Future unmet medical need as a guiding principle for pharmaceutical R&D

Matthias Vennemann[1], Vincent Ruland[2], Jan-Philip Kruse[3], Christine Harloff[4], Hubert Trübel[5,7] and Heike Gielen-Haertwig[6]

[1] Business Consulting, Bayer Business Services, Leverkusen, Germany
[2] Pharmaceuticals, Bayer AG, Berlin, Germany
[3] Open Innovation & Digital Technologies, Bayer Pharma R&D, Cambridge, USA
[4] Open Innovation & Digital Technologies, Bayer Pharma R&D, Berlin, Germany
[5] Translational Sciences, Bayer Pharma R&D, Wuppertal, Germany
[6] Open Innovation & Digital Technologies, Bayer Pharma R&D, Wuppertal, Germany
[7] University Witten/Herdecke, Witten, Germany

In pharmaceutical R&D the strategic focus is on addressing areas of high unmet medical need. 'Unmet medical need' is a widely used term in the healthcare sector but a common definition does not exist. The current standard of care determines the current unmet medical need, whereas the future unmet medical need (i.e., the unmet medical need when a new product reaches the market) and the extent to which the unmet need is addressed by the new product significantly impact its value. We have defined six dimensions as key drivers of (future) unmet medical needs of patients in a given setting. In the absence of quantifiable criteria, structured expert assessment techniques, such as the Delphi method, can guide portfolio strategies, especially for early-stage assets.

Introduction

In pharmaceutical R&D portfolio management the strategic focus lies on addressing areas of high unmet medical need, on the clinical differentiation of the future medications and on the commercial potential of the portfolio assets at different stages of development. For assets at later stages, the commercial analysis significantly contributes to decision making and pipeline valuation [1–3]. However, given the high level of uncertainties, especially during research and early clinical development phases, emphasis on commercial potential in early stages of drug development could lead to decisions to move projects forward based on commercial potential rather than scientific rigor. Higher failure rates for scientific reasons in mid-stage and late-stage development might be the consequence of such decision-making.

Addressing a high medical need is seen as a significant value driver in clinical development. Many companies therefore incorporate a medical need assessment in their evaluation for early project and portfolio decisions [4]. Although evaluation of the commercial potential of a project is based on standard methodology, such as calculation of the net present value (NPV) or risk-adjusted NPV, there is no standardized definition and methodology available to assess and compare the (unmet) medical need of development projects in a portfolio. Nevertheless, 'unmet medical need' is widely used as a term in the healthcare sector. For example, the European Medicines Agency (EMA) has launched the Priority Medicines (PRIME) Scheme to enhance support for the development of medicines that target an unmet medical need [5] but a common definition does not exist [6,7]. Different methodologies have been developed to quantitatively assess medical need in the public health sector, such as disability-adjusted life-years (DALYs) used by the World Health Organization (WHO) [8] or quality-adjusted life-years (QALYs) used for healthy economic

Corresponding author: Gielen-Haertwig, H. (heike.gielen-haertwig@bayer.com)

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value assessment by NICE in the UK [9]. DALYs provide summary measures of health across geographies that can inform assessments of epidemiological patterns and might help to prioritize investments in R&D, whereas QALYs represent an individual's preference for different health states. Both methods rely on defining the utility value (or utilities) for a disease state. This can be the conventional utility scale defining a utility of zero for 'dead' and one for 'complete health'; or utility scores that are assigned by direct measurement using techniques like the standard-gamble and the time trade-off or by indirectly using a utility-weighted index [10]. However, DALYs, QALYs and utility datasets are not yet broadly available, and the granularity is typically not sufficient for an evaluation of a diverse and innovative R&D project portfolio.

The authors therefore reviewed available information from academic sources as well as from FDA, WHO and NICE publications [11–15] and interviewed >20 internal and six external experts, working in R&D, market access, pricing, patient advocacy and regulatory fields. Literature review and interviews confirmed that none of the existing methodologies holistically captures and describes medical need in a way that is fit for our purposes. To derive a suitable methodology for the systematic description and assessment of medical need, key drivers and dimensions were developed and defined based on the insights from literature and expert interviews. In addition, decision quality relies on the reduction of uncertainty and on ways to measure things that are thought to be unmeasurable [16]. Given a project team's natural 'optimism bias', leading to a progression seeking behavior [17,18], it is not only important what to rate (i.e., here the unmet need) but also who does the rating [19] and when the rating applies (i.e., the present versus the future; e.g., time of launch). Using the input of an expert panel to assess the expected impact of all future assets of a portfolio on the unmet medical need in the respective indications can provide a semiquantitative description that can contribute to better portfolio decision making, specifically in early stages of development.

Definition of unmet medical need and future unmet medical need

The total unmet medical need of a certain disease comprises two components: the unmet medical need of the individual patient and the unmet societal need. The latter, driven for example by epidemiological data such as incidence and prevalence, the costs of disease and indirect costs to society, was not in the scope of our considerations yet certainly complements the more science-driven unmet medical need assessment. From the patient perspective, if there is no available therapy, there is clearly an unmet medical need (Fig. 1). If standard therapy is available, the current standard of care (SoC) determines the residual unmet medical need for a given indication (i.e., the difference to perfect health for the individual). The future unmet medical need at the time a new product reaches the market and the extent to which it addresses the unmet need will significantly impact the value for patients. The future unmet medical need is determined by the future SoC. The future SoC could, for example, be a competitor asset currently in clinical development with a certain probability to be launched before the new product under evaluation reaches the market.

To compile a reasonable assessment of future unmet medical need, a detailed understanding and definition of the indication and the target population to be addressed by a specific asset is key and should be the first step in the evaluation. Different phases of disease, in the case of progressing conditions, or different lines of therapy need to be taken into consideration as well, so potentially multiple distinct assessments might be needed to reflect this dynamic in a disease progression. The actual clinical SoC as well as typical background therapies, potential relevant off-label medications, alternative treatment approaches (e.g., devices or digital solutions) or supportive care measures need to be considered. In many cases there are also regional differences as well as different patient subpopulations that influence the SoC to be considered for the assessment and thereby also the clinical development strategy for an asset. The last step in the process is an analysis of the competitive landscape to gain understanding of the added net clinical benefit that relevant competitor assets might achieve and to come to an assessment of the timeframe and the likelihood for those assets to reach the market. With the advancement of new technologies such as gene or cell therapy even sustained and long-term cures in certain disease areas might need to be considered.

Dimensions determining unmet medical need

We have defined six dimensions as key drivers for (future) patient unmet medical need in a given setting (Table 1). Assessing these

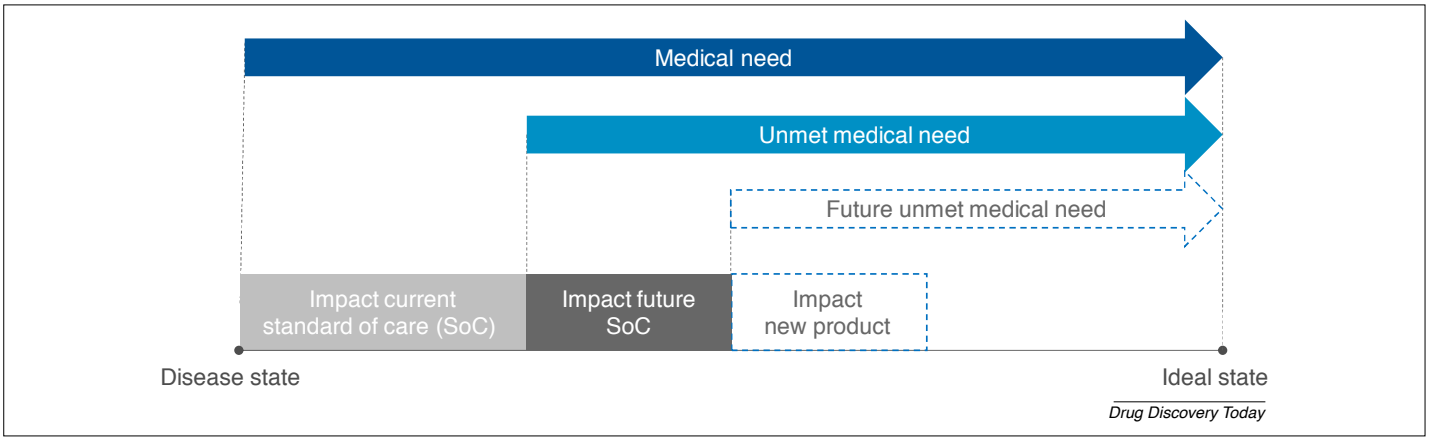

FIGURE 1

Where no therapy is available, there is clearly an unmet need. Where there is therapy available, the standard of care (SoC) determines the residual unmet medical need. The future unmet medical need is determined by the future SoC. For example, a competitor asset with a certain probability to be launched before a new product reaches the market.

TABLE 1

Six dimensions to describe patient unmet medical need in a given setting

Key dimensions	Rationale
Mortality	Median overall survival (years) or 30-day/annual death rates (%)
Symptom & disease burden	Disease-related symptoms experienced by patient
	Risk for disease progression (e.g., tumor size) or event rates (e.g., hospitalization, stroke)
Side effects	Treatment-related side effects and (S)AEs based on severity and frequency
Treatment inconvenience	Based on invasiveness, frequency and duration of treatment options
Patient perception	A patient's perceived physical and mental health as reflected in established HRQoL questionnaires
	Includes aspects of other key dimensions and impact on activities and psychological burden
Time spent in disease	The longer a disease persists, the higher the burden to individuals
	Time spent in disease to differentiate chronic vs acute diseases or symptomatic vs curative vs life-prolonging treatment options

dimensions individually enables increased transparency in project and portfolio discussions.

Mortality

Mortality is unanimously considered to be the major aspect of disease burden by interviewees as well as the regulatory and pricing bodies. Median overall survival is a generally accepted endpoint often used in oncology indications [20]. In other disease areas 30-day or annual death rates might be the more relevant parameters [21].

Symptom or disease burden

Disease burden includes the disease-related symptoms as experienced by an individual patient. In addition to the symptoms directly reported by the patient, the risk for disease progression (e.g., change in tumor size) or the risk of suffering a non-fatal event (e.g., hospitalization, myocardial infarction, ischemic stroke) are also essential factors to be taken into account. Symptom burden can be thought of as the sum of the severity and impact of symptoms reported by patients with a given disease. The Common Terminology Criteria for Adverse Events (CTCAE) list provides specific examples of possible symptoms to rank them according to severity [22]. Augmenting the CTCAE differentiation with specific patient data might help in assessing the dimension; for example, pain as assessed by a visual analog scale (VAS) or numerical rating scale (NRS) by 0 (no pain) to 10 (worst pain imaginable) [23,24]. A marker of events that will impact the health status of a patient with a certain probability, as measured in clinical studies or based on real-world evidence, could be expressed as progression-free survival or time to progression (in years) or as event rates (in %) [20,21].

Side effects

In addition to the disease-related symptoms experienced by the patient, side-effects and (serious) adverse events of available treatment options (SoC) reflect the disease burden on the patient and thereby the unmet medical need. Treatment-related side effects and (serious) adverse events are typically classified based on their severity and frequency. Severity can be based on the CTCAE ranging from mild (asymptomatic or mild symptoms, clinical or diagnostic observation only, intervention not required) to moderate (minimal local or noninvasive intervention required) to severe (medically significant but not immediately life-threatening; however, hospitalization or prolongation of hospitalization indicated) up to life-threating (urgent intervention required) [22]. Frequency is usually based on the generally accepted division between very common (affects >1 in 10 people), common (between 1 in 100 and 1 in 10 people), uncommon (between 1 in 1000 and 1 in 100 people), rare (between 1 in 10 000 and 1 in 1000 people) and very rare (<1 in 10 000 people) [25].

Treatment inconvenience

Unmet medical need based on treatment inconvenience of available treatment options (SoC) is driven by a mix of invasiveness, frequency and duration of treatment. The inconvenience of a treatment has a direct influence on the patient's perceived health-related quality of life. A treatment's invasiveness, which includes the discomfort with which it is associated, increases in importance from oral therapy, topical application or inhalation over injections or infusions to endoscopic interventions or surgery under local anesthesia up to, finally, for example, renal dialysis or surgery under full anesthesia. The frequency at which such treatment is administered can vary between once, once every few months, once monthly, weekly, daily and multiple times daily. The duration for which a treatment is warranted varies between a few days or weeks, several months, several years, >10 years and unlimited. These three factors are strongly interlinked; for example, from the patient perspective, surgery under full anesthesia undergone once to cure a disease might be preferred over once daily oral therapy for several years.

Patient perception

This dimension describes a patient's perceived physical and mental health as often reflected in established health-related quality of life (HRQoL) questionnaires (e.g., EQ-5D, SF-36 or disease-specific questionnaires) [26]. The patient perception includes many aspects of the other dimensions. Therefore, special focus might be given to aspects not covered before, such as impact on activities and psychological burden. As an example, activities of daily living (ADL) are defined through the ability to carry out usual tasks as well as recreational activities and consist of people's self-care ADL (e.g., bathing, dressing and undressing, feeding self, using the toilet or taking medications), instrumental ADL (e.g., preparing meals, shopping for groceries or clothes, using the telephone, managing money or going to the pharmacy) and mobility (such as walking, recreation, exercising or travelling) [27]. The psychological burden demonstrates how much a disease impacts a patient's mental well-being. Several aspects such as uncertainty, body image, autonomy, role or vitality can have an influence on the patient's psychological burden. Their rating can be based on the SF-36 (36-item short-form health survey) dimensions [28].

Time spent in disease or treatment (effect) duration

This dimension can be used to differentiate chronic versus acute diseases as well as symptomatic versus curative versus life-prolonging

treatment options. Typically, in the case of chronic diseases, the earlier in life a disease occurs and therefore the longer it persists, the higher the overall burden is to the individual. The correlation of time spent in disease to unmet medical need can be proportional (symptomatic versus curative treatment, shorter is 'better') or inversely proportional (symptomatic versus life-prolonging treatment, a longer time spent in disease is preferred over premature death). In addition to time spent in disease, the time factor in a given setting can also be expressed as treatment (effect) duration. Treatment duration might be used to differentiate long-term versus short-term treatments (e.g., if treatment duration is limited by side effects). The duration of a treatment effect is also relevant and might be significantly different from the duration of the treatment as such (e.g., in the case of surgery or gene therapy curing the disease).

Estimation techniques for the assessment of future unmet medical need

In the absence of quantifiable criteria, as well as in areas where precise scientific correlations have not been established, structured expert assessment techniques can guide decision making. The Delphi method, which originated in the 1960s, is a communication technique used as a systematic, interactive forecasting method that relies on a panel of experts [29,30]. The experts (e.g., scientists, patients and representatives of other stakeholder groups) answer questionnaires in several rounds of assessment. In the process they converge on the best possible answer, and the breadth of the answers will decrease as the experts are encouraged to revise earlier answers in light of the replies of their colleagues. The technique can also be adapted for use in face-to-face meetings and is then called mini-Delphi.

As a rating instrument we have chosen the VAS: a psychometric response scale used for characteristics that cannot be directly measured and used as a pain scale, for example in endometriosis patients [31,32]. A common understanding of the topics to be assessed is of the utmost importance to ensure a reasonable outcome of the process. Therefore, a diligent preparation and focused briefing of the expert panel regarding the indications as well as the assets to be evaluated is essential. To ensure that the assessment of the group of experts is not overly influenced by one or more thought leaders, it is recommended that at least the first round of assessment is conducted anonymously via an electronic voting tool.

In our approach to a more systematic assessment of unmet medical need, respondents are asked to indicate a position along the line between two endpoints: one representing a disease state without any treatment (equals 100% unmet medical need) and one representing the ideal state (i.e., the absence of this disease) (equals 0% unmet medical need). In the examples outlined in Fig. 2, a disease setting for a given asset is defined and the experts indicate positions along the line between the two endpoints. They choose positions that reflect their expectation of the current and future unmet medical need in the indication by itself as well as a position that reflects the remaining unmet medical need in this same indication once the asset being evaluated has reached the market. By this means, future unmet medical need for the indication is quantified by the remaining space up to the ideal state, which represents room for improvement. The difference between the two positions, which we called 'delta to future unmet medical need', defines the effect size or clinical differentiation potential the experts expect from the asset. As described above, we have identified six dimensions to describe patient unmet medical need. Assessing these dimensions individually for a given disease setting and asset enables increased transparency on the key drivers of the differentiation potential for the given asset. A spider graph could be used for visualization of the more comprehensive dataset (Fig. 3).

Areas of application

In early stages of R&D the strategic focus lies on addressing areas of high unmet medical need. The potential for a large effect size and a clear clinical differentiation as compared to future SoC in areas of high unmet medical need typically determine project and portfolio value. Rating of the perceived current or future unmet medical need in different (sub)indications can provide valuable insights to guide decisions on the optimal development strategy for individual projects. For determination of the overall portfolio value and prioritization across projects, the assessment of the differentiation potential (delta to future unmet medical need; Fig. 2) could be utilized as a portfolio management tool. Eliciting perspectives and

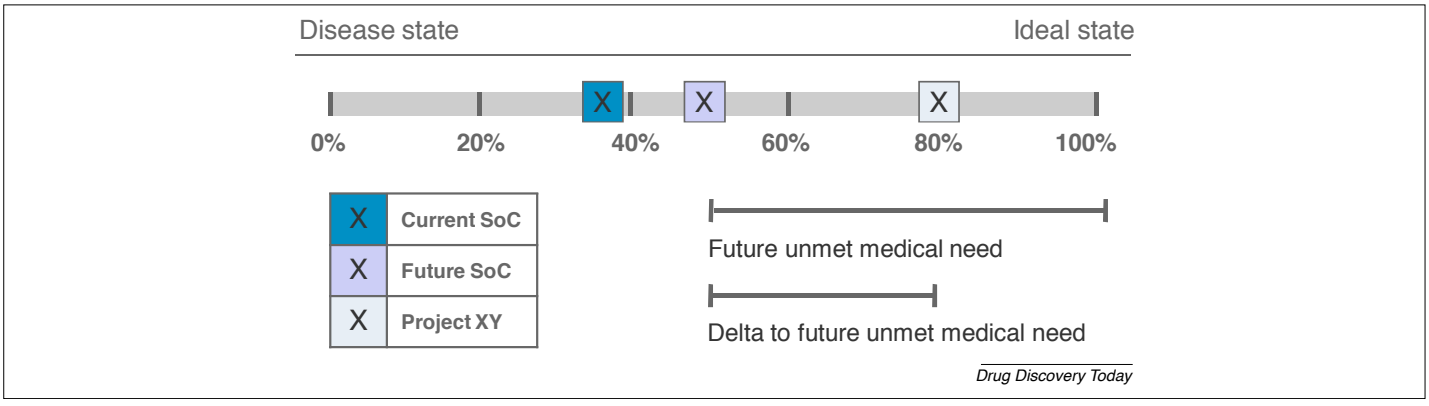

FIGURE 2

Illustrative example of Delphi or visual analog scale assessment of unmet medical need in given indications by indicating a position along the line between two endpoints, one representing a disease state without any treatment (equals 100% unmet medical need) and one representing the ideal state (i.e., the absence of this disease) (equals 0% unmet medical need).

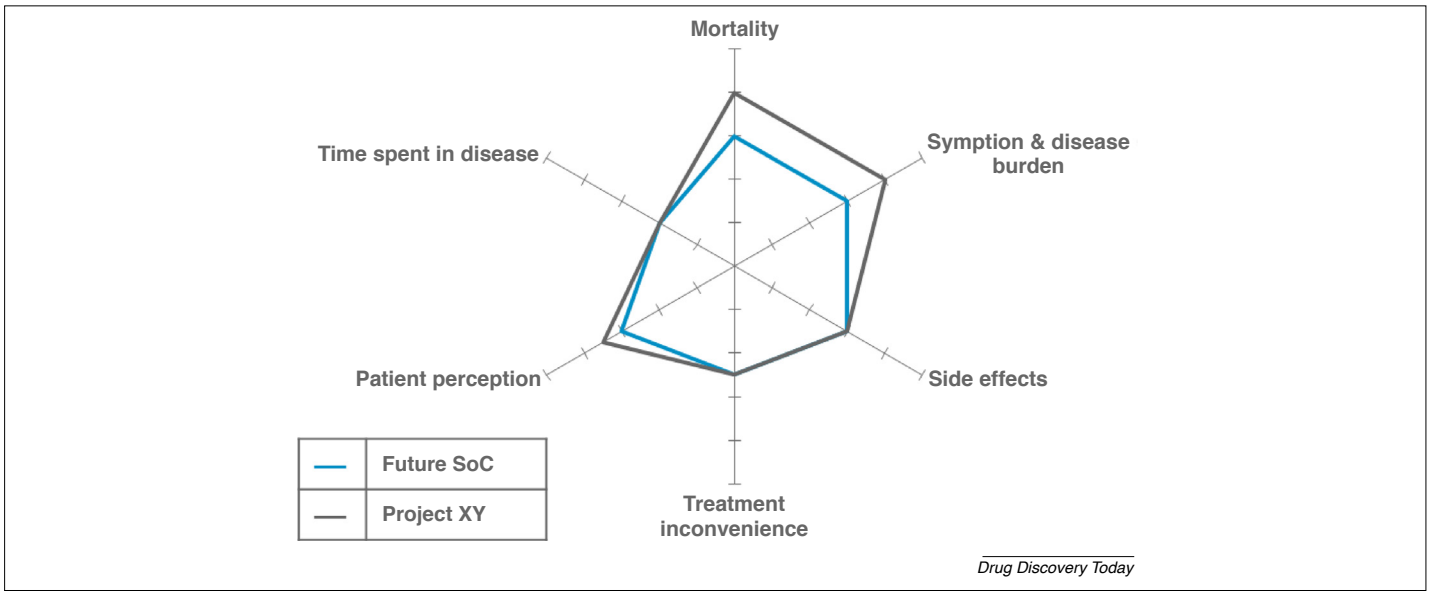

FIGURE 3

Illustrative example of Delphi or visual analog scale assessment of future unmet medical need across the different dimensions by indicating a position along the line between two endpoints.

preferences of different stakeholder groups or regions separately can generate valuable additional insights. For example, patient preferences and priorities might differ from those of medical professionals, regulators or industry, and preferences in the USA, Europe and Asia can also vary.

Selection and briefing of the expert panel is the key element for the success of the overall process. In a setting with a diverse senior management panel asked to assess our early development portfolio, we were able to clearly differentiate indications and projects with a convincing overall outcome. A broad spread of the ratings across the different indications and projects was achieved. This is in remarkable contrast to previous 'traffic light' evaluations where typically the vast majority of the portfolio was rated as being in areas of high unmet medical need and therefore ending up in the 'green bucket'. A differentiation of individual voters with more or less optimistic views regarding overall portfolio potential could also be observed, giving a clear hint that the methodology is valuable for eliciting perspectives of different stakeholder groups. In another setting, the project teams responsible for the various assets in our early development portfolio were asked to assess the six dimensions individually for a given asset in different indications. The spider graphs were then utilized for visualization during the discussions of the indication option space and enabled an easily and quickly graspable view of the differentiation potential across the portfolio.

Concluding remarks

Especially in the early stages of R&D, the strategic focus should lie on addressing areas of high unmet medical need. In later stages, further criteria for project evaluation are added, such as a commercial analysis that also contributes to decision making and pipeline valuation. The future unmet medical need (i.e., the unmet medical need when a new product reaches the market) and the extent to which the need is addressed by the new product significantly impact value. A common understanding and a methodology that enables a systematic and differentiated discussion of future unmet medical need is the fundamental basis for pharmaceutical R&D strategy and portfolio management. In the absence of quantifiable criteria, structured expert assessment techniques such as the Delphi method can guide portfolio strategies.

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