Trending 2017: Combination Products

Scientific advances have increased our understanding of complex diseases such as cancer and cardiovascular disease. This has resulted in new therapeutic approaches using combinations of drugs and medical devices directed at multiple therapeutic targets to improve treatment response or minimize adverse events.

Combination products are products that combine two or more different types of FDA-regulated products, including drugs, biologics, and medical devices. Regulators are working to make this process easier with the establishment of the Combination Product Council, identifying process improvements, and facilitating communication between agency centers.

Combination therapies are a natural outgrowth to the evolution of our industry, says Jeremy Levin, D.Phil, CEO, Ovid Therapeutics.

"I believe they are the future of many new medicines," he says. "If you look at the early history of drug development, the first drugs were seen as magic bullets, meaning they did one thing, hit one target, and they were successful. Conceptually, our industry has sought to create these magic bullets. However, we discovered over time that biology is exceptionally complex and combination therapies were or will be necessary to defeat some diseases."

Dairine Dempsey, Ph.D., VP, strategic regulatory affairs, ICON, agrees that combination products involving diagnostic devices and drugs or biologics designed to be used together in the clinical setting are the future and the need for both coordinated research and regulation in this area will be critical to new drugs making it to market.

More and more, researchers are discovering new advantages to combination therapies, which are driving an increase in product research and development.

"The increase we see in combinations is being facilitated by two key factors — science and collaboration," says Paul Biondi, senior VP, head of business development, Bristol-Myers Squibb. "The significant advances in science and therapeutic technologies have given us access to a tremendous amount of information that can unlock our ability to attack disease through a variety of mechanisms that include understanding the disease itself down to the cellular level, as well as how a disease reacts to one or more medicines."

Steve Sibley, VP, global submissions and submission leadership at Synchrogenix, a Certara company, says there are several main factors influencing the increased research into combination products.

"Combining two products that a patient needs to take concurrently into a single administration improves compliance," he says. "Taking two proven products and combining them to create a new product represents a relatively untapped potential for patent protection and market exclusivity. Furthermore, manufacturers' ability to formulate multiple

Many previously approved drugs are being investigated for use in combination with a device, as devices can bring many benefits to the administration of a drug, such as adherence, convenience, and speed of delivery.

PAUL BALAGOT
precisioneffect

As the numbers and types of combination products rapidly grow, effective regulatory capacity management is critical to maintain agency review timeline compliance and facilitate the creation of proactive, innovative regulatory pathways.

DR. ELIZABETH MADICHIE
PPD

A key factor that's leading to increasing research is the realization that combination immuno-oncology therapies seem to have better anti-tumor activity than traditional monotherapy without significant increased toxicity.

DR. JAI BALKISSOON
PPD

Combinations are almost the norm in oncology, and it is rare that single agents are used for any cancer treatment, except for settings such as maintenance or late lines of therapy.

DR. LIVIU NICULESCU
Takeda Oncology

products into a single capsule or tablet has increased significantly, making combination therapies more feasible."

It has been shown that combination products can bolster safety and effectiveness compared with either product used alone, says Greg Dombal, chief operating officer, Halloran Consulting Group.

"Bringing safe and effective products to market is the single charter that life-sciences organizations live by, and this is what makes the development of combination products so attractive," he says. "Additionally, manufacturers are continually looking for new growth opportunities, and combination products are an efficient driver. They can look to expand use of existing product lines and breathe new life into the organization's product development pipeline."

This is especially true in the area of cancer.

"Particularly in oncology, cancers can metastasize and become resistant to therapies over time, therefore we see tremendous potential in combination approaches," says Bill Hinshaw, executive VP and head, U.S., Novartis Oncology. "With the advent of personalized medicine, we are also able to use targeted combination treatments for specific patient subsets."

A key factor that's leading to increasing research is the realization that combination immuno-oncology therapies seem to have better anti-tumor activity than traditional immuno-oncology monotherapy without significant increased toxicity, says Jai Balkissoon, M.D., executive medical director, oncology, global product development at PPD.

"This has resulted in greater collaboration between small and large pharma to develop the next best combination therapies," he says. "Some of these active checkpoint inhibitors are becoming standard-of-care backbone therapies that sponsors combine with their novel agents. With the excitement and clinical activity that has been seen with immunotherapy in solid tumors, sponsors are rapidly moving their immuno-oncology development strategies into hematologic malignancies, creating another level of competition between sponsors."

Development and refinement of combination therapies provides patients suffering from chronic conditions improved treatments with the possibility of remission or even a cure.

CRAIG BAKER
Noble

Dr. Levin says oncology is not the only area where combinations of therapies are important.

"We've also seen important combination therapies in cardiology, most recently with the approval of Entresto from Novartis, one of the first new drug combinations to show a mortality benefit in congestive heart failure," he says. "Neurology is another area where combination therapies are beginning to be explored, and this is an area we are monitoring and beginning to explore at Ovid Therapeutics. As we gain a greater understanding of biology in all diseases, we will see an increase into research and development of combination therapies."

Today, combinations are almost the norm in oncology, and it is rare that single agents are used for any cancer treatment, except for settings such as maintenance or late lines of therapy, says Liviu Niculescu, M.D., VP, global and U.S. oncology medical affairs, Takeda Oncology.

"Malignant tumors are complex and have

Combination Products Insights…

ISAAC ISRAEL
Kitov Pharmaceuticals
The costs for developing new chemical entities has increased dramatically over the past 20 years. In contrast, most combination drug products utilize previously approved drug substances. This reduces the number of tests and trials required for development and thus, decreases the costs, time to NDA submission, and chances of failure.

PAUL GIUSTI
Multiple Myeloma Research Foundation
At the MMRF, we are pursuing innovative clinical trial designs that will allow us to test combination therapies with a number of different treatment arms. This model, coupled with using a patient's genomic information to project the best treatment outcome, will allow better combination trials and speed actionable insights.

ERIC RESNICK
West Pharmaceutical Services
Innovation in biological therapies is requiring innovation in the device constituent part, resulting in unique and novel combination products to address drug product characteristics, while addressing patient usability. As with any technology, combination products are being fine-tuned with every revision.

For combination therapy products, there is an added layer of complexity to identifying product quality complaints and adverse events, and regulations need to reflect the nuances of these products without being overly burdensome.

DR. KARI BLAHO-OWENS
C3i Healthcare Connections

multiple clones and multiple mechanisms for drug resistance that usually demand concomitant treatment with different mechanism of action," he says. "In multiple myeloma, a highly complex and devastating disease, triplet therapy is emerging as a standard of care, particularly for patients who have received prior treatment. There is no cure for multiple myeloma, and all patients will eventually relapse. With the introduction of novel therapies, triplet regimens allow physicians to treat the disease more aggressively than single agents or doublet therapy, potentially extending progression-free survival with minimal increases in side effects."

Pricing, Payers, and Regulators

"Combination products are designed to boost overall efficacy, to increase the percentage of patients who respond, to target specific issues with the immune response, and to strengthen the patient's underlying immune system," says Jeffrey Aroy, a consultant at Charles River Associates. "However, healthcare payers around the world are struggling with how to evaluate these combinations and how to afford them, when the combination price of two branded therapies can top $250,000 a year. In general, payers outside of the United States are signaling they will be tough on combinations. They suspect that the demonstrated efficacy gains do not warrant the total price."

Mr. Aroy says if a product with single agent activity shows a 30% improvement in overall survival, payers can deem this cost effective, even at a slightly higher price.

"However, a combination weighing in at double the price can achieve regulatory approval and clinical use with a 30% improvement in overall survival, but still be turned down for reimbursement in a health technology assessment," he says. Combinations, Mr. Aroy says, will need to show truly breakthrough improvement when applying to health technology assessment regimes such as the UK, France, and Germany.

"Manufacturers who own both halves of a combination, like BMS with Nivolumab and Yervoy, can provide concessions on overall price to make HTA math work, but if a newly launched agent is being used in combination with a marketed product from another company, the brunt of discounting may fall on the new product," he explains. "For this reason, developers who are jumping in on combinations with both feet might want to reevaluate whether their immune-oncology portfolio really is as valuable as forecast when the ultimate price of a second-to-market combination agent may require heavy discounting. It may make sense for compounds with single agent activity to launch as a stand-alone to establish pricing before pursuing indications in combination."

U.S. combination products are subject to regulatory review and oversight by one of three U.S. Food and Drug Administration Centers, with the Office of Combination Products providing oversight to the regulatory pathway decision process.

One of the key challenges in developing drug-device combination therapies is addressing the human factor considerations, says Paul Balagot, chief experience officer, precisioneffect.

"This is especially true for patient-administered drug-device combos," he says. "Many previously approved drugs are being investigated for use in combination with a device, as devices can bring many benefits to the administration of a drug, such as adherence, convenience, speed of delivery, etc. However, with any drug-device combination that requires the patient to self-administer, a deep understanding of human factors and usability will play a key role in ensuring a good patient experience."

One of the major regulatory challenges that needs to be addressed by the FDA for combination products is ensuring the appropriate processes are in place for monitoring, receiving, and identifying product quality complaints and adverse events, says Kari Blaho-Owens, Ph.D., VP, pharmacovigilance account management, at C3i Healthcare Connections.

"In drug-device combinations especially, the type or source of the product quality complaint or AE can be a range of issues — a malfunction in the device, a mislabeling on the product package, an error in auto-dispensing, lack of patient education, or another issue," she says. "So one therapy can span the

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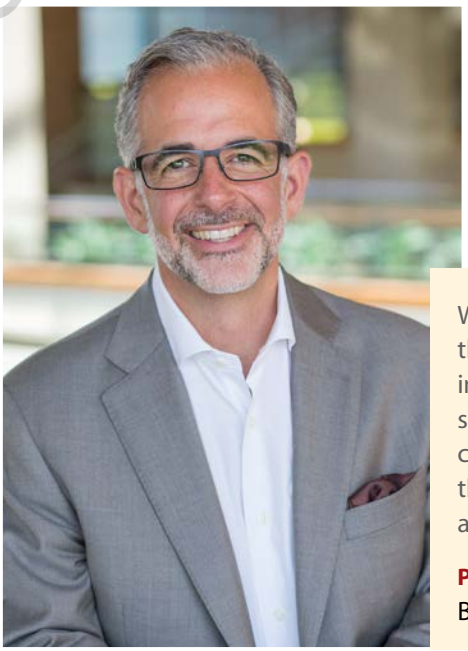
JEFFREY AROY
Charles River Associates



While we have seen individual therapies have a significant impact on serious diseases, we see a potential opportunity in certain diseases for combination therapy to surpass what we have achieved.

PAUL BIONDI
Bristol-Myers Squibb

FAST FACT

THE DRUG-DEVICE COMBINATION MARKET IS EXPECTED TO REACH $177.7 BILLION BY 2024.

Source: Grand View Research

category of drug, device, or product, or all of the above, within current FDA regulations. With the expected rapid growth of this market over the next several years, perhaps the FDA might consider making combination therapies its own category to streamline the regulatory process."

As the pharmaceutical sector continuously develops and embraces new technologies to deliver innovative healthcare, the boundary between device and drug/biologic to is becoming progressively blurred, says Elizabeth Madichie, Ph.D., executive director, regulatory affairs at PPD.

"As a direct consequence, guidance and legislative pathways need to evolve to meet these opportunities," she says. "Combination product regulation is complex and at times challenges national health authorities. As the numbers and types of combination products rapidly grow, effective regulatory capacity management also is critical to maintain agency review timeline compliance and facilitate proactive, innovative regulatory pathways."

Debra Grodt, director regulatory affairs, medical device and diagnostic division, Novella Clinical, agrees that the dividing lines between drugs, devices, and biologics continues to blur year after year. She adds that now with the emergence of digital health and personalized medicine the need for clear policies and collaboration between FDA and industry will be paramount. With the rapid changes in technology, the FDA will be challenged to maintain staff that can keep up with the development, diversity, and complexity of combination products.

Mr. Dombal says the FDA has recognized the need for visibility, transparency, and clarity in the approval process for combination products by recently establishing the Combination Products Policy Council.

"The industry is optimistic that this council will improve coordination and communication within the inter-center consultation process for combination products and streamline regulatory differences between these centers," he says.

Additional challenges for combination products lie with patients themselves.

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DEBRA GRODT
Novella Clinical

Precision or personalized medicines are a key driver for the combination products market, where identification of relevant biomarkers is integral to the treatment decision.

DR. DAIRINE DEMPSEY
ICON

Combination therapies are a natural outgrowth to the evolution of our industry. I believe they are the future of many new medicines.

DR. JEREMY LEVIN
Ovid Therapeutics

Craig Baker, executive VP of Noble, says factors such as anxiety, health literacy, and forgotten or complex healthcare provider instructions regarding self-administration create challenges for the industry post development and during the launch of combination therapies.

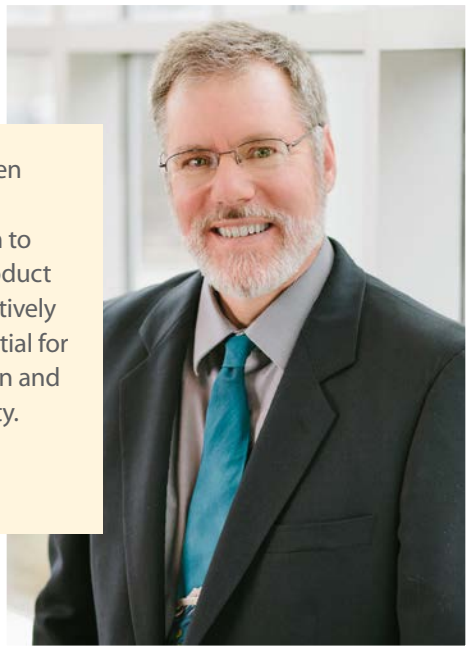
"Studies suggest 45% of patients skip or avoid injections due to fear," he says. "Additionally, 61% of patients do not completely read the instructions for use (IFU) with 12% of patients not understanding the IFU. Other findings show 40% to 80% of information provided by a healthcare provider is almost immediately forgotten after leaving the doctor's office."

Mr. Baker says to overcome these challenges, device and commercial teams are collaborating earlier in the process and leveraging human factor findings for product refinement.

"Collaborating earlier also allows for building and perfecting patient-centric training and education programs to better prepare for launching in a competitive marketplace," he says. "Development and refinement of combination therapies provides patients suffering from chronic conditions improved treatments with the possibility of remission or even a cure. Evolving the launch strategy to include patient-centric training products and materials such as auto injector and prefilled syringe training devices, smart packaging, and training IFUs prepares patients to correctly self-administer a combination therapy and provides a higher probability of adherence. Ultimately, developing a sound strategy earlier and addressing these challenges from onset of initial development to post launch leads to the increased likelihood of product success, competitive differentiation, and improvements in patient outcomes." PV

Taking two proven products and combining them to create a new product represents a relatively untapped potential for patent protection and market exclusivity.

STEVE SIBLEY
Synchrogenix



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Challenges for Development of Combination Products

Experts discuss efforts to address the development barriers.

Since its inception in 2002, the FDA Office of Combination Products (OCP) has worked to establish guidelines for how combination products will be classified and approved without the authority to review marketing applications or having standalone regulations of its own.

In 2013, the agency released a guidance for sponsors developing a combination with two or more new drugs that have not been previously developed for any indication to be used in combination to treat a disease or condition.

More recently, the agency has been evolving to provide efficiency and consistency in the review of combination products. In March 2016 for example, the FDA launched an effort called the "lean management process mapping approach" to build a better system for combination products review, one that's more cohesive, more collaborative, and more systematic.

In April the FDA launched the Combination Products Policy Council. Building on successful efforts such as the Biosimilars Implementation Committee and the Medical Policy Counsel in the Center for Drug Evaluation and Research (CDER), the Council is a senior-level, agencywide forum for discussing, resolving, and implementing product and policy issues. The Council's mission is to modernize the inter-center consultation process and related aspects of combination product and cross-labeled product review; promote development of innovative, safe, and effective combination products and cross-labeled products; and promote alignment in addressing challenging medical product classification issues.

Developing a combination therapy typically requires a larger investment than bringing a single agent to market, says Liviu Niculescu, M.D., VP, global and U.S. oncology medical affairs, Takeda Oncology. In many instances, combinations include products from multiple companies (often competitors), leading to the need to involve a wide range of stakeholders in the development, approval, and commercialization process.

"For instance, when designing a clinical trial for a new drug used in combination with standard of care, the company sponsoring the trial needs to provide not only the investigational treatment but also a supply of whatever therapy or therapies comprise the standard of care," he says. "For commercialized products, acquisition of standard of care can quickly add up to higher costs."

When testing combinations, there are multiple challenges for the FDA and for companies seeking approval for their drugs, Dr. Niculescu says.

"The comparator is usually another combination that sometimes even contains different drugs, so attributing the differential effect to one drug in the combination is difficult. The addition of another drug can lead to dose reduction and discontinuation of the co-administered drugs that may be part of the standard of care. Making this tradeoff between a reduced dose and the addition of an investigational drug is a delicate balance."

In addition, Dr. Niculescu says, because combination therapies each have their own set of adverse events, it is not always clear which agent is responsible, making defining the safety profile more difficult.

"To provide guidance on dose reduction and interruption, the FDA needs to consider both the safety of each drug as well as its efficacy outside of the combination," he says. "For example, some medicines have no activity as single agents, but they add efficacy when combined to standards of care. If a safety issue occurs, these drugs, rather than the standard of care, should be discontinued."

Dr. Niculescu says to ensure patients can access safe and effective medicines, industry must work hand-in-hand with the FDA from an early stage of development, addressing concerns and answering questions to enable understanding of the combination's benefits.

Combination products can also vary in complexity from two components packaged together to two components integrated together and in each case, each component may be the property of a separate owner/manufacturer, says Dairine Dempsey, Ph.D., VP, strategic regulatory affairs, ICON.

"Fully coordinated regulatory assessment by the various departments of the FDA — CDER, CBER, and CDRH — of each component of a combination product would greatly improve the development process for combination products," she says. "Such coordination should involve joint meetings between the sponsor(s)/applicant(s) and the FDA at all phases of development from pre-IND through to pre-new 'product' meetings as well as coordinated assessments once applications, either CTAs or NDAs/BLAs, are submitted. Flexibility in any regulatory process specifically designed for combination products will also be critically important to accommodate the potential for variability in the stages of development of individual components of a given combination."

Dr. Niculescu says once a combination treatment achieves regulatory approvals, the challenge of pricing the medicine appropriately arises.

"Each single agent in the combination has an associated cost, but pricing a combination therapy is seldom as simple as adding up the costs of each component. Industry must engage in conversations with payers to help determine a price for the therapy that recognizes the value and clinical innovation it delivers, while still enabling broad patient access," he says.

Greg Dombal, chief operating officer, Halloran Consulting Group, says one challenge is domain knowledge. Manufacturers typically have the expertise and product development experience on only one side of the combination product be it drug, device, or biologic.

"They often lack the internal expertise to address the manufacturing, scientific, and regulatory challenges in bringing a novel combination product to market," he says. "In this case, manufacturers will need to hire additional resources or bring in consulting experience to ensure success."

Steve Sibley, VP, global submissions and

Considerations for Developing Combination therapies

Clinical trial designs for combination therapies are complex. Navigating collaboration with the FDA on combination therapies is more complex than with a single drug. There are several important factors to consider and questions to ask when discovering, developing, or designing clinical trials for combination therapies:

- How to develop new animal models and assess the impact of combination therapies — animal models were traditionally designed to look at one drug, which poses challenges for drug developers
- How to design trials that are adequately powered and structured to assess the effect of two different drugs
- How to create a deeper understanding of dosing and treatment protocols to avoid toxicity
- Consideration of benchmarks and endpoints, recognizing the fact that designing a trial will critically depend on what are the signals that can be used to assess the efficacy of the combination and knowing that each part of the combination may have its own independent impact
- How to prioritize which combinations to test
- How to select patients who are most likely to respond to a specific combination

Source: Dr. Jeremy Levin, Ovid Therapeutics

submission leadership at Synchrogenix, a Certara company, says sponsors need to demonstrate their safety and efficacy both separately and together.

"With two approved drugs, the company must show that the new combined drug will be bioequivalent to the original products and that the component drugs will not interfere with each other's pharmacokinetics or pharmacodynamics," he says.

"A full nonclinical and clinical program will not be needed for these products; however, the sponsor must gain agreement from the regulatory agencies about what studies do not need to be done. With a combined approved and investigational product, a mixture of these opportunities and requirements apply."

Another inherent challenge is that each product has its own set of side effects, dosing, and specific patient population for which it is indicated. While there may be an overlap between the patients who are taking cholesterol and hypertension drugs, defining that patient population can be complicated. For example, those populations will not overlap completely and product-specific contraindications and restrictions must be addressed."

Combination Partners

Mr. Sibley says the new market opportunity for combination products is attractive to companies. As there is a significant increase in the incidence of chronic conditions such as cardiovascular disease, diabetes, and high cholesterol, there are growing patient populations for which combining medications might make sense.

Paul Biondi, senior VP, head of business development, Bristol-Myers Squibb says science is rapidly evolving, and that is never more evident than in the advances we have seen in the way many cancers and hepatitis C are treated today.

"While we have seen individual therapies have a significant impact on serious diseases, we see a potential opportunity in certain diseases for combination therapy to surpass what we have achieved," he says.

In cancer, in particular, Mr. Biondi says, our evolving knowledge of immunotherapies suggests that combinations of two or more mechanisms of action may provide an even greater benefit than what we have seen with monotherapy alone in some cancers, which warrants continued clinical research.

"Our belief at Bristol-Myers Squibb is that working together across the healthcare ecosystem is the rule, not the exception," he says. "Everyone brings strengths to the table that can benefit research, and ultimately patients. Science-led companies focused on innovation, biotech, and academia can together accelerate our collective understanding of the underlying biology of combinations as well as look for promising signals of activity to generate data that will inform future combinations."

Bristol-Myers Squibb markets the combination of two immuno-oncology agents, Opdivo and Yervoy, for the treatment of previously metastatic melanoma. The combination was approved by the FDA in October 2015 and in Europe in May 2016. BMS studies have found significantly longer progression-free survival and higher response rates with Opdivo and Yervoy combination and versus each one alone.

Novartis is another company actively pursuing combination products. One example is in the area of melanoma, a life-threatening type of skin cancer. According to recent results from the Novartis' COMBI-d Study, a combination of Novartis' BRAF inhibitor, Tafinlar and MEK inhibitor, has the potential to increase the estimated three-year survival rate of patients with melanoma receiving this combination treatment by 44%.

Another Novartis example is LEE011 (ribociclib), an investigational compound for breast cancer that recently received FDA Breakthrough Therapy designation in combination with letrozole. Results from the pivotal Phase III study demonstrate that LEE011 plus letrozole reduced the risk of death or progression by 44% over letrozole alone.

"In addition, there have been significant advancements in immuno-oncology, and we believe that there is still much more progress to be made," says Bill Hinshaw, executive VP and head, U.S., Novartis Oncology. "Our rich portfolio of investigational targeted therapies positions us to further advance the science of immuno-oncology as growing evidence supports the rationale for a combination approach for best outcomes, including the combination of immuno-oncology and targeted therapies. Seven of our immuno-oncology agents compounds are already in clinical trials, and five more are expected to enter the clinic individually and as combinations by the end of 2016." PV

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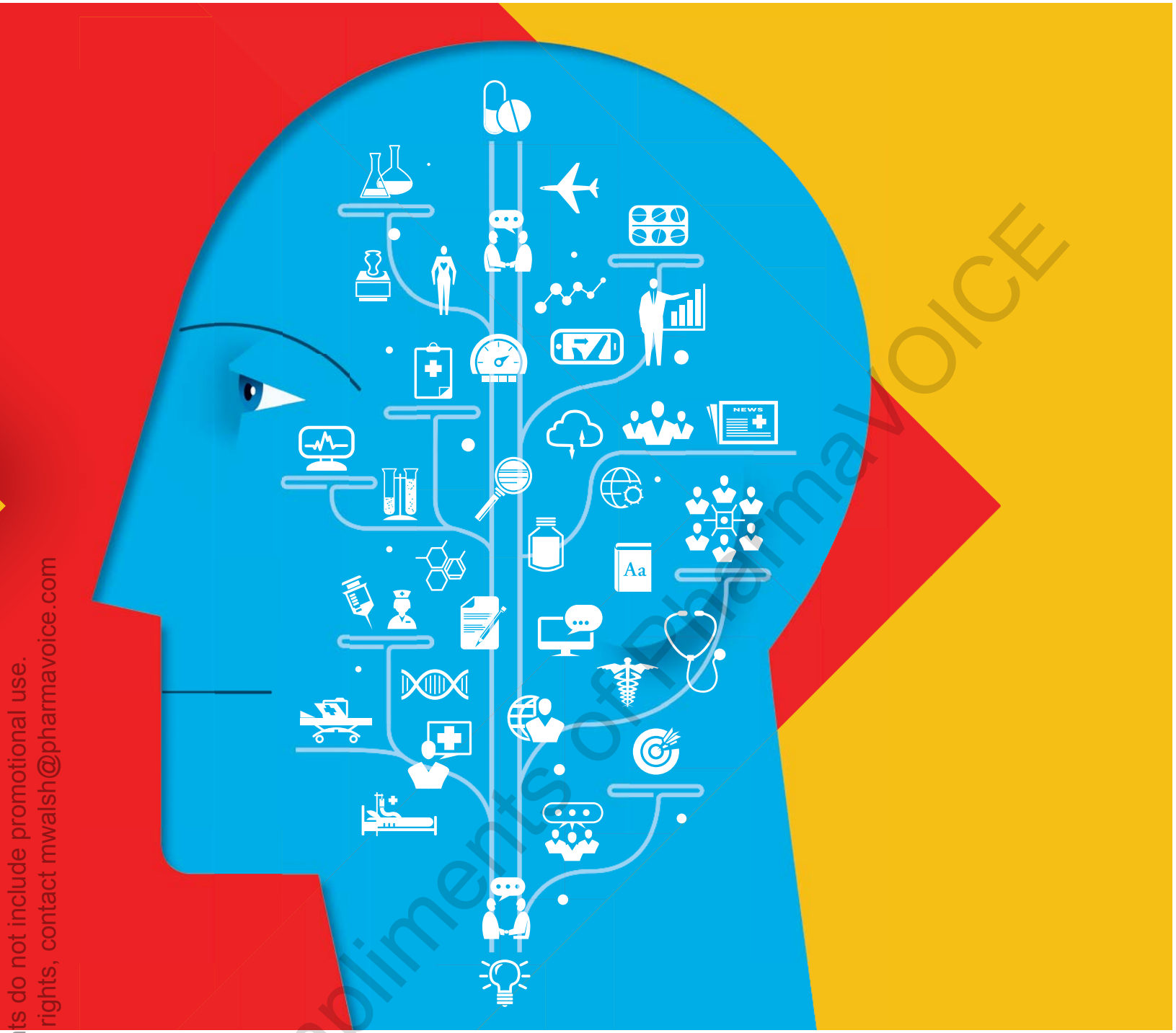

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