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Revamping the ever-changing landscape of drug development processes in the midst of COVID-19 pandemic

EDITORIAL

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Oncology is the frontline of drug development. The current pharmaceutical pipeline is disproportional focused on oncology, where about 1/3 of all phases of development is in this therapeutic area. The emphasis brings about substantial breakthroughs and has made positive impact on the quality of life. However, oncology remains a threat to human existence. To facilitate this process, a comprehensive list of novel/first molecularly targeted oncology drug approvals by the FDA from 2017 to 2020 is assessed. Here, we focus on molecularly targeted oncology drugs and not cytotoxic ones, although the latter remain important. To achieve this purpose, besides their sponsors, years of approval, drug classes, and cancer indications, clinical significance is included. The results show that approved molecularly targeted drugs span across diverse classes, including small molecule receptor inhibitors, and biologics such as monoclonal antibodies, antibody-drug conjugates, check-point inhibitors (i.e., PD1, PDL1, CTLA4) and CAR-T cell therapies. Although complete cure of cancer remains limited, we have made substantial inroads and more is yet to come. Moreover, many of these new knowledge can be extrapolated to other therapeutic areas, especially to those of currently unmet medical needs such as in neurology and other chronic diseases.

Keywords: Oncology drug class; Cancer indication; Molecularly targeted; Drug Development

> "If we have seen further, it is by standing on the shoulders of giants"
>
> (Isaac Newton, 1675)

As this adage goes, cumulative scientific breakthroughs bolster progress. The beauty of standing on the shoulders of giants is to see far, capitalize on prevailing opportunities and leapfrog to greater heights. An example is the Nobel Prize in Chemistry recognizing Charpentier and Doudna's discovery of the gene editing tool CRISPR/Cas9. Their breakthrough opens the door for curable and precise repair of mutated or heritable gene expressions, the root causes of many diseases.

At the moment, the COVID-19 pandemic is inflicting unprecedented human suffering and death tolls on a global scale. COVID-19 infection can cause severe acute respiratory syndrome that readily overwhelms ICU capacity. With social distancing and mask-wearing, it has brought many face-to-face activities to a standstill. Moreover, when restriction is lifted prematurely, or with change in virulence, COVID-19 restriction may be reinstated and lockdown recur. Such uncertainty creates disincentive for economic to strive.

One consolation is that the pandemic is revealing substantial shortcomings in drug development processes, and has accelerated many innovations to meet this health crisis. Many changes have been advocated, some of which are starting to take shape [1]. Telehealth and electronic health records are being pushed to the frontline, and vaccines and antiviral therapeutics are being developed and authorized with remarkable speed. A case in point

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is the availability of COVID-19 vaccines under Emergency Use Authorization, approximately a year after the WHO identified SARS-CoV-2 as a new type of coronavirus, in early 2020. This is a noteworthy accomplishment, since vaccine development is a long and complex process, often lasting 10–15 years.

Administration of vaccine could bring light at the end of the tunnel. Nevertheless, with global inequality of wealth and education, it is conceivable that widespread adoption and equitable distribution of vaccines will encounter challenges. With the possible scenario that pockets of COVID-19 virulence may persist, we have to prepare for the worst case scenario that emergence of COVID-19 resistant strains may not be a moment of the past. This scenario is foreseeable, with the examples drawn from recurrent common cold and influenza infections. What is certain is that after this watershed period, the practice of medicine and social behavior will never be the same again.

Here we highlight some actionable proposals within the scope of scientific communities, with examples drawn from oncology, which may further galvanize medical product development in all therapeutic areas.

Regulatory partnership and leadership

Drug development success hinges on early partnership among sponsors, clinicians/scientists and regulatory agencies. This type of collaboration was evidenced by the US-FDA, UK-MHRA and EMA initiatives in response to COVID-19. It builds on some of the innovative processes utilized during novel drug approvals by the US-FDA, and among them are the molecularly-targeted therapies in oncology, which are at the forefront of breakthrough in pharmacotherapy [2]. They include small molecules for biomarker-defined enzyme inhibition and biologics such as monoclonal antibodies (mAbs), antibody-drug conjugates (ADCs), check-point inhibitors (i.e., PD1, PDL1, CTLA4) and CAR-T cell therapies [3].

Nearly all of the recent oncology approvals were awarded the US Orphan Drug Designation and received expedited review (priority, breakthrough, accelerated approval, fast track) or rolling review that substantially shortens review time. To use an exceptional example, participation in the FDA Real-Time Oncology Review Pilot Program by the sponsor of brentuximab vedotin has resulted in an approval in just two weeks after final submission. Regulatory leadership for initiatives like this one will continue to be needed in promoting trial flexibility, information sharing, trust and transparency, and equity in access, among others.

Risk-based regulatory process and requirements

For emergency use and highly unmet medical needs, the traditional step-wise development policies will need to be accelerated. Under such circumstances, the flexible use of fit-for-purpose, risk-based efficacy, safety and chemistry and manufacturing controls (CMC) would be expedient [4]. Medical scenarios warranting regulatory transformations could include not only a pandemic like COVID-19, but also a global antimicrobial resistance crisis and even persistent serious diseases. We cannot afford delay in finding effective interventions for these health dilemmas without further increase in human suffering and death tolls.

Good science

Underpinning team success is the ability to marshal the talents of capable clinicians/scientists. Through them, remarkable progress has been made in our understanding of tumor cell resistance to treatment, ongoing rapid mutations, and the importance of the innate immune response. Breakthrough areas include the early diagnosis and detection using circulating tumor DNA (liquid biopsy), and clinical data assembly through the use of real-world evidence. New knowledgebase acquired specific to the COVID-19 pandemic include use of novel messenger RNA (mRNA) technology in producing vaccines, better understanding of genomic variants and sensitivity of existing diagnostic detection [5], and in long-term symptomatic patients of post-acute COVID-19 syndrome colloquially termed ‘long-haulers’.

Patient centricity

Addressing unmet medical need is a goal of drug development. In 2009, the FDA finalized a guidance on patient-reported outcomes (PROs) for developers seeking to incorporate PROs such as using symptomatic scores, functional status and health-related quality-of-life assessments. While meaningful to patients and healthcare providers, PROs may rarely achieve US labeling claim status that impact how medications are used; A prominent exception in hematology/oncology includes the PRO-related efficacy claim for ruxolitinib in myelofibrosis [6]. However, patient centricity will grow in prominence, with the recent FDA-initiated Patient-focused Drug Development, wearable devices, remote/virtual trials, and individualized treatments based on genomics. Such approaches accommodate diverse individual characteristics and needs, which tend to be more quantitative and objective, and no longer one-size fits all.

Complex Innovative Design (CID)

Following a standard approach of drug development through a series of trials, each investigating one or two interventions, is unsustainable. To remedy this situation, novel trial designs were piloted initially in oncology [7]. In 2018, FDA initiated the Complex Innovative Trial Designs (CID) Pilot Program, followed by a draft guidance to incorporate complex adaptive, Bayesian, and other novel designs. With the urgency imposed by COVID-19, a CID approach may be an appropriate avenue to evaluate new and repurposed medicines [8].

To elucidate further, master protocols that require a highly coordinated set-up and trial conduct in multiple diseases are more in focus now [9]. With existing master protocols, no reinventing the wheel is necessary. The beauty of master protocols is that master protocols may run trials for years, save substantial resources, and speed up drug development. However, prospective planning is needed to avoid having operational complexity that will offset saving of resources. One possible way to reduce operational complexity is through the use of more investigator-led trials where trial operators are familiar with existing processes.

Specifically, COVID-19 has made rapid learning essential, where investigators employ adaptive design in platform trials with multiple study appendices. Multiple therapeutic agents can be introduced or withdrawn based on frequent interim looks at the data, applying real-time analysis and pre-specified stopping rules [9]. In this way, modern drug discovery pipelines might be accelerated to clinical evaluation at a faster pace. Recent success in the ACTIV Trial, representing international antithrombotic master trial platforms where one of which is for COVID-19 [10], demonstrates that CID approach is applicable to global drug development.

Global perspective

Drug development is learning to tap into other larger markets besides USA/UK/EU. For example, with stimulation from economic growth and supporting government policy, the healthcare system in China has expanded vastly in the past decade. Regulatory reforms in the burgeoning oncology market in China have resulted in earlier country-level approval decisions. However, this work is hampered by poor coordination among research communities globally, which became evident in the pandemic, despite the adoption of the International Conference on Harmonization (ICH) guidance. Formation of a new healthcare standard for data exchange accredited by the Health Level Seven International (HL7) may ameliorate global efforts. One such standard is the WHO's initiative to devise a personal digital vaccination certificate of COVID-19, which could curtail the spread of COVID-19.

Team effort

Success in building high-performing teams, as in team sports, involves upholding team morale, building trust and fostering transparency and collaboration among all stakeholders. Although saving commute time, the absence of face-to-face communication under COVID-19 calls for greater teamwork. With recent advances in technology and coupled with willingness to adapt, it is conceivable that this critical hindrance can be overcome.

Concluding remarks

By focusing on patient centricity, with efficient drug development as an end-goal in mind, and by upholding team morale while practicing good science and team management, we are poised to navigate the challenges of revamping traditional drug development processes. Out of these efforts to leverage innovative learnings and momentum catalyzed by this crisis, patients with current unmet needs will greatly benefit.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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