan to address the revisions that may be needed in order to "include greater specificity on the format and structure of B-R information with the goal of harmonizing the presentation of this information in regulatory submissions".[9] It also noted that "this proposal aims to level-set all key stakeholders in drug regulation with respect to what is important in regulatory decision-making for pharmaceutical products. Greater structure in the presentation of this information should aid regulators in understanding an applicant's perspective on the benefit–risk assessment. Similarly, applicants will have a clear understanding of what is important to a regulator's benefit–risk decision."

The need for harmonisation of the methodologies and/or the presentation of B-R assessment has been identified in multiple settings by industry. Some of these efforts took place through their trade organisations. As noted by the Biotechnology Industry Organization (BIO), in its "Comments on the FDA Draft Structured Benefit–Risk 5-Year Plan":[10] "We encourage FDA to continue engaging in dialogue with other regulatory agencies on methodologies of assessing benefit–risk that acknowledge and reflect the global endeavour of drug development and regulation in which sponsors operate."

The implementation of a consistent approach has been challenging. As noted by Lawrence Liberti and his colleagues, "the use of decision frameworks with an agency should encourage a quality review leading to well-informed, quality decision making with meaningful, well-communicated outcomes".[11] Liberti also went on to note that these same frameworks could be used by companies to structure discussions around internal assessment of study findings and to help inform development decisions as well as guide the preparation of marketing applications. However, many frameworks of differing complexity exist and continue to be developed. In addition to the activities of the health authorities, trade organisations such as BIO, referenced above, the Pharmaceutical Research and Manufacturers Association in the US (PhRMA), the European Pharmaceutical Industry Association (EFPIA), the non-profit Center for Innovation in Regulatory Science (CIRS) and other public–private partnerships have all been active in the development of their own frameworks and work products relevant to B-R assessments for drugs. Some of these approaches are straightforward and qualitative in nature, whereas others rely on complex quantitative and statistical methods. However, the mere existence of multiple frameworks is confusing for practitioners who are not expert in B-R. Key to the implementation of a B-R assessment

Figure 2: IMI PROTECT classification of identified benefit–risk assessment methodologies.[8]

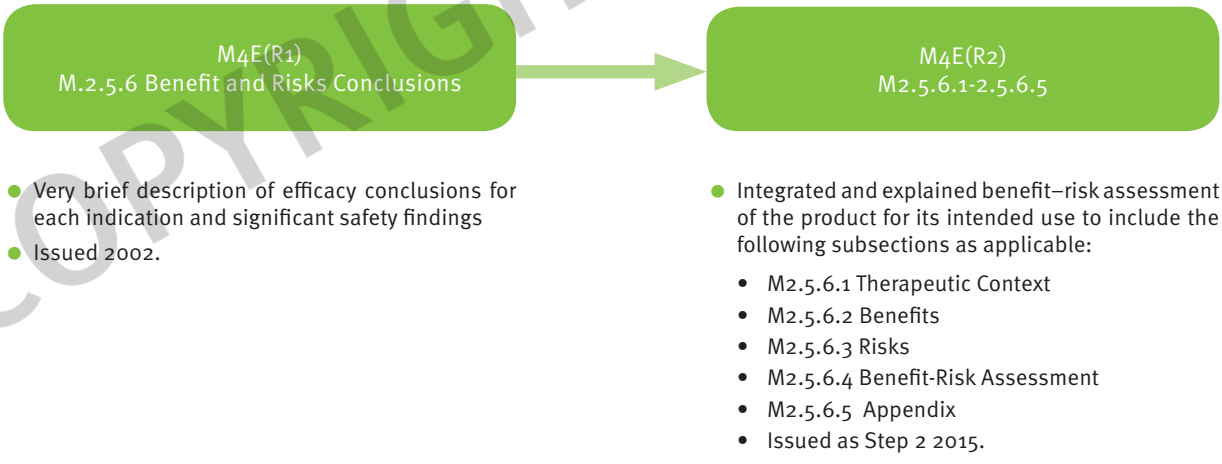


that can be used within and across constituencies is the adoption of a singular framework to structure the information and activities.

The result of the ICH EWG has been a revision the M4E, published in August 2015. In this revision, the ICH has proposed a format that includes therapeutic context (M2.5.6.1), which describes the disease or condition that are related to the indication and inclusion of current therapies in this context (see Figure 3). Benefits and risks are then summarised using existing headings and sections have been added to address B-R assessment and methodology (M2.5.6.4 and M2.5.6.5). The current draft states the following with regard to B-R assessment methods: "There are many approaches available for conducting the benefit-risk assessment. A descriptive approach that explicitly communicates the interpretation of the data and the benefit-risk assessment will generally be adequate. Beyond this, the guideline does not prescribe a specific methodology. However, an applicant may choose to use methodologies that quantitatively express the underlying judgments and uncertainties in the assessment. Before using such methodology, the applicant should consider its utility, complexity, the extent to which the methodology is established, and the ease of interpretation of the results. In this situation, a written summary and explanation of the conclusions should still be provided in this section. The detailed presentation of the methodology should be appended in Section 2.5.6.5."

The ICH approach seems to mirror the US view that a structured *qualitative* approach would be the best solution to formalise the way that decisions were reached. It could be used as a stand-alone

Figure 3: The CTD Efficacy Guidance (M4E) – Clinical Overview: Comparison of benefit–risk requirements.



framework, but also could accommodate more complex quantitative analyses in a flexible way[12] to satisfy jurisdictional requirements. It is not surprising that the FDA has already published this as draft guidance (for comment). Sponsors should become familiar with the available methods for completing this framework if they are submitting NDAs in the US to facilitate their reviews. Other regions will most likely follow. It is anticipated that B-R assessments may become a focal point for scientific advice and pre-marketing meeting discussions in recognition that this framework can serve as a foundation for all downstream documents and B-R decisions.

References

1. J M D Avorn. 'Two Centuries of Assessing Drug Risks'. *NEJM,* 367(3), 193-197, 2012.
2. H-G Eichler, E Abadie, J M Raine, T Salmonson. 'Safe drugs and the cost of good intentions', *NEJM,* 360(14), 1378-1380, 2009.
3. CIOMS. 'Benefit-Risk Balance for Marketed Drugs: Evaluating Safety Signals', 1998.
4. IoM. 'The Future of Drug Safety: Promoting and Protecting the Health of the Public', 2006.
5. P B Obama. 'Memorandum to the Heads of Agencies on Transparency and Open Government', 2009.
6. IoM. 'Characterizing and Communicating Uncertainty in the Assessment of Benefits and Risks of Pharmaceutical Products', 2014.
7. S Mt-Isa, I Tzoulaki, T Callréus, *et al*. 'Weighing benefit–risk of medicines: concepts and approaches', *Drug Discovery Today: Technologies, 8*(1), e29-e35, 2011.
8. S Mt-Isa, C E Hallgreen, N Wang *et al*. 'Balancing benefit and risk of medicines: a systematic review and classification of available methodologies', *Pharmacoepidem Drug Safe,* [Online], 23: 667–678. doi: 10.1002/pds.3636, 2014.
9. ICH. 'M4E(R2) Final Concept Paper. Enhancing the Format and Structure of Benefit-Risk Information in ICH', 2014.
10. BIO. 'Comments on the FDA Draft Structured Benefit-Risk 5-Year Plan', 2013.
11. L Liberti, N McAuslane, P Patel, *et al*. 'Regulatory Review: How Do Agencies Ensure the Quality of Decision Making?', *Clinical Pharmacology & Therapeutics,* 94(3), 305-308. doi:10.1038/clpt.2013.127, 2013.
12. T Mullin. 'Managing Risk and Uncertainty through the Drug Life Cycle – Recent FDA Initiatives' (Presentation), 2014.

Further reading

a. J J Guo, S Pandey, J Doyle, *et al.* 'A Review of Quantitative Risk–Benefit Methodologies for Assessing Drug Safety and Efficacy – Report of the ISPOR Risk–Benefit Management Working Group', *Value in Health,* 13(5), 657-666, 2010.
b. F Mussen, S Salek, S Walker. 'Benefit–risk appraisal of medicines: a systematic approach to decision-making', *Wiley-Blackwell, Chichester, UK; Hoboken, NJ, US,* 2009.
c. A Sashegyi, J Felli, R Noel. 'Benefit–risk assessment in pharmaceutical research and development', edited by Andreas Sashegyi, James Felli, Rebecca Noel, Boca Raton, Florida*: CRC Press/Taylor & Francis Group,* 2014.
d. Centre for Innovation in Regulatory Science (CIRS). Available at: www.cirsci.org/pub/
e. BIO. 'A Lifecycle Approach to FDA's Structured Benefit-Risk Assessment Framework', 2015.