Knowledge Management Advisory Board

SELECTING A COMPOUND FOR DRUG DEVELOPMENT – THE IMPORTANCE OF KNOWLEDGE MANAGEMENT

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Drug discovery requires complex and multi-faceted decisions to justify billion-dollar investments that will take years to realize. Such decisions are best made with input from multiple stakeholders who must communicate their views backed up with evidence and precedent, often in the face of circumstances that change daily. A formal, rigorous knowledge management system enhances this process not only by keeping scientific, medical, and commercial information organized and updated, but also by bringing insights to the forefront of the discussion.

This paper analyzes the decision-making process for one specific aspect of drug discovery – the choice to move forward with the development of a new drug compound. We lay out best practices for assembling a cross functional team and developing a concise rationale for the proposed plan, and we present a framework for future decisions that align with company goals, curating and leveraging the knowledge that is needed to maintain good decisions.

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Part 1 – The Decision Process

According to the PhRMA 2016 report, the average cost to bring a drug from discovery through clinical trials and to patients is estimated to be $2.6 billion. Of the thousands of compounds screened and assessed early in the R&D process, probability of clinical success (the likelihood that a drug entering human clinical testing will eventually be approved) is less than 12%. With these numbers, deciding which compounds to develop and bring to market is critical.

Before a drug candidate is tested in a human being, decisions need to be made in the absence of key information. Decisions have to be timely and dynamic, made within a framework of "go/no-go" decision points that are set up during the long path through the three phases of clinical trials.

There are many aspects to consider when deciding whether to move forward with a drug compound. After the years of testing, the drug must be proven safe, efficacious, and useful to patients. It also needs to be commercially viable. Whether the decision is to license or purchase a compound from a partner, or to move forward with a compound being developed in house, this daunting list of questions must be considered:

- What unmet medical need will the drug address?
- Is this a global need or will the drug be useful only in key markets?
- Will it meet patients' and physicians' expectations?
- Is it a strategic fit within the company's portfolio?
- Is it differentiated from the competition, both the current players on the market and the likely new market entrants?
- What is current market size and projected market growth?
- What are the development costs?
- Does the company have the capabilities to develop and bring it to market?
- What is the potential for market access in key markets? (i.e., will it be covered by insurance?)

The above list illustrates both the complexity of choosing a new compound for drug development as well as why that decision requires scientific, medical, economic, and business expertise. A balanced decision process requires expertise in understanding the unmet need and large market size, medical expertise to assess how doctors will incorporate the drug into their practice, market expertise to understand who else is working on similar approaches, expertise about current and future regulatory and reimbursement issues, and corporate expertise on the risk:reward profile of the development program at the current time.

Making the Case for a New Drug

A new drug development program invariably starts with a champion – someone who is passionate about the potential of a compound to impact a promising new drug target that will help patients and also be commercially viable for their company. This champion must convince various stakeholders that their compound is worth the investment and is better than other compounds that might be developed. The champion must set in motion a complex decision process that requires alignment across multiple functions and multiple levels of leadership. We find that the key to this process is a *comprehensively concise* approach to storytelling – the champion must outline the problem, describe the solution, and provide a summary of supporting work. These elements facilitate a constructive discussion and alignment among the many stakeholders.

What does '*comprehensively concise*' mean? Think back to your college days and those yellow Cliff's Notes that enable science-focused students the ability to pass their undergraduate literature requirements. They provided a comprehensive summary of the book, brief enough to read in an hour but with enough details to extrapolate how *A Midsummer Night's Dream* is the happy ending version of *Romeo and Juliet*. Comprehensively concise storytelling is important at all levels of business decision making; the similar BRIEF (background, reason, information, end, and follow-up) system is broadly used. (ref: "Brief: Make a Bigger Impact by Saying Less", Joseph McCormack, 2014, Wiley, https://thebrieflab.com/book_brief/)

The goal of comprehensively concise storytelling is to provide decision-makers with enough data-driven insights to inform their perspectives without adding extraneous, often distracting, information. The volume of insights necessary often decreases as the opportunity is socialized up the organizational hierarchy. While the Scientific Director will need to understand the target's specific clinical characteristics, the CSO will want to understand the rationale for the target, strategic value, and the team's level of confidence.

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This may sound simple, but it requires a team with strong storytelling skills and an ability to adapt the level of detail to meet the needs of the specific audience without impacting the consistency of the message. Indeed, a good pitch enables discussions across functions, allowing people at various levels of technical, scientific, medical and commercial expertise to all contribute.

Assembling a Cross Functional Team

Like all great endeavors, the place to start is with preparation. First, assemble a cross-functional team to conduct a thorough due diligence of the target for your new compound. Once all functions agree to progress, collaboratively map out the scientific rationale for the new drug, the strategic relevance of the drug's target, and the communication plan for the opportunity by function.

Once the framework is done, the team creates the content, which includes functional and cross-functional messages. This is important since each member of the cross-functional team will seek alignment within her or his respective organizations, leveraging the messaging, which links to the cross-functional messaging used in the governance reviews to gain official alignment.

Having cross-functional alignment is critical. Most of the time, pharma organizations are trying to look 10-20 years into the future. If the organizational silos are not looking to the same horizon, one group's view may look very different from another's.

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The project team is often comprised of senior members of Discovery, Clinical Operations, Medical Affairs, Statistics, Technical Operations, Commercial, and Market Access. Assuming the drug candidate hasn't entered preclinical or clinical trials, Discovery and Clinical Operations would champion the assessment. If this was a phase 2 asset, the assessment would be led by Clinical Operations, Global Medical Affairs, and Commercial.

Figure 1: Sample Blank TPP

General Information	
Active Ingredient	
Mechanism of Action/Class	
PK/PD Characteristics	
Regions Included	
Strategic Fit	
Value Proposition	
Date Last Updated	

	Product X	Reference Drug
Indications and Usage		
Target Population		
Dose & Administration		
Dose Forms and Strengths		
Efficacy		
HEOR		
Safety		
Tolerability		
Contraindications		
Warnings/Precautions		
Drug Interactions		
Drug Abuse/Dependence		
How Supplied/Presentation		
Shelf Life/Storage Condition		
Samples		
Time to market		
Price		
Forecast		
Patent expiration		

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Although the process at a small biotech company may involve fewer people with overlapping roles, it should follow the same general process. In this case, stakeholders often include outside advisors and investors, while a large pharma company will have more of those functions in house. Nevertheless, the process benefits from consensus from all stakeholders; drug development is hard and there are invariably reasons along the way to give up on your championed compound, so the goal of the comprehensively concise plan is to ensure all the expertise of your company is brought to bear, maximizing the chance of success and developing a roadmap for decisions along the way.

The Target Product Profile

Along with the decision to develop a certain compound comes a strategic framework that sets up the guideposts that will track the drug candidate's actual data compared to pre-defined metrics necessary for commercial success. This target product profile (TPP) defines the drug's future place in the market and how it will be differentiated from other drugs, both those currently on the market and those in varying stages of development that might be available by the time it is approved. The TPP becomes the North Star for the asset, enabling clear go/no-go conversations (Figure 1; sample TPP). The TPP outlines a vision for a product that will meet market needs. Attributes in a target profile include value drivers, investments (R&D costs, COGS, SGA), patient population, and revenue/profitability.

TPPs should be produced and maintained for all stages of development. At a minimum, inputs to the TPP include the indication, target patient population, proposed efficacy and safety endpoints, dosing and administration, patient and healthcare system benefits, and payer value. These attributes are compared to one or more known products to determine if the drug likely will be differentiated in the marketplace.

The TPP should be diligently updated as the drug candidate development progresses and more information is gathered. It is a living document, critical for "go/no-go" decisions that arise multiple times in the drug's long development process.

A huge amount of knowledge, including both data and opinion, goes into the TPP. This includes scientific and epidemiological information, medical knowledge, business expertise, market expertise, patent information, regulatory insights, and understanding of both doctors and patients. Assembling and managing the knowledge for the TPP and other aspects of the decision process are detailed in the second part of this report.

Not just a Good Compound, but a Good Compound for You

Depending on the company's strategy and size, and the size of the patient population that the compound has the potential to address, economics plays a large part in choosing a good compound to develop. Company history and culture also play a role. For example, certain therapeutic areas may be aligned with the company's reputation and expertise. Company X is "the oncology company," while Company Y owns the diabetes space. This business "tendency" plays into the decision-making process for compound selection.

The decision-making process also needs to account for the company's size and resources. For many, such decisions are vetted by a series of governance fora, typically C-Suite portfolio reviews at large companies and Board of Directors at smaller companies. Executives must buy into the overall therapeutic strategy that the new compound would be a part of.

"Not all innovation comes from our labs," tout many Business Development heads. C-Suites are quick at spotting trends, such as dips in future revenues (aka innovation gaps from the company's research engine). Balancing external innovation landscapes with internally prioritized therapeutic areas is a critical part of pulling the trigger on a new development program, requiring planning, insights, and resources.

Consequences of a Bad Decision

To understand the stakes, it is helpful to illustrate the pitfalls of the decision-making process for deciding on a new compound. What can go wrong in the selection process? While science and medicine will determine if a drug should be approved, it's understood that some factors may largely be outside the control of anyone involved in the development process. However, many factors within their control can also impact the outcome, and decisions within the company's control can potentially result in a drug never reaching the market or poor performance on the market.

A common negative outcome of bad decision-making with a drug development program is being late to the market. Even if the asset is best in class, being 4th or 5th in the market is likely to have serious impacts on the return on investment a drug will receive. When looking at a new compound, an assessment of the true development time and the competitive landscape around the time of the potential launch must be considered.

The "Bandwagon" syndrome can also lead to the under-performance of an asset against expectations. For example,

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suppose a new target is popular within the industry for a certain disease. In that case, a company will be tempted to purchase an asset to jump on the bandwagon, leading them to overpay. Worse, by the time the drug is approved, it is 3rd to a market that has moved on past yesterday's hot topic. Forecasting of the competitive space will minimize these types of mistakes, although a certain risk is always present.

Another common mistake is that a company will take the development of a certain drug candidate personally, where the success of the drug is equated with the success of the company. When the decision process is not grounded in the current and future realities of the competitive space, development loses objectivity, which can lead to a project running for longer than it should before being discontinued, draining valuable resources. In other cases, even though the drug is approved, the company's "personal" stake has blinded it to the commercial reality that the drug will not make back even a fraction of the investment that was needed to develop it in the first place. All projects and assets should be reviewed and assessed objectively. They should have a clear place in the competitive field, fit with the company objectives, and meet patient needs. Personal "pet" projects have brought companies to their knees.

THE VALUE OF RISK

"We missed that one." Hindsight is an exact science; missing an opportunity is business life. It happens. This hurts when ~~it~~ a company is persuaded not to pursue an asset, later to find that another player makes a success of it. A common cause of this is over-reliance on external experts. If something is revolutionary and the biology is poorly understood, expert opinion will generally say to leave it. If the company is risk averse, this opportunity will be left, and someone else will take the risk and develop that asset. Internal criticism of an idea can also stop the pursuit of an asset, for all sorts of reasons – political, historical business areas, internal expertise (or lack of it), a lack of risk appetite.

Risk appetite for pharmaceutical companies' early-stage portfolio refers to the willingness and capacity of these companies to accept and manage uncertainty and potential setbacks in their drug development endeavors. It encompasses the level of risk the company is prepared to undertake in pursuit of innovative therapies and new drugs. Financial resources, regulatory environment, and strategic goals influence a pharmaceutical company's risk appetite in building and managing its early-stage portfolio. A high-risk appetite leads to a more aggressive pursuit of groundbreaking treatments, while a conservative one prioritizes safer, incremental advancements. Balancing risk and reward is crucial to long-term success. Here are some key strategies to achieve this balance:

1. **Diversification of the Portfolio**
   Maintaining a diverse portfolio of drug candidates can help spread risk. By investing in a mix of early-stage, mid-stage, and late-stage projects with varying risk profiles, companies can mitigate the impact of failures in one area while optimizing the potential for successful discoveries in another.
2. **Robust Risk Assessment**
   Conduct thorough risk assessments for each drug candidate. This includes evaluating scientific, clinical, regulatory, and go-to-market risks. Understanding the potential challenges at each stage of development allows companies to allocate resources and make informed trade-off decisions.
3. **Adaptive Trial Designs**
   Employing adaptive clinical trial designs to allow for real-time adjustments based on emerging data. This approach can help save time and resources by discontinuing unpromising candidates early and focusing efforts on those showing positive results.
4. **Partnerships and Collaborations**
   Collaborate with other pharmaceutical companies, academic institutions, or research organizations to share resources, expertise, and risks. Strategic alliances can help distribute the financial burden and knowledge required for drug development.
5. **Portfolio Optimization**
   Continuously assess the portfolio's balance between high-risk, high-reward projects and those with more predictable outcomes. Adjust resource allocation based on changing circumstances and opportunities.
6. **Financial Risk Management**
   Maintain a strong financial foundation to absorb setbacks. Adequate reserves and financial planning can help companies weather unexpected challenges without compromising ongoing research and development efforts.
7. **Regulatory Strategy**
   Work closely with regulatory authorities to understand evolving guidelines and requirements. Developing a clear regulatory strategy can reduce the risk of encountering unexpected hurdles that can delay or derail a project.
8. **Market Research**
   Conduct comprehensive market research to identify potential demand, competitive landscape, and pricing strategies. Understanding market dynamics helps in assessing the commercial viability of drug candidates. The commercial viability also contributes to Financial Risk Mgmt. and Portfolio Optimization exercises.

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9. **Long-Term Vision**
   Balance short-term and long-term goals. While early-stage investments may carry higher risks, they can lead to groundbreaking discoveries and long-term success. Maintaining a clear vision of the company's strategic objectives is crucial.
10. **Risk Mitigation Strategies**
    Develop contingency plans and risk mitigation strategies for potential setbacks. This includes exploring alternative indications, formulations, or applications for existing assets.

Balancing risk and reward in the pharmaceutical industry is an ongoing process that requires flexibility, adaptability, and a commitment to innovation. Most importantly, it benefits from the collaborative multi-functional team that is guided by a pre-determined framework for success. The best practices we describe help companies with what is perhaps the most difficult part of drug discovery – managing risk.

Rigorous Decision Making

A company can guard against sub-optimal decisions by ensuring stakeholders are well informed with unbiased, detailed competitive landscape assessments and forecasts of timelines and revenue. Scientific Technical Competitive Landscape assessments are required to inform stakeholders, allowing the best decisions. The knowledge management described in the second part of this report becomes the basis for a repeatable and robust review process for the compound at every stage of its process through preclinical and clinical trials.

Defining Assumptions

The due diligence process underlying a new drug development program has many elements that are not unique to healthcare. Other sectors offer insights into best practices.

Rather than avoiding all bias, other sectors have learned that the skills of your organization and its culture are important factors to consider when choosing a new program. For example, in highly scientific companies, facts and those who deliver them are highly valued and trusted. But these companies can get bogged down looking for "enough" data to decide. Facts are clearly important, but rarely are all the facts necessary to make a sound decision known. Rarely does the team have the luxury of time to collect and verify all the facts that it would like to have.

Effective planning processes account for this reality by requiring that planning teams deliberately identify and define *assumptions* that are being made in the absence of key facts.

This list of assumptions should be a formal artifact from the planning/due diligence process. These assumptions can be focused on trends in the market overall and what competitors are up to, and may include competitive threats, regulatory changes, and other external/environmental influences on the project.

The mere act of requiring a group discussion leading to a consensus on the list of assumptions for a project is valuable. The exercise often uncovers different ways a diverse team of executives views a development decision and particular markets.

As time passes, these assumptions are monitored by everyone involved in the project. As assumptions prove to be true, they convert into facts. As they prove to be false, the plan must be adjusted. Defining the assumptions helps the entire team view them as such and not hold on too tightly when they are shown to be incomplete or false.

Part 2 – Managing Knowledge

Where do insights for internal or external innovation come from? Companies rely on knowledge management systems customized to the company ecosystem.

Company specific knowledge management systems begin with external databases. Smaller companies subscribe to drug databases to suggests targets and to describe the competitive landscape for internal candidates. Larger companies invest in knowledge management systems that amalgamate external databases with internal insights. Currently, these systems require competitive intelligence professionals to maintain.

Assessment of a competitive landscape is critical to the decision to develop a new compound. For the first few years, R&D costs are the major investment, with variation depending on the type of molecule, indication, and scope. For example, cancer treatments are known to have higher initial development costs than those impacting other indications. Data estimating development costs over time are critical to the initial decision and must be monitored over time as the drug progresses. Eventually, these differences expand to include diverse regulatory requirements, clinical trial requirements, and supply chain requirements.

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Preventing Data Overload

Knowledge management describes the process of gathering and maintaining the facts and assumptions that are critical not only to the initial decision of which drug to develop, but also to the benchmarks on how to develop it. The target product profile provides a framework for organizing this knowledge, helping to maintain a comprehensive understanding of the competitive environment in which a product will compete.

> In the 21st century, finding the data is not the major challenge. It is using that data to derive insights and make decisions.

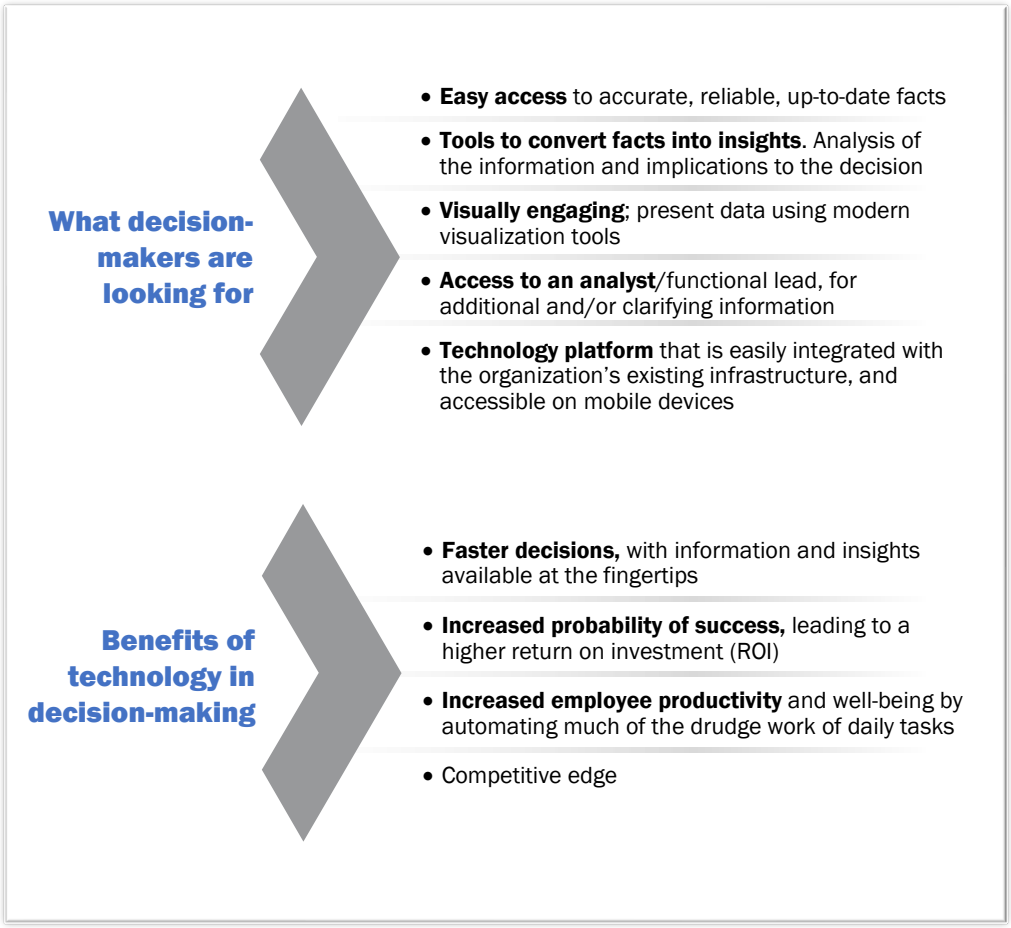
In the 21st century, finding the data (scientific, clinical, regulatory, legal, regional) is not the major challenge. It is using that data to derive insights and make decisions. It is managing the huge amount of data so that the important bits are front and center, while other information is organized and available when necessary.

Although clinical data, physician opinion, company strategy, and regulatory landscapes are daunting, several tools are available that help to organize and derive insight from the wealth of available data. A continuous monitoring program, maintained by a competitive intelligence (CI) team, is best practice. CI analysis provides insight into marketplace dynamics and challenges in a structured, disciplined, and ethical manner using published and non-published sources. The intrinsic value of competitive intelligence lies in its ability to shape and influence decision-making, and to positively impact business performance and strategy. Insights needs to be timely, address key business questions, and to be actionable.

Several types of information should be included in the continuous monitoring process:

- Pipeline – compounds are in development, what are their profiles, and when might they reach the market (launch timing)
- Clinical trials – patient populations, primary & secondary endpoints, outcomes (including trial duration), efficacy, & safety
- Competitor communications and publications – 10K, 8K & 10Q filings, earnings calls, financial presentations
- Analyst reports – Wall Street Analysts offer an interesting perspective
- Business news – various news sources should be monitored with relevant insight attached
- Conference proceedings – companies often release new data at medical conferences; the conferences are also a great place to see companies' messaging live, anticipate evolving positioning, assess level of investment and collect primary intelligence
- Regulatory agencies – behaviors, committee reports and meetings

Figure 2: Technology Solutions to Knowledge Management



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- Patents – what companies have patents in areas of interest
- Social listening – companies, physicians, patients, advocacy organizations and other relevant influencers
- Many companies offer CI platforms or systems that aggregate data sources into a single platform. Some companies build their own applications.

Various databases and platforms focus on the above information, including but not limited to:

- *Pipeline databases* – Pharmaprojects, R&D Insights, Cortellis Intelligence, Adis
- *Clinical trials databases* – TrialTrove, Clinical Trials Insights, clinicaltrials.gov, EudraCT
- *Patents* – Clarivate/Derwent patent database, various publicly available patent offices
- *Social listening* – X (formerly Twitter), Reddit, Facebook, Instagram, TikTok, LinkedIn
- *Analyst reports/Company* reports – AlphaSense, Edgar, Bloomberg.

Setting up continuous monitoring keeps your development program grounded in its real-world context as new information becomes available. This information, coupled with internal insights, must be used to regularly and aggressively update the TPP and other assessments of the drug's potential. This helps to minimize surprises and respond to new developments.

Regardless of whether you build an internal application or leverage an out-of-the-box application, such a platform is critical in monitoring, deriving insights from, and responding to questions about the information you are gathering. You can then set up a process to be alerted by the system as new information is made available.

While monitoring secondary sources is important, primary competitor intelligence should also be considered and layered on top of what you learn from data sources. One example of primary would be attending key conferences and gathering insights and reactions from medical experts (often referred to as opinion leaders), company booths and symposia, and from general conference attendees. Other primary sources of information include medical professionals (the "customer"), regulators, and employees of other drug development companies.

Your TPP is created at the beginning of the process, identifying a target and outlining what the new drug needs to deliver to be commercially viable and successful. But the TPP remains central to the knowledge management process as a touchstone for measuring success along the way. As drugs move through the development process, and more and more information becomes available, it is critical to review the TPP to ensure the drug continues to have the potential to be competitive and differentiated.

Future Best Practices

In this technology-driven world, the next generation of decision-makers demand instant information from a diverse variety of sources. Having cutting edge technological platforms to support decision-making is vital. Even big pharma, historically slow moving when it comes to technology, is starting to champion the use of artificial intelligence (AI) for decision support. For instance, Sanofi announced last year that it is *"all in" on artificial intelligence and data science to speed breakthroughs for patients"* (ref: Sanofi press release). According to Sanofi, "AI enables R&D teams to scale and accelerate ground-breaking research processes from a matter of weeks to just hours and improve potential target identification in therapeutic areas like immunology, oncology or neurology by 20 to 30%." The most valuable technologies will be the ones that organize knowledge, making it easier to derive insights. The key is not to replace the steps described above for knowledge management, but rather to simplify and streamline the data gathering and organization, shifting the emphasis from data gathering to insight generation and better decisions.

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