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Industrial Adoption of Continuous Pharmaceutical Manufacturing

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Pharma trends in China*

1. The 'Made in China 2025' initiative identifies biopharma and advanced medicinal products as one of 10 key sectors that the country will focus on.
2. Multinational companies continue to expand R&D operations in China. China's relatively lower cost base compared to developed markets globally is one of the attractions for these companies.
3. China's large pharmaceutical market and its strong growth potential provide an impetus for international pharmaceutical firms to develop medicines specifically for the country's domestic market.

*Fitch Solutions China Pharmaceuticals & Healthcare Report - Q1 2021

The Chinese Pharma Market is forecasted to grow at CAGR of

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From the Editor

Dear Readers,

In the past year, the pharmaceutical industry has been in the limelight amid the COVID-19 pandemic. From the development of rapid test kits to the manufacture of vaccines, in 2020 the pharmaceutical industry world-wide was able to prove its resilience in times of crisis. The rise of the COVID-19 pandemic though is only one aspect that contributed to this burst in net worth. Changing demands of healthcare systems, the push in demand for personalized treatments and therapeutics has also boost the pharmaceutical industry to where it is today. Business models of pharmaceutical compa-nies would also see some shifts in focus, driven by five key forces as highlighted in a report by Deloitte. These five key forces include; development of preventive and early detection, customized treatments for personal-ized medicine, curative therapies, digital therapeutics, and precision intervention.

Prioritization of digital transformation within the indus-try that allow for actionable health insights from health data and artificial intelligence will see the pharmaceuti-cal industry incline towards the use of more digital technology. Shifts in how diseases are identified, pre-vented, treated or cured may lead to how business models will change in the pharmaceutical industry. The adoption of continuous manufacturing to produce a pharmaceutical product to reduce cost and human error is another factor that would evolve the business models of pharmaceutical companies.

Within Asia, the growing ageing population has caused a paradigm shift in demographics and priorities of healthcare systems. Increase in prevalence of chronic diseases such as hypertension and cancer has drawn greater focus to preventive care and early detection and intervention in order to support the rise in elderly within Asian countries and the health complications that comes with ageing. In China, 95 percent of diseas-es are attributed to chronic diseases. As with other Asian countries such as Japan, Malaysia, Vietnam, Singapore, and Thailand, the incidence of disease due to chronic diseases are able 80 percent. This rising trend would push the demand for chronic disease care. This demand would be met by increase in the number of clinical trials testing for new and improved ways of disease treatment and detection. The use of digital technology in managing health conditions will also evolve how pharmaceutical companies develop and manufacture treatments and therapies in the coming future.

Report by The Economist Intelligence Unit showed that the aggregate pharmaceutical market in Asia rose by 28 percent between 2012 and 2017. This figure was projected to increase to 42 percent from 2018 to 2022. On top of that increase in pharmaceutical spending by emerging markets such as Indonesia and Thailand will see and increase between 5 to 10 percent over the next five years. Expansion of the pharmaceutical industry in Asia is enhanced by the region's GDP growth. Other factors such as increase in demand for better healthcare services due to growing disposable incomes would lead to increase in purchase of treat-ments and therapeutics.

China is also expected to become the world's sec-ond-largest pharmaceutical market by 2022, with India narrowing the gap with South Korea as Asia's third largest and the world's eighth largest pharmaceutical market. Based on a report by Deloitte, the increase in High-Net-Worth Individuals in China will also boost healthcare expenditures on more products, together with the growing tech-savvy generation of consumers, the way patients and consumers behave towards healthcare and lifestyle would change the way the pharmaceutical industry will provide treatments and therapies.

The COVID-19 pandemic has also seen an unprece-dented change in the way healthcare systems work.

With lockdowns and movement restrictions, the way patients consult healthcare professionals for care and obtain healthcare information has evolved to adopt remote and digital methods. Wearables and digital healthcare technologies has also enabled the generation of healthcare information by the patient for tele-monitoring. This way doctors and healthcare professionals would be able to obtain real-time information about the patient remotely.

The pharmaceutical industry is dynamic and will have to be adapted as generations change and demands shift to meet the healthcare needs of populations. In Asia, the rise in spending of pharmaceuticals due to increase disposable income, and growing ageing populations will push the pharmaceutical industry to evolve in order to support changes in healthcare demands of a country. Digital transformation in disease treatment, prevention, and detection will also change the way pharmaceutical companies operate their business and provide products that use digital technology. Artificial intelligence and the availability of a vast amount of healthcare data will also help enhance the digital healthcare transformation.

Sincerely,
Editor in Chief
Pharma Sources Insight

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Interview JIANGXI FANGZUN CHEMICAL:

Attentively Help Every Customer Create Better Market Value

1、What efforts have been made to explore into the overseas market? And What achievements have been realized?

Jiangxi Fang Zun Pharmaceutical Chemical Co., Ltd. (JIANGXI FANGZUN CHEMICAL) is a professional production factory integrating R&D and production.

Established in 2008, the company specializes in the production of nitrobenzoic acid series, aminobenzoic acid series, hydroxybenzoic acid series, chlorobenzoic acid series and other pharmaceutical intermediate products.

JIANGXI FANGZUN CHEMICAL participates in domestic and foreign pharmaceutical exhibitions every year, actively expanding the customer base. The products have been exported to Japan, India, Europe and the United States and other countries!

2、What are the blockbuster products of JIANGXI FANGZUN CHEMICAL? And in which areas can the products be used?

N,N-Dimethylformamide dimethyl acetal is one of the star products of JIANGXI FANGZUN CHEMICAL, the annual output of the product can reach 360 tons, and it is widely used in the fields of medicine, pesticide, electronics, etc.

3、How to build the core advantage and overall strength of JIANGXI FANGZUN CHEMICAL?

Constantly innovating to produce excellent products is the goal that the whole company is pursuing.

- The company has established production bases in the east coast of China and Jiangxi Chemical Park.
- With advanced scientific research strength, new product development capabilities and an experienced planning and sales team, JIANGXI FANGZUN CHEMICAL is able to improve the quality of the product, increase and stabilize the productivity, and meet the needs of the customers.

4、"Attentively help every customer create better market value" is a commitment of JIANGXI FANGZUN CHEMICAL to its customers, how to put it into practice?

JIANGXI FANGZUN CHEMICAL will carefully follow up the feedback of each customer, and make improvements according to the customers' requirements. It will seriously implement the suggestions proposed by the customer after the on-site audit, and strive to continuously optimize by itself!

A Tour to JIANGXI FANGZUN CHEMICAL's Factory

N,N-dimethylformamide dimethyl acetal
Intermediates and fine chemicals

FACTORY VIEW 01

FACTORY VIEW 02

Visit Online Shop of JIANGXI FANGZUN CHEMICAL

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Artificial Intelligence and COVID-19 Vaccines

By Lin Zhang

Keywords: Artificial Intelligence (AI), SARS-CoV-2 (COVID-19), Vaccine

COVID-19 rapidly transformed into a global challenge, costing thousands of lives, overwhelming healthcare systems, and threatening the economy all around the globe. In this worldwide health crisis, the medical industry requires new technologies like Artificial Intelligence (AI), to monitor, control and look ahead against the spread of COVID-19 pandemic, which has become a powerful tool for diagnostic test designs and vaccination development.

Currently, COVID-19 vaccine has been heralded as a big achievement, several vaccines against COVID-19 have been developed by Moderna, Pfizer and Johnson & Johnson within a year at unprecedented speed, and inoculation programs, together with improving patient treatments and regular testing, point to a way out of this pandemic. But, the work is far from done at the moment. Better and more vaccines may be required to combat the pandemic and provide a better return to normalcy. For these purposes, artificial intelligence has been quite promising and may be one of the best tools to weather the pandemic.

In regards to vaccine development, there are already options for AI programs, which can be used to analyze data and create better and better results the more data the AI receives through machine learning programs. It can predict mortality risk by adequately analyzing the previous data of the patients. AI can easily track the spread of COVID-19 virus, identifies high-risk patients, and is useful in controlling this infection in real-time, which provides opportunities for developing and improving new medications and vaccines at a much faster rate than usual.

In recent years, AI, in general, is becoming a popular tool in the pharmaceutical industry, not just in the case of COVID specifically. It has been able to support drug development, saving time and money in the process. AI can analyze tons of data in moments and assist in decision-making, determine the therapy a patient might need, manage clinical data, choose the right active ingredients, and propose alternatives among existing drugs. (1) A centralized collection of worldwide COVID-19 patient data will be beneficial for future artificial intelligence and machine learning research to develop predictive, diagnostic, and therapeutic strategies against COVID-19 and similar pandemics in future.

There have been new applications of AI in COVID-19 pandemic. DeepVacPred is one program that was developed by the Southern California Viterbi School of Engineering and was focused specifically on SARS-CoV-2.(2) The AI can realize various vaccine design cycles in minutes and was able to eliminate 95% of the candidate compounds when normally these could take years. It can work to stay ahead do the virus as it mutates.

> **AI has been applied to many subfields of drug discovery and vaccine development, it is also being proposed as an effective solution for many problems tied to the COVID-19 vaccinations. In the future, it seems likely that AI will serve more goals in regards to prevention and support.**

The current vaccines have a proven effectiveness against a specific type of COVID-19, but the virus can mutate and change, so that a new vaccination will be needed. This point is very important. By using an AI, it is possible to ensure that the vaccines that are developed can tackle the new RNA mutations of the virus. (3) This is not something human researchers can do quickly, but the DeepVacPred might be able to. This can help ensure that the world is ahead of the coronavirus and not responding to it, as happened at the start of the pandemic.

Specifically, in the case of DeepVacPred, the method has yielded 26 potential vaccines against the coronavirus, and scientists selected the best 11 to start working on a multi-epitope vaccine, which can attack the spike proteins that the coronavirus uses to bind and penetrate a host cell. The dataset involved around 700 thousand different proteins. (4)

AI has also been utilized and proposed as a tool to facilitate vaccine distribution. At the moment, the challenge is pretty complex, as populations around the globe need to receive vaccines according to priority, with more vulnerable populations coming first, and with special care being taken to avoid ethnic or other forms of bias. AI can be used effectively and give the results much quicker than an individual or a group of researchers. This could mean that entire population groups would be excluded or disadvantaged, but this means mostly that the AI is a solution that needs to be employed with care and oversight. (5)

At the moment, AI is being proposed as an effective solution for many problems tied to the COVID-19 vaccinations. Specifically, several new variants of SARS-CoV-2 include B.1.1.7 in the UK, B.1.351 in South Africa, and P.1 in Brazil have been discovered. These variants are spreading across the world now, and they each contain multiple mutations. AI can be used to develop more vaccinations and stay ahead of the virus and the potential mutations it can show. The possibility of predicting mutations and anticipating vaccines is tremendously valuable to ensure better management of the situation.

AI can play a role in specific areas in regards to vaccination, which can help establish the impact and triage, that is, see which areas need the vaccine first and which population groups should receive priority attention. Moreover, it can also be used for managing vaccine production, distribution, tracking the effects, manage the supply chain, establishing useful patterns and surveys for adverse effects post-vaccination. AI offers many distinct benefits and can manage these tasks more effectively and detect patterns that a researcher would not be able to see. (6)

Additionally, AI can produce results very quickly, hundreds of times faster than a human could, analyzing huge amounts of data right away and giving results that would help take action on a timely basis, rather than reacting to events after they unfold. However, there are also risks in choosing this approach. It is possible that the AI that is being employed is using faulty mechanisms or is biased in some way. While there is the perception that an AI is unbiased by its nature, the failure to include or consider certain factors could make the results flawed. For example, there is a debate on whether researchers should use race and ethnicity as variables for their AI program in regards to vaccine distribution or whether this is not as essential and the possible problems this can cause.

At the same time, AI's other benefits are not to be ignored, even if it cannot be always trusted blindly. For instance, outsourcing tasks to an AI could help free time and can be an excellent way of providing faster, better, and more accurate results with the potential of preventing and anticipating various issues.

AI has been applied to many subfields of drug discovery and vaccine development. In the future, it seems likely that AI will *serve more goals in regards to prevention and support. However, the technology needs to be employed carefully and with oversight to avoid any of the downsides linked to it. Furthermore, the safety and efficacy of these vaccines have not been fully tested in human clinical trials, which could be a major concern. Therefore, novel vaccines and vaccination strategies are needed to enhance the efficacy and safety of COVID-19 vaccine development.*

About the Author:

Lin Zhang

Lin Zhang, Ph.D., senior director of a health care industry company in the United States. With the experience in clinical medicine, biotechnology, health industry and other fields, he is responsible for the research and development of plant medicine, functional food and health products. He was a clinician and worked for the National Cancer Institute, FDA and the National Cancer Center of Japan for many years.

Worth Reading:

Brief Overview of Natural Adaptogens

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With Two More COVID-19 Vaccines Marketed, A Review of the Current Situation of COVID-19 R&D in China

By Yefenghong

Keywords: COVID-19 Vaccines, Inactivated Vaccine, Adenovirus Vector Vaccine

On Feb. 25, the National Medical Products Administration of China (NMPA) conditionally approved the registration applications of two COVID-19 vaccines: Inactivated COVID-19 Vaccine (Vero Cell) of Sinopharm Wuhan Institute of Biological Products Co., Ltd., and Recombinant Novel Coronavirus Vaccine (Adenovirus Type 5 Vector) of CanSinoBIO, with the latter being the first Chinese-produced adenovirus vector COVID-19 vaccine approved.

The marketing registration applications of four Chinese-produced COVID-19 vaccines have so far received the NMPA's conditional approval. In addition to the two mentioned above, the other two vaccines are the Inactivated COVID-19 Vaccine (Vero Cell) of Sinopharm Beijing Institute of Biological Products Co., Ltd. approved on Dec. 30, 2020, and the Inactivated COVID-19 Vaccine (Vero Cell) of Sinovac Life Sciences Co., Ltd. approved on Feb. 5, 2021. With real-world protection efficacy data reported in succession after vaccination, humanity is expected to usher in a new situation in the fight against the pandemic. COVID-19 vaccine R&D in China has also made new progress in succession. Let's take a look.

1. Sinopharm CNBG: The first inactivated COVID-19 vaccine approved for marketing in China

The inactivated COVID-19 vaccine from Sinopharm CNBG was conditionally approved by the NMPA at the end of Dec. 2020, making it the first inactivated COVID-19 vaccine approved for marketing in China. In a word, to make inactivated vaccines, the virus strains are first isolated, picking good "seeds", and then multiplied (by tens or hundreds of times) and cultured; the live viruses are then killed so that they lose their infectivity and replication ability but retain part of their function of stimulating the human body to generate an immune response, and then they are finally turned into vaccines through purification and other processes. Inactivated vaccines are relatively faster to develop, although the required investment is huge.

The Lancet, an international academic medical journal, published the results of Phase 1/2 clinical trial of the vaccine on Oct. 16, 2020. This randomized, double-blind, placebo-controlled, phase 1/2 trial divided 192 healthy adults into groups aged 18-59 and ≥60 to evaluate low, medium, and high doses of the vaccine. Participants in each group were randomly assigned at a ratio of 3:1 and separately receive the vaccine or the placebo. In phase II, 448 healthy adults (aged 18-59) were assigned to four groups to receive the high-dose vaccine on day 0 or the medium-dose vaccine on days 0/14, 0/21, or 0/28, mainly to assess safety and tolerability, with the secondary outcome immunogenicity, assessed as the neutralizing antibody responses against infectious SARS-CoV-2.

According to the results of the study on candidate vaccine-induced neutralizing antibodies and positive conversion rates, in phase 1 clinical trial, in the healthy adult group, seroconversion rates reached 100% at day 14 in both the low and medium dose populations and 96% at day 14 in the high dose population; in the elderly group, seroconversion rates reached 100% at day 28 for all populations; in all groups, neutralizing antibodies increased significantly from day 7 and peaked at day 42. Vaccine-induced neutralizing antibody titers in the high-dose group were significantly higher than those in the low-dose group, but not significantly different from those in the medium-dose group. Furthermore, the vaccine-induced neutralizing antibodies neutralized various viral strains, including the natural variant with spike mutant (D614G) in the current pandemic. According to phase 2 clinical results, neutralizing antibodies increased from day 14 to day 28 after the second vaccination in the D0/D14 and D0/D21 procedures; vaccine-induced neutralizing antibody titers in the D0/D21 procedure were significantly higher than vaccine-produced neutralizing antibody titers in the D0/D14 procedure.

The results showed that the vaccine was effective in inducing neutralizing antibodies in the age groups, and the neutralizing antibody levels were comparable to those reported in other vaccine studies, proving the good immunogenicity of the vaccine. Furthermore, the difference in the adverse reaction rate between the vaccine and placebo groups was not statistically significant, and the vaccine's adverse reaction rate was lower than the levels reported in the currently published clinical studies of related vaccines, indicating a good safety profile of this inactivated vaccine in humans.

According to the results of the interim analysis of the vaccine's phase 3 clinical trial, all vaccinees produced high titers of antibodies after two injections of the immunization procedure, the positive conversion rate of the neutralizing antibody was 99.52%, and the protective efficacy of the vaccine against COVID-19 was 79.34%. The data results met the relevant technical standards of the World Health Organization and the relevant standard requirements in the Guidelines for the Clinical Evaluation of Prophylactic Vaccines against COVID-19 (Trial) issued by the NMPA.

2. Sinovac: The second inactivated COVID-19 vaccine approved for marketing in China

On Feb. 5, 2021, the NMPA conditionally approved the registration application of the Inactivated SARS-CoV-2 Vaccine (Vero Cell) of Sinovac Life Sciences Co., Ltd., which is indicated for the prevention of the disease caused by SARS-CoV-2 infection (COVID-19).

It is learned that the vaccine, with a trade name CoronaVac, is indicated for the prophylactic vaccination of people aged 18 and above. It is the second inactivated COVID-19 vaccine approved for marketing in China.

CoronaVac® is made by inoculating African green monkey kidney cells (referred to as Vero cells) with SARS-CoV-2 (CZ02 strain) and then through culture, harvesting liquid of the virus, virus inactivation, concentration, purification, and aluminum hydroxide adsorption, and it contains no preservative.

On Apr. 16, 2020, the vaccine entered Phase 1/2 clinical studies and demonstrated good safety. In July of the same year, Phase 3 clinical studies were conducted successively in four geographically different and distinct countries: Brazil, Chile, Indonesia, and Turkey. These studies were conducted independently using the same vaccine batch (medium dose 600 SU), following the same immunization procedure (0,14) and according to the requirements of the Good Clinical Practice (GCP), with a total of 25,000 people enrolled.

Phase 3 clinical studies conducted in Brazil and Turkey separately evaluated the protective efficacy of CoronaVac® in the high-risk population (medical personnel treating COVID-19 patients) and the general population, and adopted a multicenter, randomized, double-blind, placebo-controlled design in both countries, the primary endpoint is the incidence of COVID-19 14 days after two doses of the vaccine or the placebo.

By Dec. 16, 2020, the study of the vaccine in Brazil enrolled a total of 12,396 medical workers aged 18 or above and obtained 253 positive cases during the observation period. After 14 days following vaccination with two doses of vaccine on the schedule of day 0,14, the efficacy rate against diseases caused by

COVID-19, including mild symptoms not requiring medical attention, was 50.65% for all cases, 83.70% for cases with significant symptoms requiring medical treatment, and 100.00% for hospitalized, severe, and fatal cases.

The target populations of phase 3 clinical trial of the vaccine in Turkey are medical workers at high risk (K-1) and the general population at normal risk (K-2), with all participants aged from 18 to 59 years old. By Dec. 23, 2020, there were 918 subjects enrolled in K-1 and 6,453 subjects in K-2, with a total of 7,371. Among them, 1,322 subjects completed the two-dose vaccination and entered the 14-day observation period after receiving the second dose of the vaccination. Based on an analysis of 29 cases, the efficacy rate for COVID-19 prevention was 91.25% after 14 days following the two-dose vaccination, in adherence with the schedule of day 0,14.

3. CanSinoBIO: Recombinant Novel Coronavirus Vaccine (Adenovirus Type 5 Vector)

The conditional marketing application of Recombinant Novel Coronavirus Vaccine (Adenovirus Type 5 Vector) (trade name: Convidecia™) co-developed by CanSino Biologics Inc. (CanSinoBIO) and Institute of Biotechnology, Academy of Military Medical Sciences, Academy of Military Sciences has been approved on Feb. 25, 2021, making it the first single-dose COVID-19 vaccine conditionally approved for marketing in China.

According to the announcement, the global multicenter phase 3 clinical study conducted by CanSinoBIO in Pakistan, Mexico, Russia, Chile, and Argentina has completed vaccination of over 40,000 subjects and interim data analysis.

According to the interim analysis results of phase 3 clinical symptoms was 65.28%; 14 days after single-dose vaccination of the vaccine, the overall protection against all symptoms was 65.28%; 14 days after a single-dose vaccination of the vaccine, the overall protection against all symptoms was 68.83%. The vaccine's efficacy of protection against severe symptoms was separately 90.07% 28 days after single-dose vaccination and 95.47% 14 days after single-dose vaccination. This means that a single dose of Convidecia™ can generate protection in only 14 days, and the product can achieve faster and more comprehensive protection for the populations.

Speed is essential in the battle against COVID-19. A single dose of vaccine works in one shot, which can make the body develop immunity in the shortest time, thereby rapidly blocking the virus. Furthermore, the single-dose vaccine means that it can protect twice as many people as the two-dose vaccine under the same capacity condition. Plus, as the vaccine uses the same adenovirus vector-based technical route as the recombinant Ebola vaccine (adenovirus vector), it can be stably preserved between 2°C and 8°C, making it easier to transport and store normally and making it more accessible.

4. Wuhan Institute of Biological Products: Inactivated COVID-19 vaccine

Following the conditional marketing of the inactivated COVID-19 vaccine of Sinopharm Beijing Institute of Biological Products Co., Ltd., the conditional marketing of the inactivated COVID-19 vaccine of Wuhan Institute of Biological Products was approved by the NMPA on Feb. 25, 2021, making it the second COVID-19 vaccine of CNBG approved to be marketed conditionally.

Wuhan Institute of Biological Products started to conduct a phase 3 clinical trial of its inactivated COVID-19 vaccine in countries including the United Arab Emirates from July 16, 2020, which is an international multicenter, randomized, double-blind, placebo-controlled one. According to the interim analysis results of phase 3 clinical trial, the inactivated COVID-19 vaccine of Wuhan Institute of Biological Products had good safety after vaccination; after the two-dose immunization procedure, all vaccinees produced high titers of antibodies, with a 99.06% positive conversion rate of the neutralizing antibody, and the COVID-19 vaccine achieved 100% protection against the confirmed moderate to severe disease, with overall protection efficacy of 72.51%. The vaccine had good cross-neutralization against the SARS-CoV-2 strains, and the anti-SARS-CoV-2 antibodies produced by the vaccine had extensive cross-neutralization reactions against 10 prevalent or representative SARS-CoV-2 strains in China and abroad.

5. Fosun Pharma and BioNTech: mRNA COVID-19 vaccine

COMIRNATY (BNT162b2), the mRNA COVID-19 vaccine of Fosun Pharma and BioNTech, received Special Import Authorization in Macao, China on Jan. 25, 2021. Earlier before, the COVID-19 vaccine based on BioNTech's mRNA technology received Authorization for Emergency Use in Hong Kong, China. BioNTech and Fosun Pharma announced entering into a strategic cooperation agreement in Mar. 2020, according to which, both parties would jointly develop and commercialize a COVID-19 vaccine in Greater China based on BioNTech's proprietary mRNA technology platform.

mRNA is a natural molecule that can produce a target protein, or antigen, which activates the body's immune response against various pathogens. Compared to traditional vaccines, an mRNA vaccine has advantages such as no viral component and no risk of infection; short development cycle, enabling rapid development of novel vaccine candidates to meet viral mutations; dual mechanism of humoral and T-cell immunity, with strong immunogenicity and not requiring adjuvants; and ease of mass production.

According to the earlier press release of Fosun Pharma, the global phase 3 clinical trial results showed that BioNTech's mRNA-based COVID-19 vaccine met all primary efficacy endpoints, demonstrating an effectiveness of 95% in preventing COVID-19 and 94% in adults aged over 65 years old.

6. Clover Biopharmaceuticals: S-Trimer COVID-19 vaccine candidates

Utilizing Clover's proprietary Trimer-Tag© technology, S-Trimer is a trimeric SARS-CoV-2 spike (S)-protein subunit vaccine candidate. Similar to other enveloped RNA viruses such as HIV, RSV, and influenza, SARS-CoV-2 is also an RNA virus that has a trimeric spike (S) protein on its viral envelope. The virus binds to the ACE2 receptor on the host cell surface through its trimeric antigen and so as to enter human cells, making it the primary target antigen for vaccine development. S-Trimer resembles the native trimeric viral spike protein and can be quickly expressed by mammalian cell culture.

According to the pre-clinical study data and preliminary phase 1 clinical data, S-Trimer COVID-19 vaccine candidates demonstrated favorable tolerability and could induce high levels of neutralizing antibodies and strong Th1-biased cell-mediated immunity, thus they worth the continuous assessments.

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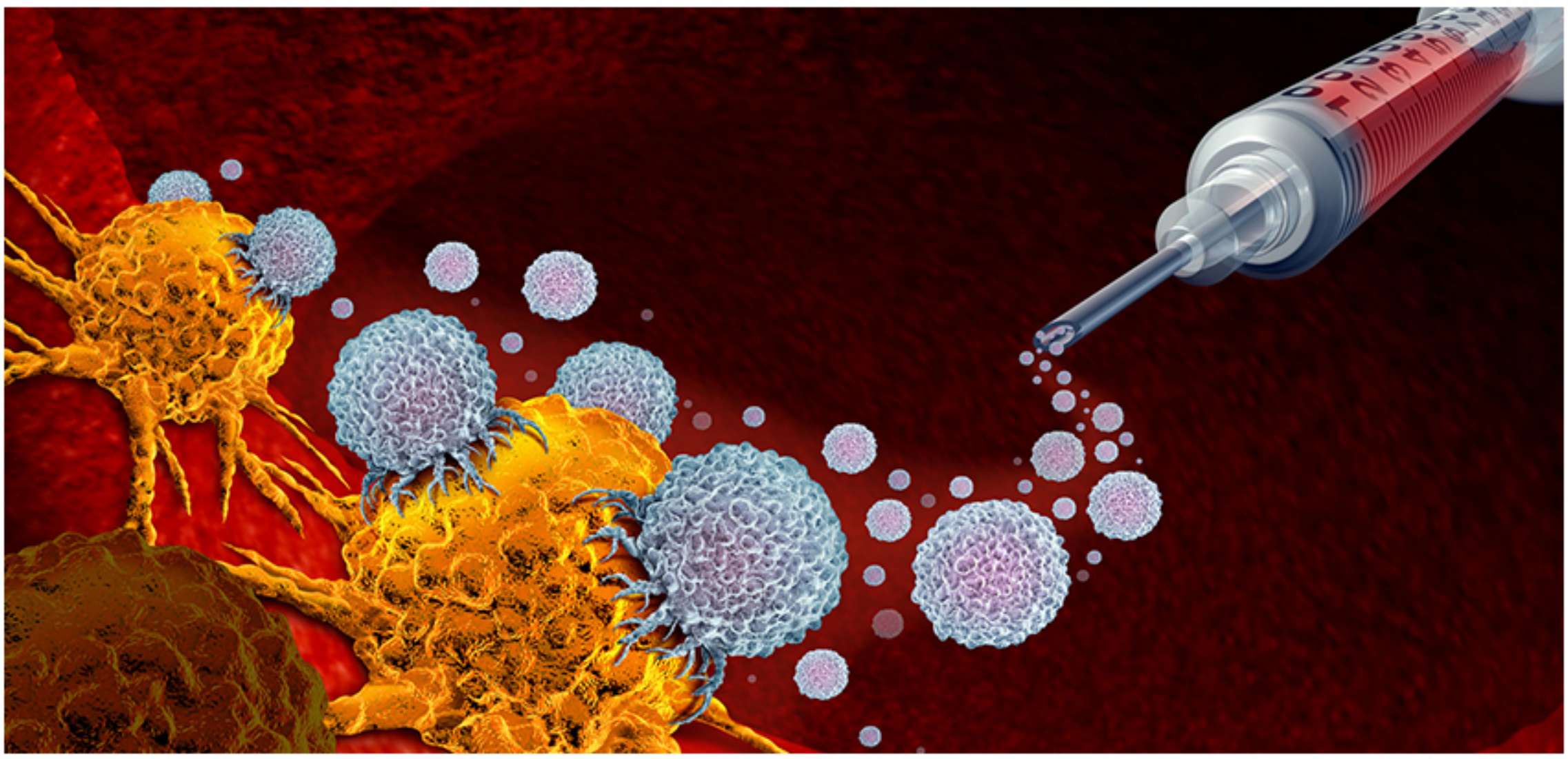
GLOBAL MARKET REVIEW APRIL 2021

Antibody-drug Conjugates – Understanding the "Trojan Horses"

By Neeta Ratanghayra

Keywords: ADCs, Antibody, Targeted Therapy



Despite advances in anticancer chemotherapy, small-molecule anticancer drugs are associated with a narrow therapeutic window and limited efficacy. A robust strategy for targeted therapy, known as antibody-drug conjugates (ADCs), has been developed to counterfeit this challenge.

What are antibody–drug conjugates?

ADCs consist of a tumor-specific monoclonal antibody covalently conjugated to a cytotoxic drug using a chemical linker. The cytotoxic drugs (chemotherapeutic agents) linked to the monoclonal antibody are known as cytotoxic payloads or warheads.

ADCs increase the efficacy and reduce the systemic toxicity associated with current chemotherapeutic regimens. ADCs can deliver highly cytotoxic payloads directly to tumor cells, and hence they are highly lethal towards the targeted tumor cells. Due to this selectivity, ADCs are also referred to as the "Trojan Horses."

How do antibody-drug conjugates work?

ADCs use monoclonal antibodies to deliver potent cytotoxic payloads to tumors that overexpress a particular target.

To enable exclusive binding of the monoclonal antibodies (mAb) to its target site, the target antigens should be expressed on the tumor cells but not on normal cells.

Once the ADC recognizes and attaches to its target antigen, the ADC–antigen complex is internalized into the cell through receptor-mediated endocytosis. The ADCs are engulfed into endosomes that eventually mature and fuse with lysosomes.

Due to the acidic environment and the presence of lysosomal proteases such as cathepsin B, the ADC is cleaved and the cytotoxic drug is released into the cytoplasm of tumor cells.

Once released, the cytotoxic warheads bind to their target, either the microtubules or DNA, and induce apoptosis, and ultimately cell death.

Key Requirements of ADCs

The success of an ADC is depends significantly on the specific properties of its four components – antibody, antigen, cytotoxic payload and the linker.

- **Target antigen selection**

Selecting a unique antigenic target for the monoclonal antibody is the most critical step during ADC development. The antigen should be selectively expressed in tumor cells and have a negligible expression in the healthy cell. The unique antigenic target should also have robust internalization properties to promote the transport of ADC into the cell, which, in turn, will increase the efficacy of the cytotoxic agent.

- **Selection of antibody moiety**

Another vital component is the antibody. Apart from delivering the cytotoxic drug to the tumor cell, the antibody should possess high binding affinity for the tumor cells' antigens. Low immunogenicity, low cross-reactivity, good retention, and adequate linkage-binding capacity are other ideal properties.

- **Linkers link the cytotoxic drug to the monoclonal antibody**

The linkers also play a vital role. When the ADC complex is released in the systemic circulation, the linker should remain stable and prevent the release of the cytotoxic payload in the off-target tissue. The linker must keep the ADC in an inactive, nontoxic state; however, upon internalization, the linker should release the cytotoxic drug.

- **Cytotoxic payloads**

The cytotoxic payloads are activated when they are released inside the tumor cell cytoplasm. The drug should be highly potent and have a small molecular weight. They should possess high stability in the systemic circulation and lysosomes. Low immunogenicity and a long half-life are other essential features of an ideal cytotoxic payload. Moreover, the cytotoxic payload's chemistry should be such that it can be easily conjugated to the linker while retaining the internalization property of the monoclonal antibody.

DNA-damaging agents (Calicheamicin, Doxorubicin) and microtubule-disrupting agents (Auristatin, Maytansinoids) are the two common classes of cytotoxic payload used in ADC development.

Antibody-drug conjugates in clinical development

The concept of ADCs may seem pretty straightforward; however, developing an optimized and functional ADC is challenging. Optimizing the formula to balance the three components right is the main issue.

Though many ADC therapies are in the pipeline, only a few have reached the market. Currently, nine Food and Drug Administration (FDA)-approved ADCs are available, and more than 100 others are in clinical studies.

SR. NO.	ADC	ORIGINATOR	INDICATION
1	Gemtuzumab ozogamicin (MYLOTARG)	Pfizer	Acute myeloid leukemia
2	Brentuximab vedotin (ADCETRIS)	Seattle Genetics/Takeda	Hodgkin lymphoma, systemic anaplastic large cell lymphoma
3	Inotuzumab ozogamicin (BESPONSA)	Pfizer	Acute lymphoblastic leukemia
4	Polatuzumab vedotin-piiq (POLIVY)	Genentech/Roche	Relapsed or refractory diffuse large B-cell lymphoma
5	Ado-trastuzumab emtansine (KADCYLA)	Genentech/Roche	HER2-positive breast cancer
6	Belantamab mafodotin (BLENREP)	GlaxoSmithKline	Relapsed or refractory multiple myeloma
7	Trastuzumab deruxtecan (ENHERTU)	AstraZeneca and Daiichi Sankyo	HER2-positive unresectable or metastatic breast cancer
8	Enfortumab vedotin (PADCEV)	Astellas Pharma	Locally advanced or metastatic urothelial cancer
9	Sacituzumab govitecan (TRODELVY)	Immunomedics, Inc.	Metastatic triple-negative breast cancer

Challenges for clinical applications of ADCs

The clinical application of ADCs comes with its own set of challenges, among which the issue of toxicity is the most critical. The toxicity of ADCs is mainly caused by the cytotoxic drugs.

The specificity of antibodies is another issue. Ideally, target antigens need to be tumor-specific and possess high expression in tumor cells and negligible expression in healthy tissues. However, practically, antigens are also expressed in normal tissues.

Current animal models are incapable of predicting the ADCs' activity in humans. Many ADCs demonstrate therapeutic benefits in rodent tumor models; however, these effects are not replicated in the clinic. The difference between rodents and human antigens is said to be the reason for this.

Conducting clinical trials of ADCs is also a challenge, particularly identifying patients who overexpress the targets of interest.

Innovations in ADCs - What the future holds

Over the past few years, advances in technologies have generated a range of possibilities to design new ADCs. For example, many novel antigen targets have been identified for both solid and hematologic tumors. Several highly potent cytotoxic drugs have been discovered, such as anthracyclines, microtubule inhibitors, and amatoxins which can be included as suitable complements to currently used cytotoxic drugs. Apart from this, new generation linkers have been characterized to enhance the therapeutic window of ADCs.

Research is ongoing to develop bispecific ADCs. With the use of bispecific ADCs, both potency and selectivity can be improved; multiple classes of payloads can also be delivered. Combination strategies such as combining checkpoint inhibitors and traditional chemotherapies are also being explored.

Although there are many challenges to overcome, the development of new ADCs provides significant opportunities for future cancer therapies.

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Neeta Ratanghayra is a freelance medical writer, who creates quality medical content for Pharma and healthcare industries. A Master's degree in Pharmacy and a strong passion for writing made her venture into the world of medical writing. She believes that effective content forms the media through which innovations and developments in pharma/healthcare can be communicated to the world.

GLOBAL MARKET REVIEW APRIL 2021

Towards a Healthier Old Age

By Sarah Harding

Keywords: Old Age, Geriatric Health, R&D

- By 2050, there will be almost 120 million people aged 80 years or older living in China alone, 434 million are expected to reach this age worldwide by the middle of the century.
- Recognizing the growing demand for treatments, research into geriatric health conditions has surged in recent years.
- Biotechnologies are revolutionizing our management of aging populations by offering regenerative and genetic interventions that heal illnesses by restoring malfunctioning cells, tissues and organs.
- Digital technologies and smart devices are already monitoring the health status of people of all ages, the world over.

Today, for the first time in history, most people in the world can expect to live into their sixties and beyond. Globally, 125 millionpeople are aged 80 years or older. By 2050, there will be almost this many (120 million) living in China alone, and 434 million people aged 80 years or older are expected to live worldwide by the middle of the century. China's latest five-year plan, for which the 'Two Sessions' meeting was held on 4th March 2021, acknowledged the problem, building on the previous year's announcement that the number of citizens aged 60 or over accounted for 18.1% of the Chinese population in 2020. As that number is expected to grow, policies aimed at boosting fertility and rebalancing the population are being initiated.

"More inclusive population policies will be introduced to improve fertility, the quality of the workforce and the structure of the population," said Yuan Xin, Vice President of the China Population Association.

Maintaining Health and Independence

All being well, children born today should live well into their 80s,

giving them precious extra years to pursue new activities, spend time with their families, and hopefully contribute to the societies in which they live. The extent of those opportunities and contributions depends heavily on them maintaining their health and independence but, according to the World Health Organization (WHO), at the moment there is little evidence to suggest that older people are experiencing better health in their later years, compared with previous generations. In other words, **we may be keeping people alive for longer, but at the moment we're not necessarily giving them a life that is as enjoyable as we might hope.**

This has driven healthcare systems across the globe to develop policies aimed toward healthier aging. As the adage goes, prevention really is better than cure. Common conditions in older age include:

- **Hearing and sight problems**
- **Back and neck pain**
- **Osteoarthritis**
- **Chronic obstructive pulmonary disease**
- **Diabetes**
- **And a range of geriatric syndromes such as frailty, urinary incontinence, and a heightened risk of fall.**

Preventing or delaying these chronic debilitating conditions would go a long way towards keeping us healthy, and could also save health authorities considerable costs in terms of medications and care.

Breakthroughs in Geriatric Health

Recognising the growing demand for treatments, research into many of these conditions has surged in recent years. For example,

Osteoporosis

Pfizer and Eli Lilly's tanezumab, a new monoclonal antibody against nerve growth factor, is currently under review by the FDA as a treatment for pain in osteoporosis patients. Possibly even more exciting, however, in the first two months of 2021, were the recent FDA approvals for Signature Biologics to proceed with a study of human umbilical cord tissue allografts in osteoarthritis patients, and for Histogen to proceed with a clinical trial of human extracellular matrix to regenerate hyaline cartilage. If successful, products such as these would be the first to repair the tissue damage caused to osteoarthritis, rather than simply managing the pain.

Diabetes

Similarly, researchers have made great advances in diabetes care in recent years. In 2019, a new artificial pancreas system was approved by the FDA, along with an immunotherapy treatment called teplizumabab that delays type 1 diabetes.

In the same year, it was discovered that a number of medications that had been approved in recent years, including SGLT2 inhibitors and GLP1s, not only helped to lower blood sugar levels, but also helped to protect the heart and kidneys. As such, 2019 was celebrated as a great year for diabetes research!

However, researchers are still looking for a cure, and perhaps that day is not so far away. For example, in March 2020, while most of the world was focussed on COVID, researchers at the Washington University School of Medicine in the US published their findings that human stem cells can be converted into insulin-producing cells to control blood sugar levels and, in effect, can 'cure' type 1 diabetes [1]. Meanwhile, various researchers have been developing a diabetes vaccine that stops the immune system from attacking its own body's insulin-producing beta cells. Other groups have been evaluating the potential for islet cell encapsulation, which uses stem cells to create insulin-producing cells that can work without immune system interference.

"Cures for both type 1 diabetes and type 2 diabetes have not yet been discovered, but progress is being made to prospectively cure type 1 diabetes in this generation", declares the British charity Diabetes UK. "Researchers are beginning to get excited again that a cure or near-cure treatment could come as

early as within the next decade or two."

Alzheimer's

Of course, it's not only the body that can fail. One of the saddest consequences of old age is seen in the 54 million people currently living with dementia around the globe. The UK Alzheimer's Society estimates that this number will rise to 130 million by 2050. Once accepted as an inevitable part of aging, the past 25 years has seen a dramatic change in attitudes, largely thanks to the cholinesterase inhibitors that offered the first effective treatments for dementia in the 1990s. However, these drugs never provided a cure – they simply relieved the symptoms and, at best, might have slowed the progression of the disease, potentially giving patients another year or two of 'being themselves'.

In searching for a curative treatment, numerous groups have worked on products targeting the microscopic clumps of amyloid plaques that characterize Alzheimer's disease, or the tau protein strands that are seen to 'tangle' in the Alzheimer brain. Other researchers have looked at modulating inflammatory processes, the effects of insulin on brain cell function, hormones, high blood pressure, heart disease, stroke, diabetes and high cholesterol... the quest for a cure for dementia continues.

Most recently, in the March 2021 issue of the New England Journal of Medicine, Phase II results of Eli Lilly's donanemab (N=257), an antibody that targets beta-amyloid, suggested that the drug was associated with better cognitive scores, compared with placebo, and appeared to slow the accumulation of tau across key brain regions in Alzheimer's patients [2]. Lilly has since announced that it will enrol another 1,000 participants into an expanded trial – TRAILBLAZER-ALZ 2 – to confirm the efficacy and safety of donanemab in a larger population. Results are expected in 2023, raising hopes that a cure for dementia might finally be imminent.

The Shift in Focus

These examples represent a shift in focus away from conventional symptomatic treatments of chronic conditions. What many of the 'new breakthroughs' have in common is a focus on prevention and – where possible – cure.

The fact that these treatments are emerging now is largely thanks to new technologies that were not available to previous generations of researchers. Biotechnologies are revolutionizing our management of our aging populations by offering regenerative and genetic interventions that heal illnesses by restoring malfunctioning cells, tissues and organs. Ultimately, biotechnologies may offer the holy grails of disease prevention and cure. Techniques to prevent or replace lost body functions can be seen to 'borrow from' the body's own natural development processes – for example, the use of stem cells for organ regeneration, or the use of hormone therapies for lost bone, cartilage and muscle mass. Biotechnology holds the promise of alleviating the disabling conditions that plague our later years.

An aging global population offers numerous opportunities for the pharma industry, both in terms of providing preventative treatments that maintain health and independence into old age, and for new service offerings that make use of the ongoing digital revolution. It is interesting to see how many pharma companies are embracing this approach, with many adapting their business models accordingly. **As well as traditional drug development, an increasing number of pharma companies are also looking for growth opportunities in pioneering technologies for data collection, analysis and interpretation.** This is another opportunity to make use of the Big Data that now seems to reach into every part of our lives.

We are already seeing automated campaigns, based on medications or disease states, that educate patients, offer helpful reminders, or check on progress at key times. Ultimately, it is hoped that drugs will eventually be customized based on patients' examination reports and medical records, providing effective, individualized preventative treatments that will help us all stay healthier and independent for longer.

The top ten medical technologies for 2021 have been identified by MedicalTechnologySchools.com as being:

- Advanced telemedicine
- New methods of drug development
- Data-driving healthcare
- Nanomedicine
- 5G-enabled devices
- Tricorders
- Digital healthcare assistants
- Smarter pacemakers
- Labs on a chip
- Wearable health trackers

Digital technologies and smart devices are already monitoring the health status of people of all ages, the world over. If those technologies were applied to detect signs predictive of conditions typically associated with old age, symptoms could be detected at an early stage and treated as effectively as possible, as soon as possible, potentially preventing or delaying those chronic debilitating illnesses that can make old age so difficult.

By 2050, those of us who have joined the ranks of our cherished older generations will perhaps see for ourselves the fruits of these labours. Hopefully, if we are fortunate enough to live long lives, we will have the chance to live them in a fulfilling and healthy manner.

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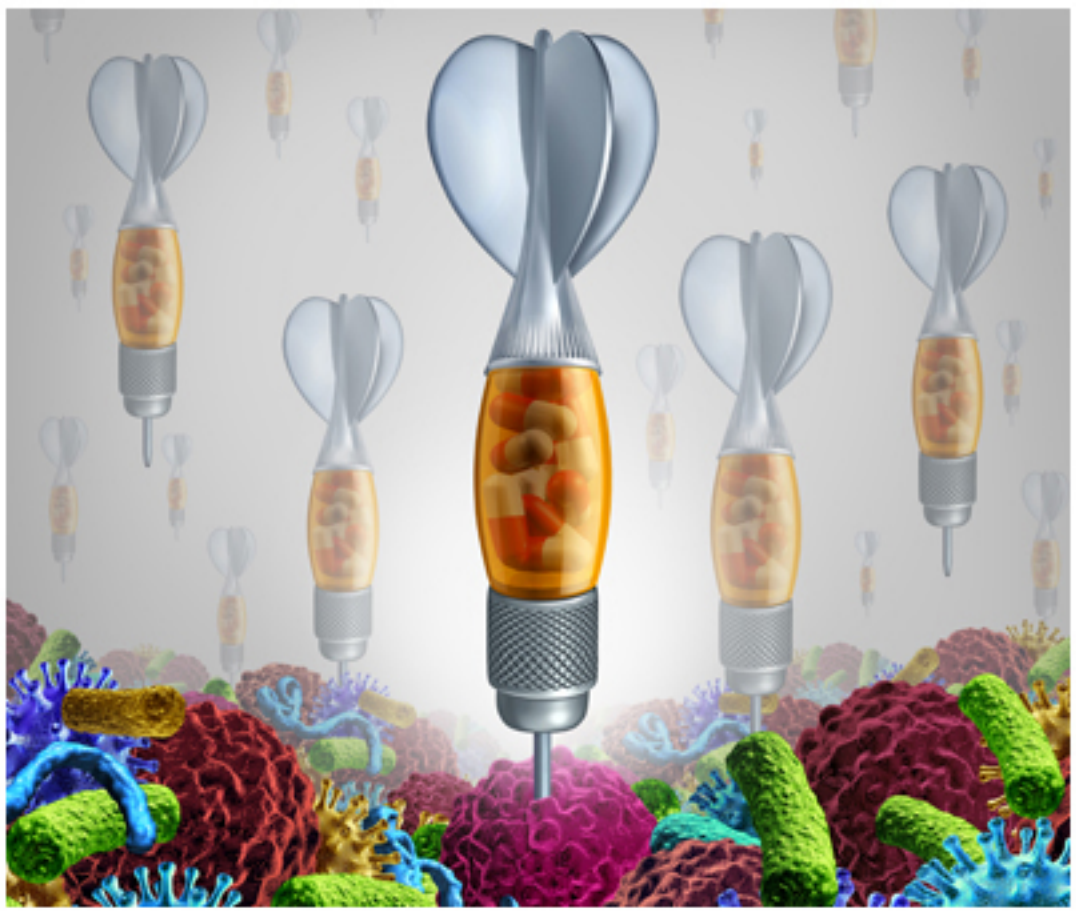
Sarah Harding worked as a medical writer and consultant in the pharmaceutical industry for 15 years, for the last 10 years of which she owned and ran her own medical communications agency that provided a range of services to blue-chip Pharma companies. She subsequently began a new career in publishing as Editor of Speciality Chemicals Magazine, and then Editorial Director at Chemicals Knowledge. She now focusses on providing independent writing and consultancy services to the pharmaceutical and speciality chemicals industry.

A Glimpse of the Oncology Drug Treatment Market in China

Xiaoyaowan

Keywords: Tumor, Chemotherapy, Targeted Therapy, Immunotherapy



According to statistics, the market size of China's oncology treatment industry reached RMB387.6 billion in 2020, with a compound annual growth rate of 10.3% in the past five years as compared to RMB261.4 billion in 2016, and this market size is expected to exceed RMB700 billion by 2025.

Lung cancer, liver cancer, gastric cancer, colorectal cancer, and breast cancer are the top five cancers in China among the various tumors with high incidence. Among them, lung cancer is the one with the most patients in China, with more than 800,000 patients/year, followed by gastric cancer, colorectal cancer, and liver cancer, with more than 400,000 patients/-year for each cancer, and then breast cancer with about 300,000 patients/year.

The Pattern of China's Oncology Drug Treatment Market

China's oncology drug treatment market is still dominated by chemotherapy drugs at present, which takes the lead in oncology drug sales. In 2019, of China's oncology drug market, chemotherapy drugs accounted for 73%, targeted drugs accounted for 23%, and immunotherapy drugs accounted for only 4%. Chemotherapy drugs such as nimustine, doxorubicin, and vinblastine are the main varieties in oncology chemotherapy drug treatment in China.

Three Types of Oncology Drug Treatment

Treatment method	Chemotherapy	Targeted therapy	Immunotherapy
Principle of treatment	Kill cancer cells and control their growth using one or more drugs	Target specific genes, proteins or tissue environments that promote the proliferation and spread of cancer cells so as to prevent the proliferation and spread	Induce, enhance, or suppress immune responses in tumor patients
Scope of use	Chemotherapy can be used alone or in combination with other therapeutic regimens for different types of cancer. It is a systemic therapy that is effective for most tumor patients at different stages of disease progression.	Targeted therapies are indicated for all types of cancers with detectable targets, using small molecule drugs or monoclonal antibodies.	Immunotherapies are indicated for all types of cancers, including solid tumors and blood cancers, using biologics.
Market share	73%	23%	4%
Minimum treatment price	RMB18,000	RMB146,000	RMB183,000

Source: Organized according to public data.

Chemotherapy is the most traditional tumor treatment, with the clear disadvantage of high toxicity. Targeted therapy can improve the effects of cancer treatment owing to its clear target, enhanced efficacy and controlled side effects. Tumor immunotherapy is considered to be the only method that may permanently cure cancer. The marketing approval and clinical trials of CAR T-cell therapies expand new clinical techniques for tumor treatment. So far, there have been three CAR T-cell therapies approved by the FDA for marketing, Novartis' Kymriah and Kite's Yescarta and Tecartus.

Top 5 Pharmaceutical Enterprises by Oncology Drug Sales in China

The current market pattern of oncology pharmaceutical enterprises is concentrated in China. Hengrui Medicine, AstraZeneca, Luye Pharma, Hansoh Pharmaceutical, and Sanofi ranked among the top five in terms of the share of the oncology drug sales market in China in 2019, with a combined share of 32.1% of the overall market. With the continuous increase of pharmaceutical policies in China, pharmaceutical enterprises with no advantages in technologies or the size of funds will be gradually eliminated from the market.

Top 5 Pharmaceutical Enterprises by Oncology Drug Sales in China		
Enterprise name	**Main product**	**Market share**
Hengrui Medicine	Apatinib Mesylate Tablets Pyrotinib Maleate Tablets Camrelizumab for Injection	8.5%
AstraZeneca	Gefitinib Tablets Osimertinib Mesylate Tablets	8.4%
Luye Pharma	Paclitaxel liposome formulation	5.3%
Hansoh Pharmaceutical	Gemcitabine Hydrochloride for Injection Vinorelbine Tartrate Injection	5.1%
Sanofi	Docetaxel Injection Oxaliplatin for Injection Rasburicase for Injection	4.7%

Source: Organized According to Public Data

The Development of Innovative Oncology Drugs Leading to Pattern Restructuring in China

It is worth mentioning that the market pattern of oncology drugs in China is quite different from that in the regulated markets such as Europe and the U.S. **In 2019, the top 10 best-selling oncology drugs in the U.S. were all innovative therapies, while four of the top 10 best-selling oncology drugs in China were traditional chemotherapy drugs**, and in the same year, the share of chemotherapy drugs in the global oncology drug sales market was only 17.1%. The oncology drug market in China has a relatively large room for adjustment.

As the government introduces a series of policies to encourage R&D, **China's oncology drug treatment market is shifting toward an innovation-driven market**, with increasing molecular targeted therapies, tumor immunotherapies, and combination therapies in development to address the unmet medical needs of tumor patients.

In the future, the development of innovative oncology drugs will lead to the pattern restructuring of oncology drugs in China, and **chemotherapy drugs will be gradually replaced by targeted drugs** and immunotherapy drugs. This trend has been confirmed by the breakdown of market sales revenue over the past years. Tumor patients in China will have options of more therapies such as targeted therapies and immunotherapy drugs with good efficacy and low toxicity.

Besides the enriching and upgrading of oncology drug varieties, another clear trend of oncology drugs in China is price reductions. The Work Program for the Adjustments of the National Reimbursement Drug List in 2019 (Draft for Comment) issued by the National Healthcare Security Administration proposes to give priority to national essential drugs, drugs for major diseases such as cancer and rare diseases, etc. At the same time, the NRDL (National Reimbursement Drug List of China) access significantly reduces oncology drug prices and tumor patients' economic burden through offer negotiations. **A total of 153 oncology varieties succeeded in four NRDL negotiations, with the lowest average price reduction of 38.56%, involving various oncology drugs.**

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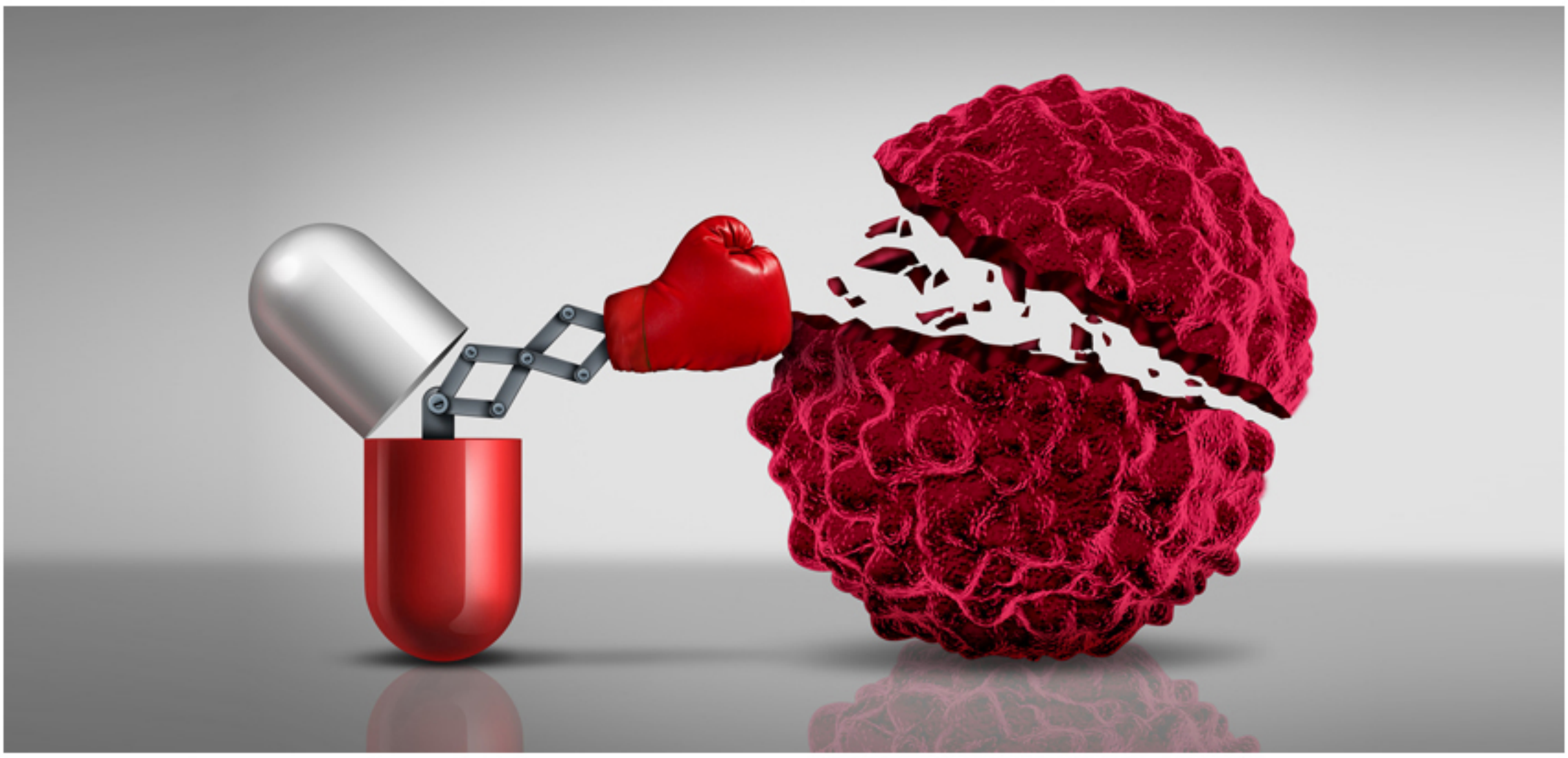
Xiaoyaowan, a pharmaceutical industry practitioner, a word carrier in the We-media era focusing on changes of the pharma industry.

Immune Drug Combination Therapies for Liver Cancer: Analysis of the Clinical Studies of the Two Approved and Two First-line Drug Combinations

By Yuntian

Keywords: Liver cancer, Immune Drug, Drug Combination



Liver cancer has recently drawn much attention by a Chinese movie star Ng Man-tat who died of liver cancer and the National Liver Day on Mar. 18. China is a big country in terms of liver cancer evidenced by the latest global cancer data 2020 released by the WHO: **more than half of new and dead liver cancer patients globally are in China**. As such, liver cancer drugs have been a highly valued pharmaceutical field in China, and immune drug combinations have also been receiving much attention as therapies that could bring more benefits to liver cancer patients.

Currently, two immune drug combination therapies for liver cancer have been approved in China, namely, atezolizumab + bevacizumab, and nivolumab + ipilimumab, separately for the first-line and second-line treatment. Furthermore, lenvatinib + pembrolizumab, and lenvatinib + nivolumab have both received clinical study approval for the first-line treatment.

Combination regimen	Treatment	NMPA approval
Atezolizumab + bevacizumab	First-line treatment	Yes
Nivolumab + ipilimumab	Second-line treatment	Yes
Lenvatinib + pembrolizumab	First-line treatment	No
Lenvatinib + nivolumab	First-line treatment	No

Fig. I Immune Drug Combination Therapies for Liver Cancer

I. Atezolizumab + bevacizumab

The regimen of atezolizumab + bevacizumab is referred to as the T+A regimen and is the world's first immune drug combina

tion therapy approved for the first-line treatment of liver cancer.

IMbrave150 is an open-label, randomized, parallel-controlled, multicenter clinical study for the T+A regimen. The study compares the T+A regimen with sorafenib for the first-line treatment of patients with liver cancer. According to the interim analysis data firstly presented at the ESMO Asia Congress 2019, both the OS and PFS met predetermined statistical values; the median OS for the T+A regimen did not reach and that for sorafenib was 13.2 months, with 42% reduction in OS risks in the drug combination group, the median PFS for the T+A regimen was 6.8 months and that for sorafenib was 4.3 months, with a 41% reduction in disease progression risks, and the ORR for the T+A regimen was 27.3% and that for sorafenib was 11.9%. Furthermore, the drug combination regimen also delayed the time of life quality deterioration as reported by patients.

II. Nivolumab + ipilimumab

Based on the CheckMate-040 clinical study, the U.S. FDA was the first to approve the nivolumab + ipilimumab regimen on Mar. 11, 2020 for the second-line treatment of liver cancer patients previously treated with sorafenib.

Patients enrolled in the CheckMate-040 study are those with advanced HCC who are intolerant to or have progressed on sorafenib therapy, and BICR was assessed according to RECIST v1.1; for patients on the combination regimen, 8% achieved CR, 24% achieved PR, and DOR was 4.6 months to 30.5 months, of which 88% lasted at least 6 months, 56% lasted at least 12 months, and 31% lasted at least 24 months. And the safety of the combination regimen was good.

III. Clinical studies of two advantageous first-line combination regimens

A. Lenvatinib + pembrolizumab regimen: This regimen, known as the "K+L combination", has not been approved in China at present, however, it has been included in the latest China Anti-cancer Association Guidelines for Patients with Primary Liver Cancer. According to the KEYNOTE-524 lb study, the K+L combination was evaluated according to the mRECIST, with the ORR reaching 46.3%, mTTR reaching 2.4 months, mPFS reaching 9.7 months, and mOS reaching as high as 20.4 months.

B. Lenvatinib + nivolumab: According to the study of lenvatinib in combination with nivolumab for the first-line treatment of patients with unresectable liver cancer presented at the ASCO GI 2020, the ORR reached 76.7%, the DCR reached 96.7%, and the clinical benefit rate reached 83.3%, as evaluated according to the mRECIST, while according to the IRC assessment based on the RECIST 1.1, the ORR reached 54.2%, the DCR reached 91.7%, and the CBR reached 62.5%.

IV. Summary and outlook

As a "punch combination" for liver cancer treatment, combination regimens have shown great advantages in the treatment, and combination regimen has become a new treatment option for patients especially when the effects of monotherapies are not good. Furthermore, as more and more immune drugs are approved for liver cancer, more immune drug combination regimens will emerge in the future, which will greatly improve the current severe situation of liver cancer treatment.

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Yuntian, Ph.D. in medicinal chemistry, is mainly engaged in small molecule drug research, especially good at small molecule drug synthesis process and later stage drug development research. He has completed the synthesis and activity evaluation of multiple anti-cancer drug molecules.

With Anlotinib Sold over RMB4 Billion in 2020, Which will be the Next Blockbuster of Sino Biopharmaceutical?

By Caicai

Keywords: Anlotinib, Sino Biopharmaceutical, Innovative Drugs

Sino Biopharmaceutical has recently released its 2020 annual results, with total revenue of RMB23.647 billion, down 2.4% year on year, net profit attributable to the parent of RMB2.771 billion, up 0.3% year on year, net profit attributable to the parent of RMB3.114 billion excluding the impacts such as intangible assets amortization and convertible bond arising from the acquisition of Beijing Tide, decreased by 0.3% year on year, and R&D expenditure of RMB2.853 billion, accounting for 12.1% of the total revenue.

Anlotinib Sold Over RMB4 Billion

Sino Biopharmaceutical disclosed in a call meeting earlier that the sales of anlotinib in China were expected to reach RMB4-4.5 billion in 2020, which means that the blockbuster anlotinib contributed over 1/6 of the total revenue of RMB23.647 billion.

The Class 1 new drug anlotinib independently developed by Chia Tai Tianqing, a subsidiary of Sino Biopharmaceutical, was first approved in May 2018 for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) who have undergone progression or recurrence after at least two lines of systemic chemotherapy and was subsequently approved for the treatment of soft tissue sarcoma, small cell lung cancer (SCLC), and medullary thyroid cancer.

Anlotinib's NSCLC indication was successfully included in the NRDL (National Reimbursement Drug List of China) in 2018; anlotinib was once again included in the NRDL in the new round of NRDL negotiations in 2020, with a price reduction by 37%, covering three indications: NSCLC, SCLC, and soft tissue sarcoma.

Chia Tai Tianqing is actively developing other indications for anlotinib, with a total of over 20 clinical trials underway. Among them, combination regimens of anlotinib and anti-PD-1/L1 drugs in development, which involve gastric cancer, liver cancer, and gastroesophageal junction adenocarcinoma, are already in Phase III clinical trials.

Which will be the Next Blockbuster?

Undoubtedly, anlotinib will be a powerful growth engine for Sino Biopharmaceutical in the next three to five years. Then, with the full implementation of China's centralized drug-procurement program, which will be the next innovative drug to be marketed by Sino Biopharmaceutical? Which will be the next blockbuster following anlotinib?

Sino Biopharmaceutical has now over 100 innovative drug varieties in development, with two marketed, three applied for production, and 33 in clinical stages.

CXHS1700002	May-18	Patients with locally advanced or metastatic NSCLC who have undergone progression or recurrence after at least two lines of systemic chemotherapy
CXHS1700003		
CXHS1700004		
CXHS1800025	Jul-19	Adenoid soft tissue sarcoma, clear cell sarcoma and other advanced soft tissue sarcoma patients who have progressed or relapsed after at least one line of a chemotherapy regimen containing anthracycline
CXHS1800026		
CXHS1800027		
CXHS1800039	Sep. 2019	Patients with SCLC who have undergone progression or recurrence after receiving at least two chemotherapy regimens
CXHS1800040		
CXHS1800041		
CXHS1900040	Dec. 2020	Patients with unresectable locally advanced or metastatic medullary thyroid cancer
CXHS1900041		
CXHS1900042		

Source: NMPA

S/N	Registration No.	Trial status	Indication	Common trial title
1	CTR20210230	Underway; having not recruited	First-line treatment of metastatic nasopharyngeal carcinoma (NPC)	Study of the efficacy and safety of penpulimab (AK105) in combination with chemotherapy ± anlotinib hydrochloride in the treatment of advanced NPC
2	CTR20200879	Underway; recruiting	Advanced hepatocellular carcinoma (HCC)	Clinical study of AK105 injection in combination with anlotinib for the first-line treatment of HCC
3	CTR20200753	Underway; recruiting	Gastric cancer or gastroesophageal junction adenocarcinoma	Evaluation of the efficacy of anlotinib hydrochloride capsules in combination with AK105 injection for the treatment of advanced gastric cancer
4	CTR20200342	Underway; recruiting	Patients with advanced MSI-H or dMMR solid tumors	Safety and effectiveness of anlotinib in combination with AK105 for the treatment of patients with advanced MSI-H or dMMR solid tumors
5	CTR20192554	Underway; recruiting	Intrahepatic cholangiocarcinoma (IHCC), extrahepatic cholangiocarcinoma (EHCC), gallbladder carcinoma (GBC), recurrent or metastatic colorectal cancer, metastatic or recurrent gastric cancer or gastroesophageal junction (GEJ) adenocarcinoma, etc.	Efficacy of anlotinib in combination with AK105 in patients with gastrointestinal, urologic and neuroendocrine tumors
6	CTR20192550	Underway; recruiting	Patients with advanced head, neck and chest tumors	Evaluation of the safety and effectiveness of anlotinib in combination with AK105 in advanced head, neck and chest tumors
7	CTR20182026	Underway; recruiting	Unresectable HCC	AK105 in combination with anlotinib hydrochloride and bevacizumab for unresectable HCC, respectively

Source: China Drug Clinical Trial Registration and Information Publicity Platform

Among the three drugs applied for marketing, AK105 and TQ-Z2301 are not considered to be Sino Biopharmaceutical's own innovative drugs. AK105 is an anti-PD-1 monoclonal antibody independently developed by Akeso, and Chia Tai Tianqing only has exclusive sales rights for AK105 in China. TQ-Z2301 is an adalimumab biosimilar. Only the recombinant human coagulation factor VIII for the treatment of Hemophilia A is considered to be Sino Biopharmaceutical's own innovative drug and is expected to be approved for marketing this year, however, it is unlikely to become a blockbuster due to the restricted indication for the treatment of hemophilia A.

Besides these three applied for marketing, **anti-PD-L1 monoclonal antibody TQB2450, ALK inhibitor TQB3139, and ROS1 inhibitor TQB3101 are expected to be approved for marketing in 2022, and PI3K inhibitor TQB3525 is expected to be approved for marketing in 2023.**

Among them, the ALK inhibitor TQ-B3139 has the fastest progress, with a phase III clinical study of TQB3139 in combination with crizotinib in NSCLC initiated in 2019, and the drug is **expected to be the first innovative drug applied for production.**

Four ALK inhibitors have been approved in China, namely Pfizer's crizotinib (Jan. 2013), Novartis' ceritinib (May 2018), Roche's alectinib (Aug. 2018), and Betta Pharmaceuticals' ensartinib (Nov. 2020), with only ensartinib being the Chinese-produced drug, however, the sales of these drugs are lackluster, and it remains to be seen how the subsequent results of Betta's ensartinib will be.

As for PI3K inhibitors, several have been approved worldwide, however, none have been approved in China. Among them, Bayer's copanlisib has been applied for marketing in China, while Novartis' alpelisib and Roche's GDC-0077 are in the Phase III clinical stage.

Furthermore, no Chinese-produced anti-PD-L1 monoclonal antibody has been approved, therefore, there is still some market space for the anti-PD-L1 monoclonal antibody TQB2450. CDK4/6 inhibitors such as TQB3616 will also be applied for approval and production in succession.

The author holds that **it is unlikely that Sino Biopharmaceutical will have another blockbuster like anlotinib in the next three to five years, however, its products will be like 'hundred flowers in bloom' in Chinese.** By then, the marketing of ALK inhibitor, PI3K inhibitor, ROS1 inhibitor, CDK4/6 inhibitor and other innovative drugs will greatly enrich the innovative drug pipelines of Sino Biopharmaceutical and together become the future growth engine of Sino Biopharmaceutical.

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Caicai, a Master of Pharmacy from Shanghai Jiaotong University, used to work in the Institute of Science and Technical Information. Currently as a practitioner in the drug surveillance system, she is good at interpreting industry regulations, pharmaceutical research developments, etc.

Innovative Drug Pipelines in Development by Sino Biopharmaceutical					
Stage I Clinical Trials		**Stage II Clinical Trials**	**Stage III Clinical Trials**	**Applied for Marketing**	**Approved**
TQB3233: Braf Advanced malignant melanoma	**TQB3455: IHD2** Leukemia	**TQB3525: PI3K** Various tumors	**TQB3139: ALK** Non-small cell lung cancer	**AK105: PD-1 Monoclonal antibodies** cHL	**Anlotinib** NSCLC/SCLC/STS
TQB3234: MEK1/2 Various tumors	**TQ05105: JAK2** Bone marrow proliferative tumor	**TQB3101: ROS1** Non-small cell lung cancer	**TQB2450: PD-L1 Monoclonal antibodies** Various tumors	**Recombinant Human Coagulation Factor VIII** Hemophilia	**Magnesium isoglycyrrhizinate** Chronic viral hepatitis
TQB3395: panHER Various tumors	**TQB3203** Advanced solid tumor	**FHND9041: EGFR T790M** Non-small cell lung cancer	**TQB2303: Rituximab** Lymphomar	**TQ-Z2301: Adalimumab** Rheumatoid arthritis	
TQB3456:EGFR Non-small cell lung cancer	**TQB3616:CDK4/6** Breast cancer	**TQA3334: TLR7** Hepatitis B and C	**TQB211: Trastuzumab** Breast cancer		
TQB3203:TOP1 Various tumors	**TQB3720** Tumor	**TQA3729** Hepatitis B	**TQB2302：Bevacizumab** Non-small cell lung cancer		
TQB3804: 4th Generation of EGFR Non-small cell lung cancer	TQB2858: Bispecific antibody Tumor	**TQA3526** NASH	**AK105:PD-1 Monoclonal antibodies** Various tumors		
TQB3474: HSP90 Various tumors	**TQB3728:clAP1** Various tumors	**RD-101: PC-SOD** Myocardial infarction			
TQB3562 Various tumors	**TQB3602** Multiple bone marrow cancer	**TQ-F3083: DPP4** Diabetes			
TQB3303 Breast cancer	**TQB3473** Chronic lymphocytic leukemia				
AL2846: cMet Various tumors	**TQA3454: IDH1** Brain astrocytoma				
TQB3558 Pain and cancer	**TQA3326: NS5A** Hepatitis A/C				
TQA3810 Liver Disease	**TQA3563** Nonalcoholic steatohepatitis				
TQA3572 Hepatitis C	**TQB3399** Bone marrow proliferative diseases				
TQ05510 Type II diabetes	**TQC3564** Asthma				
TQF3354 Type II diabetes	TDI-01 Pulmonary fibrosis				Independent R&D
RD03 antibiotic	**TQC3721** COPD and Asthma				Overseas Clinical Trials
(Source: Company announcements, Pharmcube, Zhongtai Securities Research Institute)					

Analysis and Policy Review of Pediatric Drug Market in China

By Zhulikou431

Keywords: Policy Review, Pediatric Drug, Chinese Pharmaceutical Market

The U.S. is currently the largest pediatric drug market in the world, followed by China. However, compared to the U.S. which has formal pediatric drug legislation and mature pediatric drug policies and regulations, the development of pediatric drugs in China has many shortcomings:

Firstly, Chinese pharmaceutical enterprises lack enthusiasm for pediatric drugs due to the characteristics of pediatric drugs:

- high R&D expenses;
- big drug evaluation (clinical trial) difficulties
- the need for long-term efforts in market layout to achieve market stickiness;

most Chinese pharmaceutical enterprises are not willing to research or produce pediatric drugs.

Secondly, there are not enough pharmaceutical manufacturers of pediatric drugs in China, there is a relative lack of the produced varieties and suitable dosage forms, and the produced varieties are homogeneous without sufficient product advantages. According to publicly reported data, **there are only 30 companies with R&D and production capabilities for pediatric drugs among more than 4,500 pharmaceutical enterprises in China, and very few enterprises focus on R&D and the production of pediatric drugs. Pediatric drugs account for less than 2% of the total drug formulations, and there is a serious supply-demand imbalance.**

China's pediatric drug market is dominated by respiratory system drugs, digestive system drugs, anti-infective drugs, and nutritional supplements, with respiratory system drugs accounting for a much higher share of the market than drugs in other therapeutic areas. The mainstream manufacturers of pediatric drugs in China include China Resources Double Crane, Sunflower Pharmaceutical, Jumpcan Pharmaceutical, Honz Pharmaceutical, Yipinhong Pharmaceutical, Sanjing Pharmaceutical, and Yabao Pharmaceutical, which mainly focus on therapeutic areas of children's colds, indigestion, coughs and phlegm, and nutritional supplements. With the Crane, Sunflower Pharmaceutical, Jumpcan Pharmaceutical, Honz Pharmaceutical, Yipinhong Pharmaceutical, Sanjing Pharmaceutical, and Yabao Pharmaceutical, which mainly focus on therapeutic areas of children's colds, indigestion, coughs and phlegm, and nutritional supplements. With the enhancement of people's consumption power in China, Chinese manufacturers of pediatric drugs need to strengthen market analysis and cultivation.

Thirdly, there is no systematic legal and regulatory system for pediatric drugs, neither a perfect essential pediatric drugs list in China. The 2017 NRDL (National Reimbursement Drug List of China) (2,535 western and Chinese patent drugs) specifies 540 pharmaceutical products or dosage forms for children, and the 2020 NRDL (2,800 western and Chinese patent drugs) which officially implemented on Mar. 1, 2021, has added several varieties of pediatric drugs. The security efforts for pediatric drugs are gradually enhancing, however, there is still a significant gap in the proportion compared to other drugs of all varieties.

The concept of 'children' usually refers to minors aged 0-14 in China. According to the data of the National Bureau of Statis

tics of China, **the population of children aged 0-15 was 249.77 million in 2019, accounting for about 17.9% of the total population in China, however, the market size of pediatric drugs accounts for only about 5% of the pharmaceutical industry, showing that the market is far from saturation**. Actively developing the field of pediatric drugs may be a good way to profitability for Chinese pharmaceutical enterprises despite the pressure of costs and regulations.

The new edition of the Drug Administration Law has officially come into force on Dec. 1, 2019, in China. In Article 16 it specifies, "The state shall adopt effective measures to encourage drug R&D and innovation for children's use, support the development of new varieties, dosage forms and specifications of medications for children's use that meet the physiological characteristics of children, and prioritize the review and approval of medications for children's use." Furthermore, the state government departments of China have introduced a series of policies in the recent decade to encourage R&D, priority review, and also in other related aspects, to encourage Chinese pharmaceutical enterprises to increase the R&D and production of pediatric drugs:

Date	Regulatory document	Main content
Jun-11	*Child Development Outline of China (2011-2020)* adopted at an executive meeting of the State Council	Proposing to promote the marketing of pediatric drugs through the formulation of laws and regulations for the first time
May-14	*Several Opinions on Guaranteeing Children's Medication* issued by the National Health and Family Planning Commission, the National Development and Reform Commission, the Ministry of Industry and Information Technology, the Ministry of Human Resources and Social Security, the China Food and Drug Administration, and the National Administration of Traditional Chinese Medicine	The first comprehensive guidance document on pediatric drugs in China
Jul-14	*Technical Guidelines for Pediatric Pharmacokinetic Studies* issued by the China Food and Drug Administration	Giving guidance on general considerations, test designs and methodological and ethical considerations for pediatric pharmacokinetic studies
Jun-15	*Notice on Establishing the Expert Committee on Pediatric Medicine of National Health and Family Planning Commission* issued by the General Office of the National Health and Family Planning Commission	Establishing an Expert Committee on Pediatric Medicine composed of experts in pediatric medicine, pharmacy and other fields
Jan. 2016	*Announcement on Basic Principles for Evaluating Varieties of Clinical Urgent Pediatric Drugs Qualified to Apply for Priority Review and Approval and First Batch of Varieties for Priority Review* issued by the CDE	Giving priority review and approval to pediatric drugs for serious diseases and having more obvious advantages, with the first batch including five varieties
Mar. 2016	*Technical Guidelines for the Clinical Trials of Pediatric Drugs* formulated under the organization of the China Food and Drug Administration	Proposing the principles and requirements for extrapolation from adult data to pediatric data
Jun-16	*List of First Batch of Pediatric Drugs Encouraged for Development and Application* formulated by experts organized by the National Health and Family Planning Commission, the Ministry of Industry and Information Technology, and the China Food and Drug Administration	>30 specifications
May-17	*Recommended List of Second Batch of Pediatric Drugs Encouraged for Development and Application* proposed by the National Health and Family Planning Commission, the Ministry of Industry and Information Technology, and the China Food and Drug Administration	Nearly 40 specifications
Oct. 2017	*Opinions on Deepening the Reform of the Review and Approval System and Inspiring Innovation of Drugs and Medical Devices*	Improving and implementing the drug trial data protection system to offer certain data protection periods to drugs including pediatric drugs
Jan. 2018	*Guidance on Strengthening and Promoting Food and Drug Science and Technology Innovation* issued by the China Food and Drug Administration and the Ministry of Science and Technology	Focusing on supporting food safety and security; R&D of innovative drugs, pediatric drugs, drugs catering to clinical urgent needs and rare disease drugs and medical devices; quality and efficacy consistency evaluation of generic drugs; post-marketing drug and medical device monitoring and re-evaluation; and R&D, clinical evaluation and quality control technology research of innovative TCM, ethnic drugs, natural drugs, traditional Chinese patent drugs, etc.
Mar. 2018	*Opinions on Reforming and Improving the Policy for Supply Guarantee and Use of Generic Drugs* issued by the General Office of the State Council	Driven by demand, encouraging imitation of pharmaceutical products that are clinically imperative, definite in efficacy and in short supply as well as pharmaceutical products for the prevention and treatment of major infectious diseases and treatment of rare diseases, pharmaceutical products needed to deal with public health emergencies, pharmaceutical products for children, and pharmaceutical products for which no registration application has been filed one year before patent expiration

Sep. 2018	*Opinions on Improving the National Essential Drugs System* issued by the General Office of the State Council	Proposing that appropriate numbers of essential drugs shall be elected to meet common diseases, chronic diseases, emergency rescue, and other main clinical needs, taking into account the drug needs of children and other special populations as well as prevention and treatment with respect to public health
Sep. 2018	*Notice on Seeking Opinions on Adding Indications for Pediatric Patients and Revising Usage and Dosage of the Package Inserts of Three Drugs of the First Batch* issued by the CDE	Proposing the list of varieties of the first batch recommended for package insert revision and the detailed revision content
Apr. 2019	Announcement on *Work Program for the Adjustments of the National Reimbursement Drug List in 2019* issued by the National Healthcare Security Administration	Giving priority to national essential drugs, drugs for major diseases such as cancer and rare diseases, drugs for chronic diseases, drugs for children, drugs for emergency rescue, etc.
Jul-19	*List of The Third Batch of Pediatric Drugs Encouraged for Development and Application issued by the National Health Commission, the Ministry of Industry and Information Technology, and the National Medical Products Administration (NMPA)*	Nearly 40 specifications
Dec. 2019	New edition of *Drug Administration Law*	Proposing that the state shall adopt effective measures to support the development of pharmaceuticals for children's use and support the development of dosage forms and specifications of new pharmaceuticals for children's use
Jun-20	CDE releasing a notice on seeking public opinions on the *Guidelines for the Pharmacological Development of Drugs for Children (Chemical Drugs) (Draft for Comment)*	
Sep. 2020	*Technical Guidelines for Using Real-World Evidence to Support the Development and Review of Pediatric Drugs (Trial)* issued by the CDE	Proposing that real-world evidence can be used as an aid to support evidence of rational clinical drug use in children when traditional randomized controlled trials (RCTs) are difficult to provide adequate information

Furthermore, the NMPA has successively issued some announcements on package insert revisions in recent years which require additional content related to children's medication, showing that China is gradually strengthening the regulation of pediatric drugs.

Summary

Many small and medium-sized pharmaceutical enterprises in China are struggling in the market in the context of regulatory and cost pressure and medical insurance expense control, however, we can see from above that **the population using pediatric drugs will continue to expand in the next five years with the continued loose of the family planning policy in the Chinese market.**

Note: This article does not constitute any value judgement or investment advice.

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Zhulikou431, as a senior engineer, PDA member, ISPE member, ECA member, PQRI member, senior aseptic GMP expert, has deep knowledge in aseptic process development and verification, drug development and registration, CTD document writing and review, regulatory audit, international certification, international registration , quality system construction and maintenance, as well as sterile inspection, environmental monitoring and other fields. In recent years, he has focused on the analysis of trends in the macro pharmaceutical field and the risk management of pharmaceutical enterprise mergers and acquisitions projects.

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Industrial Adoption of Continuous Pharmaceutical Manufacturing

By Deepak Hegde

Keywords: Pharmaceutical Manufacturing, Continuous Processes, US-FDA Approvals

ABSTRACT: This article, which is Part 2 of the series on continuous manufacturing focuses on the uptake of continuous manufacturing by the pharmaceutical industry for both API and drug products, scaleup to pilot scale and successes in commercialization. Adoption of continuous manufacturing by CRO's/CDMO's is also reviewed. Challenges associated with continuous manufacturing are outlined.

Industrial Adoption of Continuous Pharmaceutical Manufacturing

Continuous manufacturing has been common in certain sectors like the oil and gas for a long time. However pharmaceutical industry has been slow to catch onto this concept and has adapted it only since about 2005 and has produced success, albeit limitedly, at commercial scale in the past decade.

API manufacturing processes typically have more steps and therefore is more complex when compared to solid dosage manufacturing. But with continuous anufacturing's production efficiencies, interest in and adoption of continuous API manufacturing should increase once approvals comes through.

At a pilot plant level, the first continuous manufacturing plant was demonstrated in 2013 by Mascia et al. when Aliskiren hemifumarate was synthesized, purified, crystallized, and subsequently formulated into the desired DP while mitigating solids handling issues and removing the need for intermediate solvent swaps between unit operations[1]. In 2016, Adamo et al. also demonstrated a compact, end-to-end production of multiple DPs with different APIs[2]. In 2016, Monbaliu et al. developed an automated system for the end-to-end CPM of lidocaine hydrochloride[3]. In 2019, Cole et al. described the end-to-end CPM of merestinib (a new biliary tract cancer drug) from synthesis to crystallization[4,5] The above-mentioned demonstrations were implemented on pilot or production plant level. In 2017, Eli Lilly's continuous API GMP facility could produce 3 kilograms a day of prexasertib monolactate monohydrate, a chemotherapy candidate for clinical trials.[6] The process links each stage in the process to quality-control systems, combin-

ing synthesis with purification and crystallization. It also enables chemistries that would be impossible or too dangerous using traditional methods.

The implementation of continuous manufacturing at production level has begun to appear more prevalently in recent years for plant subsystem and plantwide designs.[7-9] Vertex committed to continuous Orkambi (containing lumacaftor and ivacaftor for cystic fibrosis treatment) tableting.[10] In 2016, Janssen received FDA approval for the continuous tablet production for Prezista, whose API, darunavir, is used as part of HIV/AIDS combinative treatments. [11]

US-FDA has publicly backed continuous manufacturing, and this has also reflected in the product approvals for the US market in Table 1. have been approved by the US-FDA and have been launched in the US market.

Table 1: US-FDA Approvals of Drugs Produced by Continuous Processes (At time of writing this article in Mar 21)

Approval	Approved Brand	Generic Name	Company	Indication
2015	Orkambi	Lumacaftor/ ivacaftor	Vertex	Cystic Fibrosis
2016	Prezista	Darunavir	Janssen	HIV
2017	Verzenio	Abemaciclib	Eli Lilly & Company	Advanced Breast cancer
2018	Symdeko	Tezacaftor/ivacaftor	Vertex	Cystic fibrosis
2018	Daurismo	Glasdegib	Pfizer	Acute Myeloid Leukemia

Europe has been relatively slower in terms of product approvals using the continuous manufacturing technique as is reflected in the comparatively lower number of approval of products in Table 2.

Table 2: EU Approvals of Drugs Produced by Continuous Processes (At time of writing this article in Mar 21)

Approval	Approved Brand	Generic Name	Company	Indication
2017	Prezista	Darunavir	Janssen	HIV
2018	Orkambi	Lumacaftor/ ivacaftor	Vertex	Cystic Fibrosis
2018	Symdeko	Tezacaftor/ivacaftor	Vertex	Cystic fibrosis

GSK began continuous production of amoxicillin at a fully continuous plant in Singapore 12 and also began a continuous line for daprodustat (an anemia medication). 13-14 GSK believes that anywhere between one-third and one-half of their drug portfolio could be transitioned to continuous manufacturing.15 In addition to building the Singapore plant for GSK, Zeton, a global equipment and process technology supplier, recently helped design, build, and install a continuous API manufacturing skid for GSK in their Global R&D hub in Upper Providence, PA, USA.16 Eli Lilly recently committed a significant capital investment to a continuous production plant in Ireland.[17]

Pharmaceutical companies have been outsourcing activities to CRO's/CDMO's for capacity or capability reasons. If the pipeline in the pharmaceutical industry starts getting meaningfully skewed towards continuous manufacturing, then CRO's/CDMO's will also have to start adapting to this to keep in line with that industrial trend and investing quite significantly in this field.

However, CRO's/CDMOs face several obstacles[18] setting up the building blocks of continuous manufacturing, the most prominent one is the upfront investment for new equipment and the sensors that check for quality as drug product moves along the assembly line as most products require customized processes for every product, even though it is common equipment. Secondly, more than buying the technology, recruitment of automation experts and process scientists, who have experience in handling this technology is key as the pool of such experts is relatively small given the fact the fact that this technology is still relatively new. Most discussions that CDMO's are having about this technology with clients are more detailed than those for batch production with a majority of them being focused on things like process controls, logistics and skills tests.

Notwithstanding these issues, CDMO's like Lonza, Catalent, Aesica, Snapdargon Chemistry, and Patheon (now Thermo Fischer) are CMOs and CROs that have invested early in continuous manufacturing technologies, Patheon (now Thermo Fischer) has recently invested in a 50 kg h−1 powder-to-tablet continuous manufacturing system.[19,20]

Challenges in Continuous Manufacturing

Compared to batch manufacturing, there are several challenges associated with continuous manufacturing. Figure 1 outlines some of the challenges associated with continuous manufacturing.

Fig.1: Challenges in continuous manufacturing

One of the key risks in in terms of Quality Risk Management. While the expectation for product quality is the same for a product manufactured by continuous manufacturing when compared with batch manufacturing, some key differences in Quality risk Management are highlighted.

1. Risk assessment: Hazards identified for a continuous manufacturing process are different than for batch manufacturing process. Hence, understanding the process dynamics in relation to process conditions and material properties is the foundation for effective risk management.

2. Risk mitigation: Control strategies may be different for continuous manufacturing process than for batch manufacturing process. Examples include more frequent use of model-based control, multivariate monitoring, analysis of large of data sets, automation and/or Real-Time Release Testing (RTRT)

3. Risk communication: Communicating residual levels of risk is vital. Linking adopted control strategy approaches to risk assessment can be an effective mechanism for communicating product and process development, as well as life cycle management

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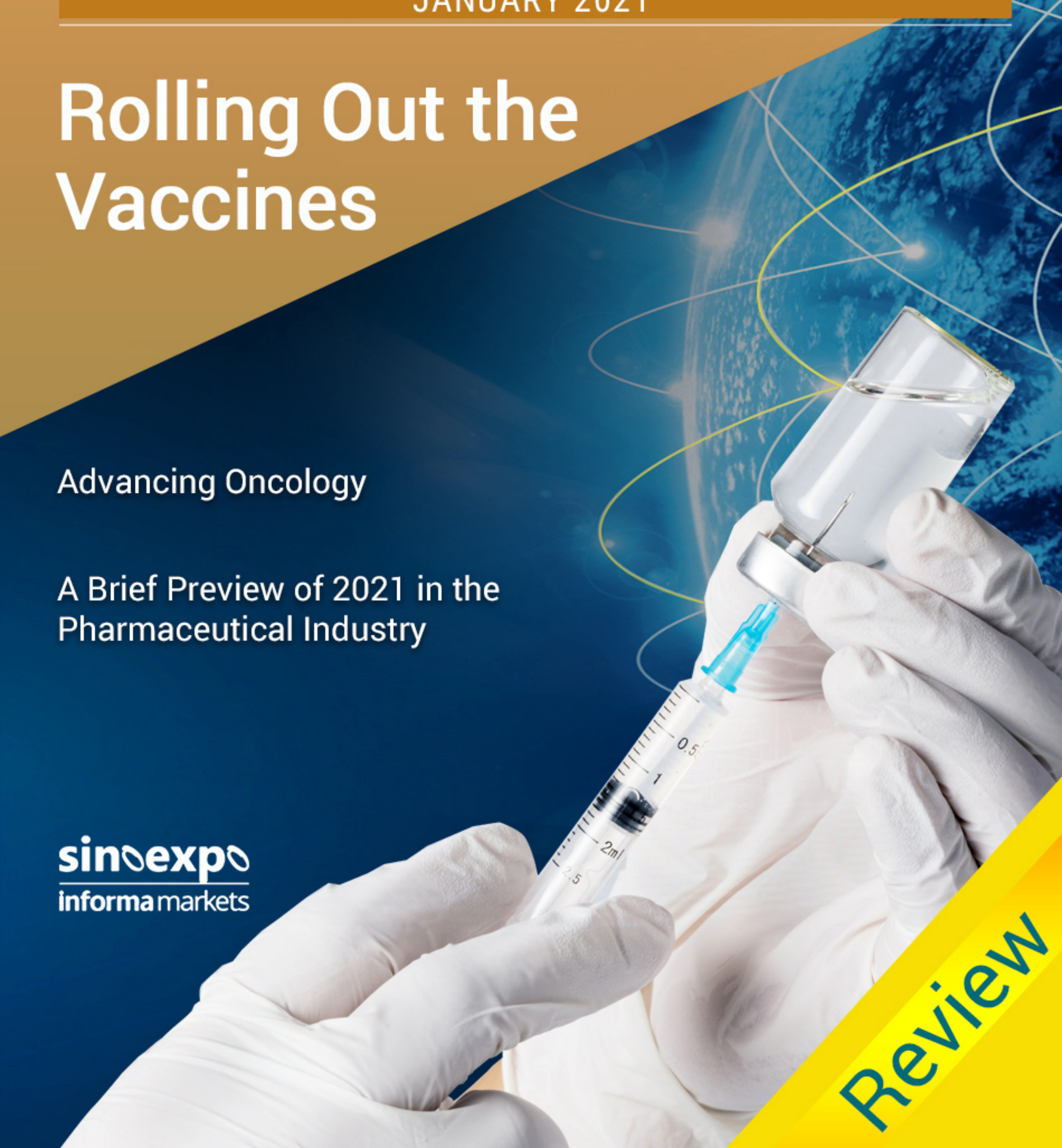

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