

Commentary

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Current trends and challenges in the pharmaceutical industry - we are here to make a difference

Introduction

The pharmaceutical industry is currently undergoing a major shift, driven primarily by groundbreaking new therapeutic approaches and a radical technological revolution. Issues such as the growing population of our planet, high unmet medical needs in various disease areas, and the rise of certain emerging markets to global players represent further challenges the industry must overcome.

On top of this, there is the lasting impact of the pandemic and the energy crisis caused by the war in Ukraine, which have led to supply chain disruptions and the need to adapt business and operating models to the "new normal". Finally, sustainability has stepped up from being a "feel-good topic" to being a business-critical success factor across the entire value chain. We need to act responsibly now to achieve challenging climate goals and safeguard our planet's resources for generations to come.

Against this backdrop, the pharmaceutical industry has to refocus and prepare for the future by establishing highly efficient and innovative R&D, agile marketing, and especially resilient and sustainable product supply organizations.

This commentary aims to reflect on a number of questions associated with industry trends and challenges. How do current trends impact our core business? How can we leverage our key strengths to unleash the full potential of our assets? How are we to deal with increasing regulatory requirements? Why should we make sustainability our top priority? How are we to rise to the challenges resulting from the pandemic and continue with renewed strength to make a difference for patients – now and in the future?

Megatrends and current challenges shaping the future of our industry

The effects of the pandemic are currently still very present in our daily routine, in both our working environment and our private lives. On top of this has come the terrible war in Ukraine, which has led to an unforeseen energy crisis, a rise in inflation, and higher raw material prices. Even without these global crises, the pharmaceutical industry was already undergoing a major transformation, driven primarily by the combination of radical inventions in the biology and biomedicine fields and digital innovations. This is still ongoing. Overall, we are facing a situation that makes one thing very obvious – we have to critically question our processes and long-established modes of (inter)action in the pharmaceutical industry to reorient and reinvent ourselves and be prepared for current challenges and those that lie ahead.

Amongst the most pressing global trends that will heavily affect our industry are the following:

- Our planet's growing and aging population – two billion people worldwide will be over the age of 60 by 2050, a doubling of this age group as compared to 2015.¹
- The increase in "prosperity" diseases – for example, the number of people with diabetes is predicted to rise to 578 million by 2030, and to 700 million by 2045. (Datta, 2019)
- High unmet medical need for various indications – more than ten million patients globally suffer from Parkinson's disease, which is one of the fastest-growing diseases in terms of prevalence, disability, and mortality.²

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¹ For statistical data, see: <https://www.who.int/news-room/fact-sheets/detail/ageing-and-health>, accessed July 27th 2022

² For statistical data, see: <https://www.parkinson.org/Understanding-Parkinsons/Statistics>, accessed July 27th 2022.

In line with our primary aim and purpose – improving patients' lives – we in the pharmaceutical industry need to switch gears and find ways to address these challenges. And we have already taken up the gauntlet. The combination of breakthrough discoveries in biological science (CRISPR-CAS was awarded the Nobel Prize in 2020) and the dynamic development of digital and computer science (from computing and automation to artificial intelligence) is propelling an unprecedented wave of innovation, referred to as the "biorevolution" (Chue et al., 2020). As a consequence, novel biological, biochemical, and biomedical applications are already improving our response to global challenges, with the best example being the recent pandemic. The speed at which scientists sequenced the coronavirus genome within weeks rather than months would not have been possible just a few years ago. In addition, new biochemical tools such as mRNA technology have reached maturity, enabling real-life applications such as the rapid introduction of mRNA-based vaccines to fight the pandemic. The development of smart devices, remote health monitoring, and precision medicines tailor-made to meet the need of individual patients are further examples of recent technological advances.

The rapid evolution of new technologies obviously opens up a range of unforeseen opportunities, especially for customers and patients. For example, we could unlock applications for biomedical tools that actually cure rather than just treat some of the most serious and deadly diseases such as cancer. As always, however, those opportunities are accompanied by challenges that need to be overcome first.

- Transforming Active Pharmaceutical Ingredient (API) portfolios from conventional small molecules to new chemical modalities and biomolecules requires an expansion of expertise and the establishment of new production technologies.
- End-to-end supply chains have been hit hard by the pandemic and must be turned into a future-proof setup with improved resilience.
- Sustainability has evolved into a huge, business-critical task that is increasingly relevant to keeping our license to operate.
- Artificial Intelligence opens up a vast array of options, but we still have some miles to go as an industry if we are to leverage the huge potential of digital solutions.

Further current challenges include reduced development timelines. One major focus of the pharmaceutical industry is to make new treatment options available to patients in need – as safely and yet as quickly as possible. In addition, new regulatory requirements and changes in reimbursement regimes are being driven forward. Speeding up development cycles raises the need to ramp up external innovation and partnerships, requiring new ways of thinking, for example by focusing on creative collaboration models with the clear goal of making full use of the knowledge capacity of other agile companies and start-ups.

Finally, the lasting impact of the pandemic has brought to the fore the need to transition to what is being called the "new normal", with remote working models (e.g. working from home, virtual audits, etc.) putting employees and new ways of working even more prominently at the center of attention. This is of crucial importance – not least because people and employees are the most valuable resource for companies to build on. Beyond the highly motivated workforces in the companies and organizations, we must put all patients in need at the heart of everything we do.

Selected challenges – dangers to our business or opportunities for growth?

Portfolio transformation – from conventional small molecules to new (chemical) modalities

As we have already pointed out, large parts of our industry are currently undergoing a portfolio transformation based on the increasing importance of new modalities. Over the past decade, the conventional drug discovery toolbox has been expanding continuously from traditional, small molecule APIs to new chemical modalities such as peptides, oligonucleotides, PROTACs, RNA-targeting therapeutics, antibody drug conjugates, and gene-editing approaches (Blanco et al., 2020).

While the transformational breakthroughs in bioscience offer invaluable opportunities for patients in need of new therapeutic approaches, the situation also poses challenges to the pharmaceutical industry. Firstly, we must extend our technological capabilities – including employees' knowledge, but specifically also engineering and manufacturing

expertise – across the whole value chain from development to routine production on both a medium and a large scale.

Accepting that many key players in the pharmaceutical industry aim to build their future portfolio on new modalities to a significant extent, the question arises: “What about conventional small molecules and traditional organic chemistry – will they disappear?” Our clear answer is no! Instead, we are convinced they will continue to play a key role going forward. There will be many unsolved problems where chemical know-how, creativity and a deep knowledge of conventional process chemistry are of vital importance when it comes to uncovering the best methods of synthesis and scaling up, thus making next generation APIs accessible for patients (Nising and von Nussbaum, 2022). Chemical API manufacturing that applies state-of-the-art technology platforms in all necessary volumes will significantly contribute to driving economical and sustainable supply and growth.

However, even the small molecule business is currently undergoing a significant transformation. Most importantly, there has been a clear trend towards APIs that are structurally more complex. Among the main reasons for this progression over recent years are the lower druggability of several disease-specific targets and a narrow patent space due to increasing competition. Having said that, complexity in the small molecules API field is increasing in many directions. Increasing molecular complexity (i.e., higher molecular weights, moving toward more complex structural features such as macrocycles, greater number of stereogenic elements, etc.) often results in a higher step count in the initial synthetic approach. In addition, a broad range of production scales across the API portfolio – from small-scale APIs for treating rare diseases to chronic treatment of cardio-vascular indications typically characterized by high peak demands – often places additional pressure on the manufacturing and supply chain setup. Quite regularly, the volume variances in larger API portfolios range from just a few hundred grams to three-digit ton demands at peak sales. Special technologies in the areas of highly potent APIs, biocatalysis, electrochemistry, photochemistry, or unit operations such as ultrafiltration, lyophilization, and chromatography are often required to produce next-generation APIs and drug products at scale.

The rising complexity and the trend toward more complex clinical trials, sometimes involving a higher number of patients in earlier clinical phases and higher costs per patient, result in a significantly increased cost of goods pressure. Contrary to previous experiences, this is increasingly driven by API manufacturing. The need to support even shorter development timelines so as to bring life-saving medications to patients as quickly as possible often means the production process is less well developed at launch. This increases the need for post-launch changes or the development of “second-generation processes”. It goes without saying that the very high quality standards for pharmaceutical products need to be safeguarded at all times.

In summary, there is an increase in the challenges for and expectations of pharmaceutical manufacturing organizations to supply innovative drugs in a fully reliable, cost-efficient, competitive, and sustainable way. At the same time, these reasons are offering opportunities to adapt traditional ways of working and make a difference in people’s lives.

As an industry, we should always aim to establish first-in-class development and technology platforms with state-of-the-art, digitally transformed product supply networks. We must strive to be at the forefront of innovation and technological development. To safeguard the reliability of supply and commercial competitiveness, we firmly believe that strong in-house launch capabilities with a fully integrated interface between chemical and pharmaceutical development and product supply functions are key success factors for ensuring best-in-class supply of key brands to meet patients’ needs and impact their lives for the better.

Resilient supply chains – impact during the pandemic and how we safeguard our future

The shock to supply and demand that arose out of the epidemic situation in China in January 2020 and the resulting global pandemic exposed vulnerabilities in the production strategies and supply chains used across many different industries. Concrete effects of the pandemic included:

- Lockdown and quarantine regulations affecting resource availability in production plants and distribution centers
- Temporary trade restrictions

- Transport capacity shortages, especially air- and sea-freight containers
- Changed demands and stockpiling
- Shortages of many products, highlighting weaknesses in supply chains

The economic turmoil caused by the pandemic has exposed many vulnerabilities in supply chains. There has therefore recently been widespread speculation in policy circles and the popular press as to whether globalization is still a valuable guiding principle for the future. Will or should the experience of the pandemic lead to supply chains becoming more local again?

It is our firm view that it should not! Going back to a domestic setup will not solve the issues described above but would instead cause knock-on effects such as increased costs and capacity shortages, the rise of a global recession and decreased flexibility. We strongly believe that the key to success is a global supply network with strong regional footprints, relying on free trade and cooperation in industrial operations. If we are to overcome future crises with global impact, what we need are global and resilient supply chain solutions, globally diversified production and distribution networks, and global capacity reserves that offer flexible room to maneuver, among other things.

As the pharmaceutical industry, we should stand up for a transparent, rules-based system of trade, managed globally by international institutions. We must strive for resilience rather than isolation. At the same time, we should foster balanced and diversified global networks, including backup systems within well-defined, segmented supply chains. Localization reduces the scope for fallback options and capacity reserves. In addition, we must further exploit the opportunities that Industry 4.0 offers for increasing supply chain transparency and improving risk management.

Digitalization is a key lever for optimizing supply chain processes and creating end-to-end transparency. Although "end-to-end" is regularly used as a buzzword, all too often we fail to look beyond the bounds of our own companies. The pandemic taught us that we must have a deep understanding (and ideally a real-time picture) of the entire value chain from 1st/2nd tier suppliers all the way downstream to distributors and pharmacies and ultimately the patient. We need to be able to receive early alerts when supplier problems arise and

proactively manage demand signals. This includes merging suppliers and CMO partners on integrated platforms, increasing data transparency, cloud-based, real-time tracking of transports, and intelligent control tower solutions.

Digitalization and Industry 4.0 – a challenge that offers immeasurable chances for improvement

The ongoing automation of traditional manufacturing and industrial practices using modern smart technology based on cyber-physical systems (CPS) and dynamic data processing is commonly referred to as "Industry 4.0" (Arden et al., 2021). This is having a major impact on manufacturing in the chemical and pharmaceutical industry, too. While it seems obvious that digitalization offers a variety of options for improvement in production, the challenge we often face is keeping pace with the overwhelming speed at which digital solutions sometimes evolve in adjacent industries. To be honest, the traditional pharmaceutical industry (especially the big players) is not noted for its ability to adapt quickly to new technologies, and isn't typically known for being particularly agile and dynamic in this regard. Even so, we are facing the reality of having to digitize our processes and change data and business processes to achieve digital transformation. This is a must – even in a strongly regulated environment.

In the pharmaceutical industry, we have access to data from research studies, production campaigns and marketing and sales, for instance. Digital technologies such as machine learning and artificial intelligence (AI) have the ability to connect and leverage this data so as to uncover new insights and improve decision making. With the help of data and digital technologies, we are able to develop new solutions that better fit our patients' needs. This enables us to manufacture more efficiently in digital factories and reduce our own environmental footprint.

A clear vision for implementing digital solutions in API production is typically driven by advanced analytics technologies, alongside transforming the ongoing automation into smart manufacturing. It might seem natural to assume that, for the majority of mature products, the respective manufacturing processes have been exhaustively optimized over the years. It was therefore all the more surprising and highly motivating to learn that there

is still potential to unleash by applying data science tools, even for long-established products. One thing is essential for the digital transformation – it has to be closely linked to the business by using digital insights to unlock additional value with relevant impact. It does not make sense to simply introduce technology just because it's all the rage. Doing so can bring with it a major risk of failure (Hotz, 2022). Taking this as a basic guiding principle for selecting meaningful use cases, it is advisable to follow a gradual process, starting with a plant readiness assessment (rating digital maturity), followed by a process improvement analysis (problem identification), clustering, and finally, prioritizing potential digitalization projects through the creation of implementation plans. In our experience, the key success factors of every advanced analytics project are best summarized as follows:

- 10% of the success is due to the algorithms identified
- 20% is based on successful application of new tools and improving the IT and computing landscape
- 70% can be attributed to sensitivity in the change management process, driven by the excitement and involvement of the interdisciplinary teams

Most importantly, “digital” must become an integral part of our thinking and mindset. In this context, it is worth pointing out that there is much to learn from next-generation employees – let's empower them to speak up, to share their views and knowledge and thus propel our digital transformation efforts in our industry to reach unprecedented speeds.

Sustainability – a challenge we must take seriously to safeguard our planet's resources

The scientific evidence could not be clearer. Global climate change caused by human activity is happening now and poses a growing threat to society. The pace of change and the evidence of harm have increased markedly over recent years. The time to significantly reduce greenhouse gas emissions is therefore now. Sustainability has quickly grown from a “feel-good” topic to a business-critical success factor. Society at large is increasingly aware of sustainability issues and has developed a strong desire for responsible action and change. As the pharmaceutical industry, we have a responsibility to deliver on the expectations of customers, policy makers, and investors. Most importantly, however, we should strive to push ourselves even beyond benchmarks and regulations imposed from the outside, since we

are aware that it is us who can make a difference for the generations to come. API manufacturing organizations in particular have a huge lever when it comes to improving our industry's ecological balance (Flessner, 2022).

In order to improve our ecological footprint, we need to consider the following relevant aspects – science-based climate targets, water and waste reduction targets applying the principles of circularity, and the responsible use of substances, focusing on green chemistry. A strong basis for fulfilling challenging climate targets is typically a sound and forward-looking sustainability and green energy strategy. We need to aim for compliance with the carbon reduction ambitions defined by the European Green Deal as a business imperative. We should foster an even more intense dialog and partner up across divisions, companies, and even industries to reach the most challenging goals. Especially in the area of circularity, we strongly believe there are many opportunities beyond those currently being addressed. Once we enter into open discussions, we can come up with joint ideas that make the most of our creative potential and technological expertise.

Furthermore, sustainability must be a factor in everything we do, including hiring next-generation scientists and leaders with an eco-centered mindset to proactively design production and packaging processes, focusing our downstream distribution on reducing, recycling and/or reusing waste streams and optimizing our value streams across the entire value chain – from suppliers to customers and patients. Examples from API manufacturing include the recycling of starting materials, reagents or catalysts from production waste, with subsequent repurposing of the recovered material, and the use of biocatalytic platforms to replace the conventional chemical routes of synthesis with less resource-intensive alternatives. Using raw materials from biogenic sources can further reduce our overall footprint.

We should also keep in mind that sustainability goes beyond waste treatment, circularity, and handling emissions. The final – but no less important – dimension is social responsibility. For example, it is well worth acknowledging the valuable impact of funding regional initiatives, engaging in the field of social innovation and hands-on support for science education. Both in the communities around our sites and in society as a whole, these efforts can bring about improvements and really make a difference.

What actually makes the difference – people are our greatest asset

As the saying goes, “If you want to go fast, go alone. If you want to go far, go together!” A high level of commitment among employees is essential when it comes to achieving progress in our industry, mastering the challenges of today so as to be prepared for the future, and coming up with innovative solutions that address the needs of both our own generation and those to come – from sustainability to unmet medical need in a growing and aging population. To achieve this, we need to go from “command and control” to “agility and adaptability”, with a key element of personal development and leadership being empowerment. In addition, we need to really live up to our commitment to inclusion and diversity. As employers, we must therefore take on the challenge of creating a working environment that values all people, supports them in their (self-)development and fosters creativity. On the other hand, it is up to every single employee to embrace a mindset based on a constant willingness to learn and adopt a culture of interaction.

Summary and conclusion – we are here to make a difference!

There are several key challenges that we need to take seriously to successfully shape the future of the pharmaceutical industry – the increasing cost pressure in production, the need to implement supply chain concepts with greater resilience, full commitment to driving sustainability, and the question of how to unleash the full potential of digital solutions in an industry that has historically not been very agile.

We need to act now to maintain the strong momentum of our industry and safeguard pharmaceutical companies as innovative and competitive global players with strong footprints in their home countries. If we approach this proactively, it is a big opportunity – but it might become a threat if we do not foster collaboration and joint action now. We must also not forget that it’s all about the people, because every change needs strong commitment among staff, coworkers, and collaborators. Ultimately, this means we need to face and tackle the challenges for our industry together – across leading pharma companies, across the interface between industry and academia, and across colleagues with diverse backgrounds and opinions.

Our challenge to you today, therefore, is this – let’s tackle it together. Let’s team up and strengthen collaboration to shape the future of our industry together. Let’s go hand in hand, using collaborative network approaches as a basis wherever feasible.

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