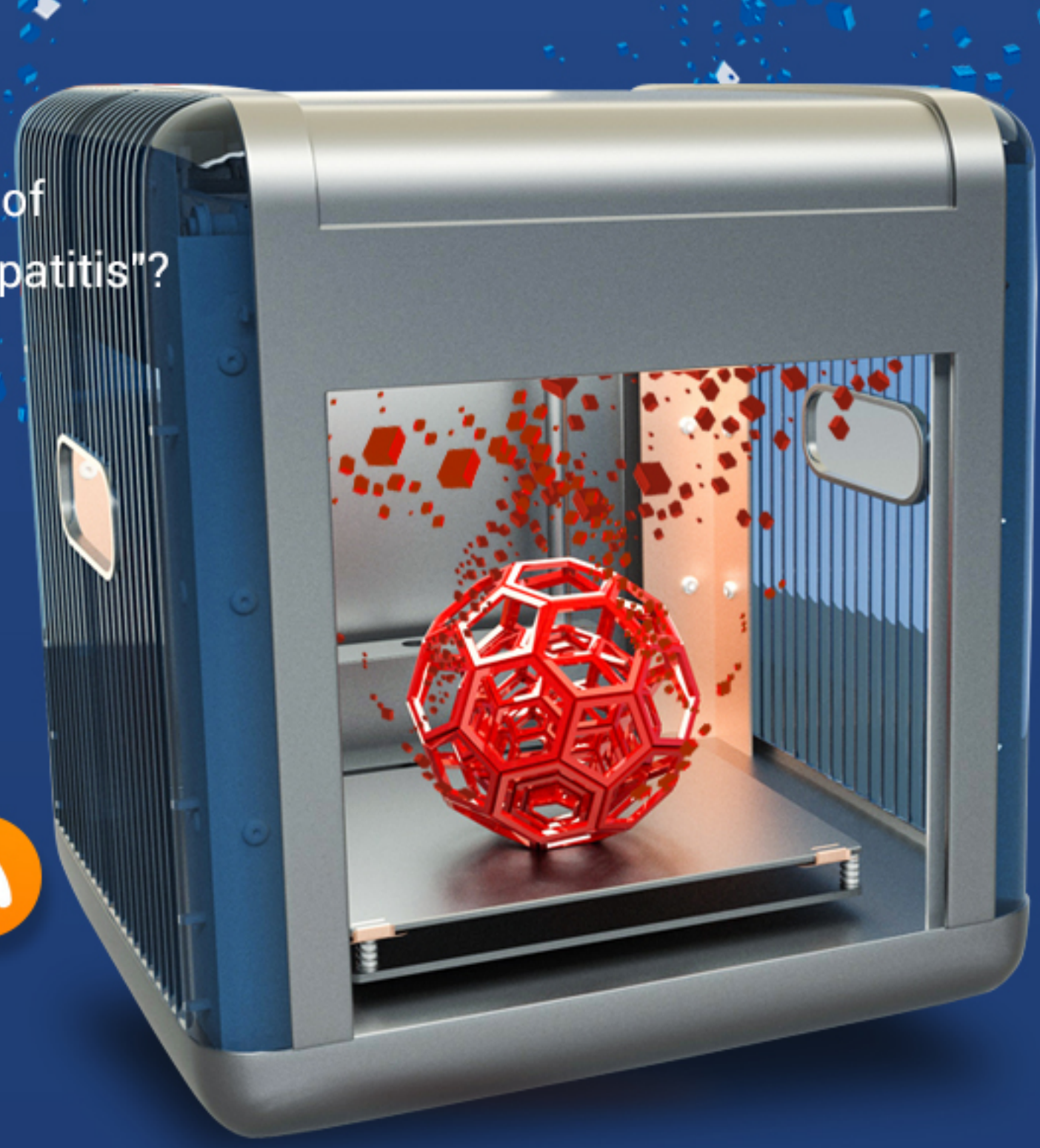
Pharma Sources Insight

JUNE 2022

New Developments, Greater Imapct

Is mRNA Vaccine the Source of Intricacies of "Mysterious Hepatitis"?

3D Printing, A Perfect Storm for Pharma Industry and Regulatory Agency



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Dear Readers,

More than 2 years since the outbreak of COVID-19, the fight against the pandemic continues as the new Omicron variants XE, XD, XF, etc., are identified in the UK and other countries. Furthermore, **the mystery hepatitis cases have been reported in the United States, Europe, and Japan since January this year.**

Therefore, the June Pharma Sources Insight will keep looking at the new developments of COVID-19 worldwide and its impact on the pharma Market, view "**Outlook for Covid-19 in 2022 H2 and Its Broader Impact on the Pharma Market**" by Dr. Preet Pal S.B. **In China, it seems that the first small-molecule oral drug for COVID-19 is coming** , which brings new hope as well as opportunities for the development of the related industry chain.

In the biological field, global pharmaceutical companies are making effort to explore the potential therapy targeted to the B7-H3 target, with the first B7-H3 targeted CAR-T therapy expected to be approved in the Chinese market. Part of the B7-H3 target drug in development could be viewed **at First Drug Coming Soon as Pharmaceutical Companies Take Actions in the B7-H3 Immune Target Products Layout** by PharmaSources contributor Yi. While in China, **DC Vaccine R&D received tens of millions of financing, with more Chinese pharmaceutical companies having entered the market**. Besides, we are going to have **a review on the IPOs of Chinese Biomedical Companies in 2021**, and the landscape of some hot R&D areas such as **ADC**.

According to Dr. Eric Sun, 3D printing has proved itself to have the potential of revolutionizing the way we make almost everything. Nowadays, 3D printing has been employed in aerospace, manufacturing, construction, medicine, and biomedical engineering. In the Industry Insight, Dr. Sun will introduce the technical, compliance, and regulatory challenges of 3D printing, view more at **3D Printing, A Perfect Storm for Pharma Industry and Regulatory Agency**. Also, Mr. Muhammad Asim Niazi will introduce standards for pharmaceutical integrity testing for professionals in the pharmaceutical packaging industry in the Industry Insights.

With the launch of "**Popular Products and Companies at PharmaSources**" in Pharma Sources Insight in 2021, it has become a most welcomed section where suppliers and buyers could find hot products and companies at www.PharmaSources.com. We do hope that the readers find the list helpful to their sales and procurement businesses and let's make it even hotter by registering to become a member of PharmaSources.com, listing your products, and displaying your brand profiles to more overseas drugmakers and pharmaceutical professionals, and meanwhile, receiving the notification of each new issue of Pharma Sources Insight at the first minute!

Anyways, thank you for all the support from our contributors in China and worldwide. For the fans of Pharma Sources Insight, if you are interested in new developments and insights into the Chinese and global pharmaceutical market, and up-to-date information on the industry's popular products and suppliers, please stay with us. Thank you so much!

Editor in Chief
Pharma Sources Insight

International Perspective, Cutting-edge Technology Learning Entering into HongKe Technology Co., Ltd.

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At present, HongKe has branches in **Guangzhou, Beijing, Shanghai, Xi'an, Chengdu and Suzhou, and sales representatives in South Korea, Japan, Shenyang, Tianjin, Nanjing, Hefei, Hangzhou, Wuhan, Shenzhen, Zhengzhou, Chongqing, Qingdao**, etc. The company also set up branches in **Taiwan, Hong Kong and Silicon Valley**, with partners and users around the world.

Products & Services

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HongKe 虹科

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Outlook for Covid-19 in 2022 H2 and Its Broader Impact on the Pharma Market

By Dr. Preet Pal S.B.

Keywords: COVID-19, Antiviral Drugs, Biologicals, Generics

The initial shock of Omicron is over, and it appears that the covid-19 cases are declining globally. Moreover, vaccine availability and its acceptability are improving. It almost looks as if the covid-19 epidemic will end in many places. But it is too early to make any conclusions. Emerging data suggest that covid-19 still poses a significant risk, and it will continue to be one of the leading causes of morbidity and mortality in 2022. Not only that, it may make a sudden and unpredictable comeback in many places.

Cases of covid-19 might be declining, but the chances of rebound are high

Cases of covid-19 are indeed declining sharply and globally. However, it is still causing a significant number of infections. The number of infections is almost close to what it used to be about a year back, in mid-2021.

Although the number of people affected by covid-19 in spring and early summer of 2022 remains moderately high, the number of covid-19 related deaths is relatively low. There are many reasons for low covid-19 associated mortality from vaccination, and improved treatment, to low mortality associated with prevalent variants like Omicron[1].

However, one should be careful in interpreting all the data. For example, the WHO covid-19 dashboard shows that about 6 million plus people died by May 2022 due to covid-19 since the pandemic's beginning. However, at the same time, WHO suggests that actual deaths are perhaps twice more and are close to 15 million. Such a significant difference is due to the fact that many infections and deaths go unreported in developing economies[2].

Considering that covid-19 is highly mutative, it is quite likely that new variants may keep emerging. Thus, the probability is high that the infection may rebound in autumn 2022.

We might see localized eruptions of infection in the near future

There are already early signs of it that instead of a sudden upsurge in the cases worldwide, we are more likely to witness epidemics in one or another region. There are many reasons for that, such as the use of medications, different levels for vaccination, varied approach to a booster dose, genetic differences between the people, and more.

It is pretty clear that despite the declining number of covid-19 cases, it will not disappear completely. The recent upsurge of the infection in Shanghai indicates what lies ahead. We are more likely to witness localized and significant upsurges of the infection.

However, due to a better understanding of the infection, there are also greater chances that most countries would be able to control the spread of infection. Thus, in early May, covid still continues to be a significant health threat in South Korea, Italy, Germany, France, North America, and some other nations. However, by autumn picture may be pretty different.

Evolving approach to preventing and managing covid-19

When it comes to preventing and managing covid-19 infections, apart from vaccines, perhaps the pharma industry will start playing a more significant role.

Unlike 2021, there are now few pharmacological options that can help prevent covid-19 spread. Additionally, covid-19 treatment is now supported by greater evidence, and thus medical experts know what works and what does not.

Covid-19 causes biphasic illness. The first phase, which may last as long as a couple of weeks, is about increasing the viral load. It causes symptoms reminding viral respiratory tract infections. During this early phase, a person can readily infect others. However, there are low chances of hospitalization or fatal outcomes during this phase. During this first phase, antiviral drugs are pretty good at preventing the progress of the disease.

Early initiation of antiviral drugs during this phase may help reduce infection severity and prevent the spread of infection. However, antivirals help if started quite early, within 2-5 days of the beginning of symptoms. The drugs that may help during this phase are nirmatrelvir and ritonavir combo, Molnupiravir, Sotrovimab, and Remdesivir[3].

It is evident that life-threatening illness occurs in the second phase. In this phase that starts after 10 to 14 days, viral load is relatively low due to the initiation of the immune response. However, severe illness ensues mainly due to a cytokine storm or hyperinflammatory response. Thus, there is little benefit from antiviral drugs during this phase, and greater focus is on controlling the cytokine storm.

During this phase, drugs that may help control cytokine storm work well and help reduce mortality. Thus, treatment with corticosteroids, IL-6 receptor blockers, Baricitinib, casirivimab and imdevimab combo, ruxolitinib, and tofacitinib combo may help. In addition, there is weak evidence that ivermectin and convalescent plasma may also have a role in this phase of the disease[3].

Now, WHO guidelines are against the recommendation of treatments like early initiation of convalescent plasma, hydroxychloroquine, and the use of the lopinavir-ritonavir combo.

Continued covid-19 epidemic, along with reduced mortality, means a greater need for drugs to manage the post-covid syndrome

When discussing covid-19 disease management, it is also essential to consider post-covid therapy options. WHO guidelines primarily focus on saving lives and treating acute infections. However, there are many pharmacological drugs needed in the post-covid phase. Those affected by covid-19 are at a greater risk of cardiovascular events and report chronic fatigue, brain fogginess, and various other health issues.

It means that there would be a continued higher demand for some cardiovascular drugs like anticoagulants. Additionally, covid-19 would also result in a greater need for anti-inflammatory drug therapy, antibiotics, vitamins, mineral supplements, and more.

How would covid-19 affect the pharma market in the second half of 2022

Covid-19 would continue to influence the pharma market in many ways. Each pharma company would need to fine-tune its business strategy according to its core strengths.

Despite some decline in vaccine requirements, long-term demand will remain stable in the coming years. Additionally, one can expect consistent demand for biologicals to control cytokine storms like IL-6 receptor blockers. It is pretty likely that some new biologicals may also get regulatory approvals in the coming months. About 20 vaccines are in the late clinical stage, and close to 30 biologicals are in phase III/IV. This just suggests what to expect in the near future[4].

There will be a considerable increase in the demand for antiviral drugs as doctors would try to curb the infection in its early stages as vaccines cannot be expected to prevent disease in all cases. Thus, drugs like nirmatrelvir and ritonavir combo, molnupiravir would see a consistent demand. It is interesting to note that Merck expects molnupiravir to emerge as its next block-bluster drug with an expected per annum revenue of above $7 billion from the molecule[5]. Therefore, no surprise that another 23 antivirals are in phase III/IV[4].

Problems with biologicals and antivirals are that they are produced by a limited number of companies. Moreover, most of these drugs are challenging to manufacture, and more importantly, they are protected by patents. Thus, for most players in the emerging markets, who specialize in generics, it would be good to focus on supporting drugs like antibiotics, analgesics, hypnotics, antithrombotic agents, anticoagulants, adrenergic and dopaminergic agents, corticosteroids, and more. Additionally, there would be a consistently higher demand for anxiolytics and vitamin supplements[6].

Apart from the supportive drugs, generic manufacturers need to keep a close eye on the repurposed drugs as many might already be in their production pipeline. Some of the repurposed drugs in an advanced phase of clinical studies are valsartan, methylprednisolone, heparin, enoxaparin, atorvastatin, and many more[4].

To sum up, covid-19 mortality is expected to decline, but not the infection rates. Thus, covid-19 will continue to shape the pharma market for the foreseeable future. Therefore, apart from vaccines and monoclonal antibodies, there would be a higher demand for antiviral agents and supporting drugs. Additionally, doctors would focus considerably on managing post-covid syndrome.

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About the Author:

Dr. Preet Pal S.B.

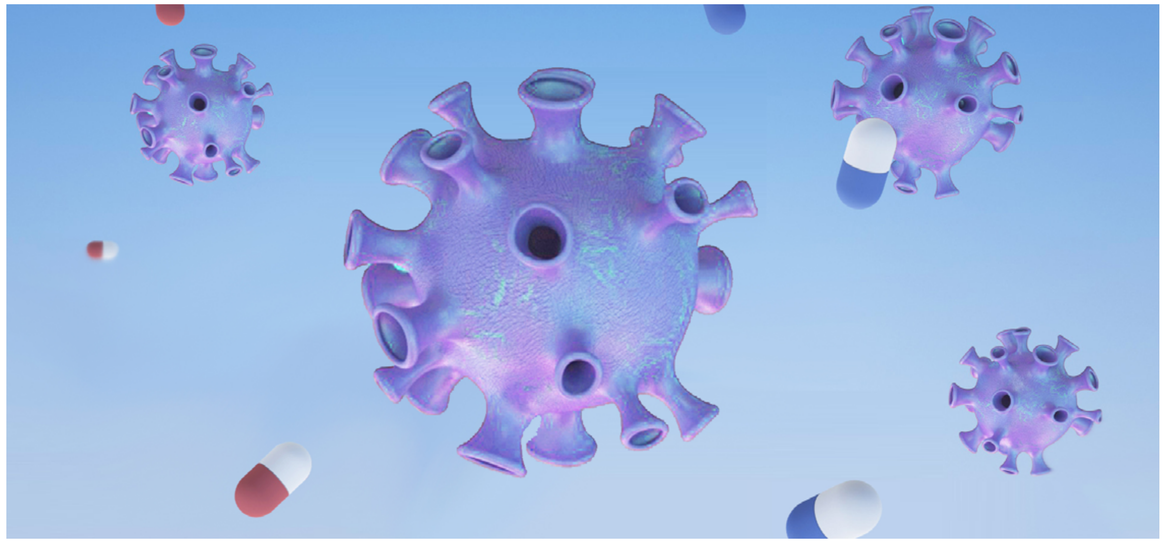
Dr. Preet Pal S.B. is a physician (M.D. Medicine, Kazakh National Medical University) specializing in diabetes (Fellowship in diabetes), a lifetime member of the Indian Medical Association. Dr. Preet has vast business development experience in the ex-soviet republics/CIS region (Ukraine, Kazakhstan, Uzbekistan, Russia, Kyrgyzstan, Azerbaijan, and so on). Dr. Preet is a multilinguistic. He has held senior management posts in various healthcare/pharmaceutical companies like SEARLE – central Asia (now a subdivision of Pfizer), Shreya life sciences, AGIO pharma, Indian Immunological Limited (Human and veterinary biologicals).

Dr. Preet is also a prolific writer and loves sharing my experiences. He firmly believe that an approach towards emerging markets differs considerably from developed markets. The bigger part of the global population resides in emerging markets. Yet, regretfully, most market reports remain focused on the developed markets. Even if they focus on emerging markets, they often use insights gained from developed markets.

With First Chinese Small-molecule Oral Drug for COVID-19 Coming, What New Opportunities are Ushered in by the Relevant Industry Chain

By Yefenghong

Keywords: VV116, Proxalutamide, Azvudine, API, CDMO



News about the progress of Chinese small-molecule oral antiviral drug for COVID-19 has been disclosed in recent days and the related R&D ushers in a critical point.

On the evening of April 17, Junshi Biosciences released the latest research results of VV116, an oral antiviral drug for COVID-19. The antiviral effect of VV116 is a lot better than that of ribavirin in a mouse model, and it could alleviate the pathological damage to lung tissues.

On April 6, Kintor Pharmaceuticals announced key data results from Phase III global multicenter clinical trials of proxalutamide for the treatment of outpatients infected with mild and moderate COVID-19. The research showed that proxalutamide was effective in reducing hospitalization/mortality rates in patients infected with mild and moderate COVID-19. Especially, it has a protection rate of 100% for all patients taking the drugs for more than 7 days.

On April 2, the official website of the Center for Drug Evaluation revealed that the status of the application for a Class III exchanging meeting submitted by Genuine Biotech had been changed from "in process" to "feedback received". In the market, it was interpreted as the indication of the clinical unblinding of Azvudine Phase III and the imminent declaration of marketing.

The first Chinese small-molecule oral antiviral drug for COVID-19 will be launched soon, and it will probably come from the above three drugs. What are the stories of these three drugs? What new opportunities will the development of oral antiviral drugs for COVID-19 bring to the companies in the related industry chain in China?

Junshi Biosciences: VV116

VV116 is a new nucleoside oral antiviral drug against SARS-CoV-2, which can inhibit the self-replication of viruses. In September last year, DreamTop Biotech, a holding subsidiary

of Junshi Biosciences, entered into a co-development contract with Vigonvita to jointly undertake the clinical development and industrialization of VV116 in the cooperation zone.

The preclinical research has shown that VV116 has significant effects against SARS-CoV-2 both in vitro and in vivo, exhibiting antiviral activity against both the original and known significant variants (Alpha, Beta, Delta, and Omicron) of SARS-CoV-2. There are also high oral bioavailability and good chemical stability. VV116 is now approved in Uzbekistan for the treatment of patients infected with mild and moderate COVID-19. Results of the clinical research conducted in Uzbekistan in 2021 revealed that: in the VV116 group, compared with the control group, the patients' clinical symptoms can be improved, shortening the time to change from positive to negative results of nucleic acid tests for COVID-19, and significantly reducing the risk of developing into severe ones and even death.

Kintor Pharmaceuticals: Proxalutamide

Kintor Pharmaceuticals' proxalutamide is an ACE2 and TMPRSS2 degradation agent that has shown promising efficacy throughout the period (including early and mid-late stage) of infection with COVID-19.

On April 6, Kintor Pharmaceuticals announced the final analysis results of a global multicenter Phase III clinical trial (NCT04870606) of its self-developed oral antiviral drug for COVID-19, proxalutamide, for the treatment of patients infected with mild and moderate COVID-19.

According to data, proxalutamide is effective in reducing hospitalization/mortality rate in patients infected with COVID-19 (mainly infected by Delta and Omicron mutant strains). Especially, for all patients taking drugs for more than 7 days, and middle and high age patients suffering from COVID-19 with high-risk factors, there is a protection rate of 100%, which is statistically significant. Moreover, proxalutamide can significantly reduce the viral load of SARS-CoV-2 and improve the symptoms. The safety of proxalutamide administration was further validated (for adult men and women aged over 18).

When the data were released, the share price of Kintor Pharmaceuticals jumped nearly 2 times in one day.

Genuine Biotech: Azvudine

Azvudine is one of the new oral antiviral drugs for COVID-19 that has received the most public attention recently. It was initially an anti-HIV drug. In February 2020, Azvudine was found to be effective in SARS-CoV-2. In April of the same year, it was approved by the National Medical Products Administration for Phase III clinical trials against COVID-19. Phase III clinical trials in China, Brazil, and Russia have been completed.

On April 2, Genuine Biotech applied for Class III exchanging meeting, which was regarded by insiders as a sign that "the first Chinese antiviral drug for COVID-19 is about to hit the market".

On April 16, at the Chinese Development Conference on Medicine, Jiang Jiandong, Member of the Chinese Academy of Medical Sciences and Academician of the Chinese Academy of Engineering, reporting on the R&D and progress of Azvudine in the treatment of COVID-19 indications, said that as a new nucleoside antiviral drug for COVID-19, oral Azivudine 5mg is more effective than intravenous 100mg Remdesivir because Azivudine is only phosphorylated in the thymus, thus protecting the immune system and enabling chemotherapy to be converted into immunotherapy.

Small-molecule oral antiviral drugs for COVID-19 support the development of Chinese related industry chain.

There are two oral antiviral drugs for COVID-19 that have been approved for marketing worldwide, namely MSD's Molnupiravir and Pfizer's Paxlovid.

In November 2021, the UK Medicines and Healthcare Products Regulatory Agency (MHRA) approved Molnupiravir for the treatment of adult patients infected with mild and moderate COVID-19 at US$ 709 per course of treatment.

Molnupiravir was developed by MSD in collaboration with Ridgeback Biotherapeutics and is an oral polymerase (RdRp) inhibitor. Molnupiravir binds to the RNA polymerase of SARS-CoV-2 and by introducing the wrong nucleotide into the newly synthesized RNA molecule, the viruses can be killed because of the error in RNA.

On December 22, 2021, FDA approved an Emergency Use Authorization (EUA) for Pfizer's Paxlovid for the treatment of ambulatory adult outpatients infected with COVID-19 who are at high risk of developing severe symptoms. Paxlovid is priced at US$ 530 per course of treatment.

Paxlovid is a compound formulation of the 3CL protease inhibitor, nirmatrelvir, (PF-07321332) and ritonavir. Nirmatrelvir inhibits the replication of SARS-CoV-2 protein, while ritonavir slows the breakdown of nirmatrelvir, allowing its effective concentration in the body to maintain for a longer period.

Paxlovid has now been fully introduced into China as a first-line drug for the treatment of patients infected with COVID-19. As oral antiviral drugs for COVID-19 are being put into use, attention is paid to related industry chain companies, mainly including CDMO enterprises, APIs, and intermediates.

Benefitting from CDMO companies

The first category of benefiting companies is CDMO companies that directly provide contract customized R&D and manufacturing services for oral antiviral drugs for COVID-19. Some Chinese leading CDMO companies producing the small molecule drugs have already occupied an important position in the industry chain by their strong capacity supply, cost advantages, and delivery capabilities.

On February 20, 2022, Asymchem announced that it has been providing services of contract development and manufacturing organization (CDMO) for a small molecule chemical innovative drug of a pharmaceutical company. Meanwhile, it has recently entered into a new Supply Contract with the client for the relevant products, with the contract amount equivalent to approximately RMB 3.542 billion this time, and the delivery time of the year 2022.

On November 17, 2021, Asymchem signed a small molecule drug supply contract with an equivalent amount of approximately RMB 3.1 billion and the delivery time from 2021 to 2022.

On November 28, 2021, Asymchem signed a new supply contract for approximately RMB 2.720 billion, with a delivery time of the year 2022.

In the same month, Proton also announced a "mysterious order", stating that it had received an order from a large US pharmaceutical company for services for a small molecule drug. Proton will provide CDMO services for the company, with a total order amount of US$ 681 million. The announcement said that the relevant purchase order had come into force and the delivery time is the year 2022.

On November 30, 2021, Proton also made a major order announcement. According to the announcement information, the cumulative order amount for the drug has reached US$ 217 million in the past 12 consecutive months. The delivery time is from 2021 to 2022.

Although Proton and Asymchem said that it is inconvenient to disclose the client and product-related information due to the commercial secrets, in combination with the layout and time nodes of small molecule drugs by various industry players, it is believed in the market that these orders are related to Pfizer's Paxlovid. Moreover, Asymchem and Proton have previously had long-term cooperation with Pfizer. However, these two companies did not respond in depth.

In addition to CDMO companies, the second category of companies benefiting from the oral antiviral drugs for COVID-19 is API industry chain companies. What about the API companies?

The API industry chain of Molnupiravir

Molnupiravir (nucleoside inhibitor EIDD-2801/MK-4482) is an oral ribonucleoside drug jointly developed by MSD and Ridgeback. On January 20, 2022, Medicines Patent Pool (MPP) announced an agreement with 27 generic drug manufacturers to license the production of low-cost, oral antiviral drugs for COVID-19, Molnupiravir, for supply to 105 low- and middle-income countries.

MPP (known as the MedicinesPatent Pool), based in Geneva, was established with the support of the United Nations, UNITAID (international drug procurement agency), and the Swiss Agency for Development and Cooperation (SDC). MPP was initially established to promote and facilitate access to new, high-cost anti-AIDS drugs in developing countries.

MPP itself does not produce and sell generic drugs. It negotiates voluntary licenses for drug patents with original R&D drug companies, which place their drug patents in a patent pool, and generic drug companies apply to MPP for licenses to implement the patents in the pool and produce and supply generic drugs to low- and middle-income countries.)

5 of the 27 companies are from China, including Fosun Pharma, Lonzeal (a shareholder of Aidea), Langhua Pharmaceutical (a holding subsidiary of Viva Biotech), Brightgene, and Shanghai DESANO. Among them, Langhua Pharmaceutical is only authorized to produce APIs, while the other four can produce both APIs and finished products.

Uridine is the raw material for the production of EIDD-2801, which is the raw material for the production of Molnupiravir. Molnupiravir is a nucleoside analog, and its suppliers involved in the upstream API intermediates are Tuoxin Pharmaceutical and Tianyu Pharmaceutical.

The API industry chain of Paxlovid

Paxlovid is a combination of two main drugs: one is nirmatrelvir, a tablet designed to inhibit the 3CL protease, thereby preventing viral replication, and the other is ritonavir, a tablet that slows the breakdown of Paxlovid to help it to remain a longer active time in the body at higher concentrations.

On March 17, MPP announced that it had signed agreements with 35 pharmaceutical companies to allow them to manufacture APIs and preparation of one of Paxlovid's components, nemativir tablets. Five Chinese companies were authorized, namely Shanghai DESANO, Huahai Pharmaceutical, Apeloa Pharmaceutical, Fosun Pharmaceutical, and Jiuzhou Pharmaceutical.

The combination of 300mg (150mg/tablet) of nirmatrelvir and one tablet of ritonavir (100mg) is administered twice a day for 5 days, according to 100PEI. Considering Pfizer's forecast of 120 million Paxlovid treatments in 2022, 360 tons of nirmatrelvir APIs would be required.

The upstream drug suppliers of Paxlovid mainly involve intermediates and APIs such as caronic anhydride, azabicyclic, SM1, SM2, and ritonavir. Major manufacturers of caronic anhydride are Aba Chemicals and Jianfeng Group.

For SM1 and SM2, suppliers with supply capacity and sufficient production capacity in China are Menovo, Tianyu Pharmaceutical, Hicin Pharmaceutical, and Aurisco.

For ritonavir, the subsidiary of Jinghua Pharmaceutical, Senxuan Pharmaceuticals, accounts for 70% of the market share of ritonavir intermediates, ranking first in the industry.

At this point in the development of the pandemic, vaccines alone will not completely stop the spread of SARS-CoV-2. The oral specific drug is the key to finally saving people from the fear of the virus and is the last step to end the impact of the pandemic. With oral antiviral drugs for COVID-19 successively developing from the R&D into the commercialization, the production will rapidly increase under the catalyst of the pandemic, and the demand for upstream intermediates and APIs also shows explosive growth. This industry chain is popular as ever before. At the same time, several Chinese companies in oral antiviral drugs for COVID-19 led the way. It is expected that the pharmaceutical companies in the forefront can withstand the heavy test before the marketing and usher in the first Chinese antiviral drug to market as soon as possible.

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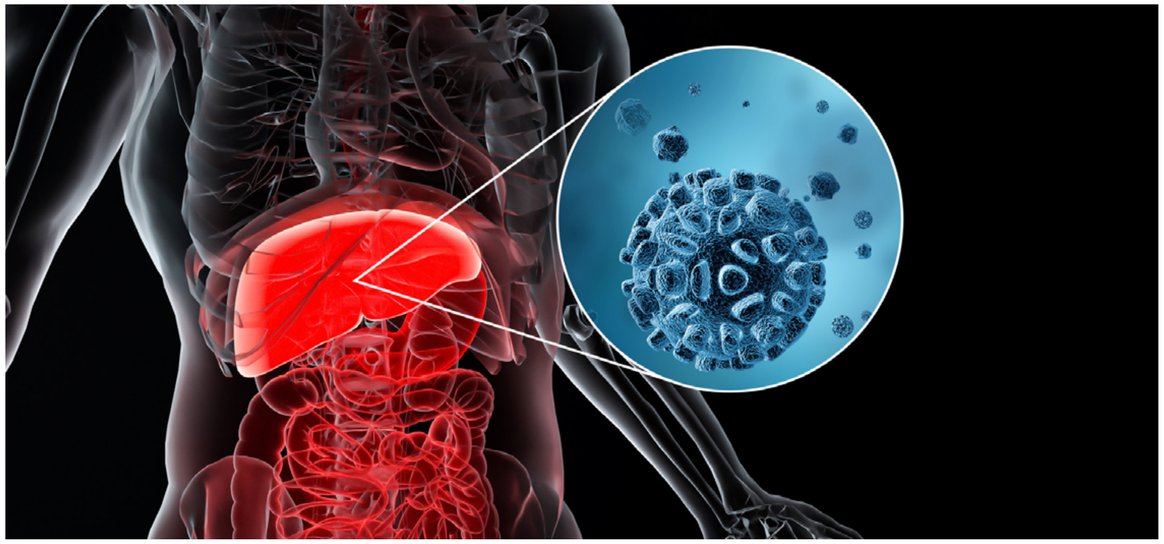
Is mRNA Vaccine the Source of Intricacies of "Mysterious Hepatitis"?

By Yefenghong

Keywords: mRNA Vaccine, Autoimmune Hepatitis, COVID-19



3 years into the COVID-19 pandemic, it has had a significant impact on human health and economic development. Based on WHO statistics, as of April 22, there are approximately 497 million confirmed patients and 6.179 million deaths in the world because of COVID-19.

Novel Coronavirus (SARS-CoV-2) shares a partly similar structure with the SARS virus 18 years ago, while it is more infectious and accommodates better to temperature changes. Besides, seasonal changes have little sway over the virus. As a consequence, people lay their hope of eradicating the pandemic on vaccines.

During the research and development of the vaccines, enterprises like Pfizer, Moderna, Johnson & Johnson, AstraZeneca, and Sinovac have contributed much to the combat of the disease and also acquired a great revenue from the new COVID-19 vaccines. Among those vaccines, the mRNA vaccine has risen sharply and set off a global boom in development for its short R&D cycle and high protection rate. COVID-19 mRNA vaccine (BNT162b2, brand name: Comirnaty), jointly developed by Pfizer/BioNTech, is one of the earliest widely used mRNA COVID-19 vaccines globally, which has gained 36.781 billion US dollars in profit last year.

However, on April 21, a case released in the Journal of Hepatology, an international authoritative journal in the field of liver diseases, struck BNT162b2. According to the research, BNT162b2 may cause a T cell-mediated autoimmune hepatitis.

Autoimmune hepatitis is a chronic progressive liver inflammatory disease mediated by the autoimmune reaction. Its clinical features are elevated serum transaminase of various levels, hypergammaglobulinemia, and positive autoantibody. Its histological features are interfacial hepatitis mainly infiltrated by lymphocytes and plasma cells. Severe cases can rapidly progress to liver cirrhosis and liver failure.

This clinical research from Germany has disclosed a bimodal attack of acute hepatitis after vaccinating two doses of the

Pfizer mRNA vaccine (the attacks occur after two vaccinations). This male patient is 52 years old with no other medical history except hypothyroidism.

Diagnosis

The patient began to show symptoms of progressive nausea, fatigue, anorexia, and pruritus nearly 10 days after the vaccination of the first dose of BNT162b2. He experienced jaundice next and paid a visit to a primary health physician on the 25th day after vaccination. Liver function examination (LFT) revealed acute mixed hepatocyte/cholestatic hepatitis (ALT: 2130 U/l, AP. 142 U/l, γ-GT: 217 U/l, bilirubin 7.7 mg/dl).

Serological and/or PCR tests excluded the possibility of viral hepatitis A, B, C, and E, as well as cytomegalovirus and Epstein-Barr virus infections. The patient recovered quickly without special treatment and was discharged 3 days later. The level of liver enzymes of the patient gradually decreased to the normal condition over the next 2 weeks.

Subsequently, the patient was inoculated with the second dose of BNT162b2 41 days after the first one. After 20 days, the patient relapsed with acute mixed hepatitis. The patient's liver function improved after oral taking budesonide daily. However, his disease relapsed after 39 days, and finally eased under the treatment of systemic steroids combined with ursodeoxycholic acid.

Autoimmune serological examination showed that the patient had mild hyperglobulinemia, antinuclear antibody (ANA), antimitochondrial M2 antibody (AMA-M2), and anti-smooth muscle antibody was critically positive, while the anti-LKM test was still negative.

Analysis of liver tissue showed that immune infiltration was dominated by activated cytotoxic CD8 T cells with panlobular distribution. Enrichment of CD4 T cells, B cells, plasma cells, and bone marrow cells were also observed compared with the control. Compared with peripheral blood, intrahepatic infiltration showed enrichment of CD8 T cells with SARS-CoV-2 specificity.

It is worth noting that the T lymphocyte cluster in the liver tissue of patients is the richest among their immune cells, which differs from typical autoimmune hepatitis, and the researchers found that there is a wider infiltration of immune cells around the portal vein of patients.

The researchers finally concluded that the vaccination with the BNT162b2 vaccine may cause immune-mediated hepatitis through the cellular immune mechanism. These results imply that: T cells are the key pathogenic immune cell type of this vaccine-associated immune hepatitis, and this "mysterious hepatitis" is a new subtype of autoimmune hepatitis.

Cause Analysis

While this is the case, some professionals in the vaccine industry believe that: in the BNT162b2 vaccine, liposome encapsulation technology is introduced, and liposome is easy to get enriched in the human liver, which remains a safety concern of mRNA vaccine in the industry before, but no related problems have been identified in clinical researches. The recently popular Omicron variant can infect the liver. In this case, if the virus infects the liver, and the vaccine antigen carried by liposome is also enriched in the liver, the situation may become very complicated. **Some others stand opposite instead**. It is of little possibility that the liposome of the mRNA vaccine will be enriched in the liver to trigger an unexpected T cell hyperimmune response since the amount of vaccine is very small and it is difficult to reach the liver.

There is no conclusion on the causes of the above case, and further research is required.

In fact, before the release of the article, the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) published the discussion results of the above case on April 8 local time and concluded that: the existing evidence does not prove the causal relationship between COVID-19 mRNA vaccine and autoimmune hepatitis, and there is no need to update the vaccine product information currently. EMA showed that it would keep closely supervising any new situation reports and take corresponding measures when necessary.

Children's "mysterious hepatitis" has also emerged in the world other than the above case. Since January this year, there have been many cases of acute hepatitis in children of unknown origin in the United States, Europe, and Japan. As of April 26, more than 190 cases of unexplained hepatitis in children have been reported worldwide. Besides, 17 cases suffer from hepatic failure and 1 case dies. Among them, about 74 cases are positive for F41 adenovirus, 20 cases are found to catch SARS-CoV-2, and another 19 people are infected with both. Till now, experts are still researching whether this disease is caused by such adenovirus.

Diagnosis

Now WHO tentatively defines this "mysterious hepatitis" as "acute severe childhood hepatitis of unknown origin", with judging criteria as follows. The patient develops the disease after January 2022. He or she is at the age of 16 years old younger and suffers from acute hepatitis (not caused by hepatitis A, B, C, D, and E viruses). The level of aspartate aminotransferase or alanine aminotransferase exceeds 500U/L.

Currently, most of the affected children are 5 years old or younger. Observation shows that the duration from infection to onset of pediatric patients is usually no more than half a year, and the possible symptoms include influenza-like symptoms, gastrointestinal problems, fever and jaundice, alkaptonuria, etc. About 17 children in the world have received or need to receive liver transplantation due to liver failure. Adenovirus is a seasonally transmitted disease, and most adenovirus diseases are self-limiting. But for those with low immune function, a fatal infection may occur. This happens occasionally in healthy children and adults.

Cause analysis

At present, adenovirus infection combined with COVID-19 is likely to be considered the cause of this hepatitis by the international analysis. According to researchers, the control measures during COVID-19 decrease children's exposure to external pathogens. After reopening, children may get easier to catch the virus as well as more serious symptoms when exposed to the adenovirus on account of the decline of existing immunity, which means that they are not stimulated by pathogen immunity for a long time. Besides, adenovirus infection is accompanied by SARS-CoV-2 or previous infections. Adenovirus infection combined with current SARS-CoV-2 or other pathogen infections is also one of its causes. Experts also believe that a new adenovirus variant may have appeared.

At present, the world is still enveloped in the cloud of "mysterious hepatitis". Compared with the disease itself, the unknown cause of the disease is more frightening. According to the current evidence, the mRNA vaccine is safe, and the expansion of vaccination should not be affected. According to WHO, the priority at present is to determine the etiology, guide further clinical and public health actions and clarify risk factors.

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First Drug Coming Soon as Pharmaceutical Companies Take Moves in the B7-H3 Immune Target Products Layout

By Yi

Keywords: TAA06, B7-H3, Omburtamab

On April 11, CDE's official website revealed that the application for an Investigational New Drug, the new first-in-class [TAA06 Injection] by PersonGen BioTherapeutics (Suzhou) Co., Ltd. was accepted. Based on public information, TAA06 is an independently developed B7-H3-targeted CAR-T therapy of PersonGen. The drug was granted the Orphan Drug Designation (ODD) for treating neuroblastoma by the FDA (Food and Drug Administration) in March of this year.

B7-H3 (CD276) is a type I transmembrane protein and a member of the B7 immune co-stimulation and co-suppression family. It is overexpressed in solid tumors such as bladder cancer, prostate cancer, and melanoma, but its expression is limited in normal tissues. The early discovery of B7-H3 was mainly demonstrated to function as a co-stimulatory receptor, promoting the proliferation of CD4+ and CD8+ T cells, inducing cytotoxic T cells, and producing immunostimulatory functions by selectively stimulating interferon γ (IFN-γ) in the context of T cell receptor signaling. As the research progressed, there is increasing evidence showing that B7-H3 plays a major role in immune cells as a co-inhibitor, facilitating the evasion of tumor cells from immune surveillance. Therefore, the overexpression of B7-H3 is related to the poor prognosis of tumor patients and the invasion and metastatic potential of tumor in vitro models.

S/N	Acceptance No.	Drug name	Drug type	Application type	Registration classification	Company name	Date of undertaking
1	CXSL2200164	TAA06 Injection	Therapeutic biological products	New drug	1	PersonGen BioTherapeutics (Suzhou) Co.,Ltd.;	April 11, 2022

B7-H3 is an emerging target for immunotherapy. Among all the products, omburtamab by Y-mAbs Therapeutics progresses the fastest and has resubmitted the BLA (Biologics License Application) for the treatment of pediatric patients with the central nervous system (CNS) or leptomeningeal metastasis neuroblastoma to the FDA in early April. Omburtamab is a radionuclide iodine-131-labeled B7-H3-targeted monoclonal antibody that targets B7-H3-expressing cells in solid tumors and binds to the FG loop-dependent conformation, a critical region of biological function in the B7-H3 molecule. In December 2020, SciClone Pharmaceuticals reached an agreement with Y-mAbs Therapeutics and obtained exclusive rights to the co-development, registration, and commercialization of the drug and GD2 targeted monoclonal antibody-Danyelza (naxitamab-gqgk) in Greater China (including Chinese mainland and Hong Kong/Macau/Taiwan Regions of China). Moreover, Y-mAbs Therapeutics has developed 177Lu-omburtamab-DTPA radiolabeled by lutetium-177 for the treatment of pediatric patients with relapsed or refractory medulloblastoma and adult patients with positive CNS tumors or leptomeningeal metastasis, among which the medulloblastoma indication was granted rare pediatric disease designation (RPDD) by the FDA.

And the B7-H3-targeted monoclonal antibody enoblituzumab developed by MacroGenics also sees good progress, now in Phase II clinical trials. Enoblituzumab is an immune optimized anti-B7-H3 monoclonal antibody. It combines the exclusive Fc optimization technology platform of MacroGenics, with unique antibody advantages and therapeutic potential. The published interim analysis results of Phase I clinical trials of enoblituzumab for refractory solid tumors show that: the drug can be tolerated up to 15 mg/kg without maximum tolerated dose (MTD) and dose-limiting toxicity (DLT). In July 2019, I-Mab Biopharma reached an agreement with MacroGenics to obtain the exclusive development and commercialization rights of the drug in Greater China (including the Chinese mainland, Hong Kong/Macau/Taiwan Regions of China).

In addition to monoclonal antibodies, pharmaceutical companies have also developed bispecific antibodies, antibody-drug conjugates (ADC), and CAR-T therapies around B7-H3 targets, as shown in the table below.

Some of the global B7-H3-targeted drugs under R&D

Drug type	Drug name	Company name	Indications	R&D stage
Bispecific antibody	ATG-027	Antengene Corporation	Hematologic tumor, solid tumor	Preclinical
	TJ-L1H3	I-Mab Biopharma	Tumors	Preclinical
ADC	DS-7300	Daiichi Sankyo	Solid tumors	Phase II clinical trials
	MGC018	MacroGenics	Solid tumors	Phase II clinical trials
	ABBV-155	AbbVie	Hematologic tumor, solid tumor	Phase I clinical trial
CAR-T	TAA06	PersonGen	Neuroblastoma, etc.	Clinical application

Sources: Public data

- ATG-027 is a B7H3 and PD-L1-targeted bispecific antibody researched and developed by Antengene Corporation, which is developed for the treatment of hematological malignant tumors and solid tumors.
- DS-7300 is an ADC developed by Daiichi Sankyo with its proprietary DXd technology. It consists of a humanized anti-B7-H3 monoclonal antibody and a new topoisomerase I inhibitor coupled with a tetrapeptide linker. Preclinical research reveals that the drug showed activity in the expression of B7-H3 tumors, and the activity was related to the target expression level. Phase I/II clinical trials data presented at the 2021 European Society of Medical Oncology (ESMO)

Annual Meeting showed that in clinical trials of a series of patients with solid tumors (n=70), including Metastatic Castration-Resistant Prostate Cancer, head and neck squamous cell carcinoma, small cell lung cancer, endometrial cancer, esophageal squamous cell carcinoma and squamous NSCLC, 15 patients achieved partial response (PR), of which 10 had confirmed PR and 5 had PR pending confirmation.

- MGC018 is a B7-H3-targeted ADC that delivers the DNA alkylating agent duocarmycin to tumor cells expressing B7-H3. Duocarmycin is capable of damaging the DNA of dividing and nondividing cells, leading to cell death. Results from the Phase I dose-escalation clinical trial presented at the 2021 ASCO Annual Meeting showed that the drug demonstrated preliminary antitumor activity with excellent efficacy, particularly in patients with advanced metastatic castration-resistant prostate cancer.

- ABBV-155 (mirzotamab clezutoclax) is a B7-H3-targeted ADC with a load of BCL-XL inhibitor which can promote apoptosis.

Overall, the competition for B7-H3-targeted drugs is not that fierce currently, and the types of drugs under R&D are relatively diversified, most of which are in the initial stage with the constant exploration of indications. Chinese pharmaceutical companies are also actively exploring the field of B7-H3-targeted drugs, in addition to independent R&D, but also from foreign pharmaceutical companies to introduce. Omburtamab, the world's first B7-H3-targeted drug, is expected to debut as soon as possible, to drive the R&D of competitive pharmaceutical companies to great extent.

About the Author:

Yi

Yi, a pharmacist pays attention to the research and development trends of new drugs at home and abroad, expects to improve himself in the continuous input and output, and grow together with medical we-media.

Antibody-Drug Conjugates - Lessons Learned

By Neeta Ratanghayra

Keywords: ADCs, Mylotarg, Gemtuzumab ozogamicin

Antibody-drug conjugates (ADCs) have made significant progress in tumor therapy and show a promising future. As per insights from Clarivate experts, the global market for currently marketed ADCs is expected to cross US$16.4 billion by 2026. However, designing an ADC is a challenge requiring a careful combination of the antibody, linker, and the cytotoxic drug.

The approval of Pfizer's Mylotarg® in 2000 marked the beginning of an era of targeted oncology therapy. But it took almost a decade for the second ADC, Brentuximab vedotin (Adcetris®), to enter the market. What were the problems with the earlier ADCs?

This article highlights the recent advances in ADCs and lessons learned from the developmental challenges faced with the earlier ADCs.

Antibody-Drug Conjugates - A Sneak Peek

Antibody-drug conjugates are biotherapeutics that utilize antibodies to selectively deliver cytotoxic (payloads) drugs to the tumor site.

The antibody in an ADC is attached to the cytotoxic drugs via a linker system. The linkers act as a specific bridge, helping the antibody release the cytotoxic drug selectively and accurately at tumor sites. The linkers also help maintain the ADCs' stability during their preparation, storage, and systemic circulation.

The antibody in the ADC is designed to target a specific antigen (receptor) that is highly expressed in tumor cells. By selectively delivering the cytotoxic drug to tumors, ADCs limits their systemic exposure, leading to greater efficacy and minimal side effects.

The First Antibody-Drug Conjugate Was Launched In 2000

In 2000, the U.S. Food and Drug Administration (FDA) approved

Pfizer's Mylotarg® (gemtuzumab ozogamicin) for acute myeloid leukemia (AML). In 2010, Pfizer voluntarily withdrew Mylotarg in the U.S. after a confirmatory trial failed to demonstrate clinical benefit and showed increased toxicity compared to chemotherapy. However, in September 2017, the FDA reapproved Mylotarg for adults with newly diagnosed CD33-positive AML and relapsed or refractory CD33-positive AML in patients aged 2 years and older. The FDA specifically highlighted the modified dosing regimen that improved gemtuzumab ozogamicin's safety and efficacy and led to its reapproval.

It Took Almost a Decade for The Second ADC To Enter the Market - What were the problems with the earlier ADCs?

Seagen's Brentuximab vedotin (Adcetris®) was the second ADC to be approved. The drug received FDA approval in 2011. A gap of 11 years for the second ADC to enter the market highlights the challenges which manufacturers faced while developing the earlier ADCs.

First-generation Antibody–Drug Conjugates - Gemtuzumab ozogamicin

BR96–doxorubicin and KS1/4–methotrexate were the first ADCs to be developed. These ADCs were basically chemotherapy drugs linked to murine antibodies using a non-cleavable linker. Both drugs were unable to show clinical benefit, and their further development was discontinued.

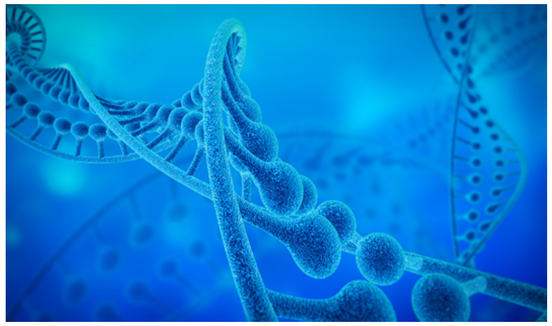
Next, the researchers experimented with combinations of potent cytotoxic agents and humanized monoclonal antibodies. Gemtuzumab ozogamicin was a humanized anti-CD33 IgG4 antibody, conjugated to calicheamicin using an acid-labile hydrazone linker. Gemtuzumab ozogamicin showed increased efficacy in clinical studies and became the first ADC to enter the market in 2000. However, in subsequent studies, the drug showed poor efficacy and increased toxicities which lead to its withdrawal in 2010. (Gemtuzumab ozogamicin was reapproved in 2017 by the FDA).

Unstable linker, high amount of unconjugated antibody, poor CMC (chemistry, manufacturing, and control) properties, and high toxicity were some of the disadvantages of the first-generation ADCs. Learning from these drawbacks lead to the development of the second-generation ADCs.

Second-generation Antibody–Drug Conjugates - brentuximab vedotin, ado-trastuzumab emtansine, and inotuzumab ozogamicin

The second-generation ADCs showed better safety, efficacy, and CMC characteristics. These ADCs were introduced after optimization of monoclonal antibodies isotypes, cytotoxic payloads, and the linkers. Several potent chemotherapy drugs, such as auristatins and mytansinoids, with improved water solubility and coupling efficiency, were also discovered. The improved linkers helped achieve better plasma stability and homogeneous drug-to-antibody ratio (DAR) distribution.

Though better than the first-generation ADCs, there were still challenges with the second-generation ADCs. Off-target toxicity led to insufficient therapeutic windows. Problems of aggregation or rapid clearance (hence decreased efficacy) were observed in ADCs with high DAR. Competition with unconjugated antibodies for antigen binding was another issue.



Third-generation Antibody–Drug Conjugates - polatuzumab vedotin, enfortumab vedotin, fam-trastuzumab deruxtecan

Optimization of DAR using site-specific conjugation played a pivotal role in developing successful third-generation ADCs. Site-specific conjugation led to improved pharmacokinetics, desired cytotoxicity, and homogeneous ADCs with DAR 2 or 4. Consistent DARs also led to less off-target toxicity.

The use of fully humanized antibodies instead of chimeric antibodies in the third generation ADCs helped reduce immunogenicity. Research is ongoing to replace intact mAbs with antigen-binding fragments (Fabs), which are more stable in systemic circulation and may be internalized more readily by tumor cells.

Another feature of the third-generation ADCs is the use of potent payloads such as pyrrolobenzodiazepine dimer (PBD), tubulysin, and immunomodulator. Fleximer platform and hydrophilic linker modulation such as PEGylation are some novel developments in the linker space.

The latest innovations and developments confer third-generation ADCs with higher stability and efficacy as well as lower toxicity.

Antibody–Drug Conjugates Currently on The Market

The crafting of a perfect ADC is easier said than done. But despite the challenges, many companies have succeeded in designing the right combination. As of December 2021, there are 14 ADC drugs approved worldwide and over 100 candidates are at various stages of clinical trials. Here is a quick overview of the approved ADCs.

Product	Company	Target	Approved by				Indication
			FDA	EMA	NMPA	PMDA	
Gemtuzumab ozogamicin (Mylotarg®)	Pfizer	CD33	√	√	X	√	Acute myeloid leukemia
Brentuximab vedotin (Adcetris®)	Seagen	CD30	√	√	√	√	Hodgkin lymphoma Anaplastic large cell lymphoma
Inotuzumab ozogamicin (Besponsa®)	Pfizer	CD22	√	√	X	√	Relapsed or refractory B-cell precursor acute lymphoblastic leukemia
Moxetumomab pasudotox (Lumoxiti®)	AstraZeneca	CD22	√	√	X	X	Relapsed or refractory hairy cell leukemia
Polatuzumab vedotin (Polivy®)	Roche	CD79b	√	√	X	X	Diffuse large B-cell lymphoma
Belantamab mafodotin (Blenrep®)	GSK	BCMA	√	√	X	X	Relapsed or refractory multiple myeloma
Loncastuximab tesirine (Zynlonta®)	ADC Therapeutics	CD19	√	X	X	X	Relapsed or refractory large B-cell lymphoma
Ado-trastuzumab emtansine (Kadcyla®)	Roche	HER2	√	√	√	√	HER2-positive early breast cancer
Enfortumab vedotin (Padcev®)	Seagen	Nectin-4	√	X	X	X	Locally advanced or metastatic urothelial cancer
Fam-trastuzumab deruxtecan (Enhertu®)	Daiichi Sankyo	HER2	√	√	X	√	Unresectable or metastatic HER2-positive breast cancer Locally advanced or metastatic HER2-positive gastric or gastroesophageal junction adenocarcinoma
Sacituzumab govitecan (Trodelvy®)	Immuno-medics	TROP2	√	X	X	X	Metastatic triple-negative breast cancer
Cetuximab sarotalocan (Akalux®)	Rakuten Medical	EGFR	X	X	X	√	Unresectable locally advanced or recurrent head and neck cancer
Disitamab vedotin (Aidixi®)	RemeGen	HER2	X	X	√	X	Locally advanced or metastatic gastric cancer
Tisotumab vedotin (Tivdak®)	Genmab/ Seagen	Tissue factor	√	X	X	X	Recurrent or metastatic cervical cancer

Antibody–Drug Conjugates in Late Phase Development

The success of recent drugs has ignited new hopes in the field of ADCs. Learnings from past failures and advances in chemistry have encouraged several companies to invest in this space. Below is a list of selected candidates in the late phase of development:

Company	ADCs in late phase development			Comment
	Candidate	Indication	Phase	
Daiichi Sankyo	Patritumab deruxtecan	EGFR mutated NSCLC, HERTHENA-Lung01	II	FDA breakthrough therapy designation for metastatic or locally advanced EGFR+ NSCLC
		EGFR mutated NSCLC, HERTHENA-Lung02	III	
	Datopotamab deruxtecan	NSCLC (w/ actionable mutation)	II	.....
		NSCLC 2/3L HR+ BC 2/3L NSCLC (w/o actionable mutation, pembro combo)	III	
Seagen/Merck	Ladiratuzumab vedotin	1L Metastatic triple-negative BC	II	.....
		R/R Metastatic solid tumors	II	
Seagen	Disitamab vedotin	HER2+ urothelial cancer	II	Licensed from RemeGen. ex-Asia rights and rights in Japan and Singapore
ADC Therapeutics	Camidanlumab tesirine	R/R Hodgkin lymphoma	II	.....
	ADCT-602	Relapsed or refractory B-cell acute lymphocytic leukemia	I/II	
Gilead Sciences	Magrolimab	Higher risk myelodysplastic syndrome; Acute myeloid leukemia	III	Partial clinical hold on magrolimab in combination with azacytidine was lifted by the FDA in April 2022
		Head and neck squamous cell carcinoma; Solid tumors; Multiple myeloma	II	
Mersana Therapeutics	Upifitamab rilsodotin	Recurrent ovarian cancer	I/II	Phase III planned for Q2 2022
AbbVie	Telisotuzumab vedotin	c-Met+ NSCLC	III	FDA granted Breakthrough Therapy Designation
ImmunoGen	Mirvetuximab soravtansine	Platinum-resistant ovarian cancer	III	.....
	Pivekimab sunirine	Blastic plasmacytoid dendritic cell neoplasm and acute myeloid leukemia	I/II	EMA/FDA orphan drug designation FDA Breakthrough Therapy Designation
Sanofi	Tusamitamab ravtansine	Non-small-cell lung cancer	III	.....
		Exploratory solid tumors/gastric cancer	II	

R/R, relapsed or refractory; NSCLC, Non-small cell lung cancer; EGFR, epidermal growth factor receptor; FDA, Food and Drug Administration; EMA, European Medicines Agency; HER, human epidermal growth factor receptor; BC, Breast Cancer.

Antibody–Drug Conjugates Market – Significant Growth, But Challenges Remain

The ADC market is set to witness phenomenal growth with several candidates across various cancer types entering late-phase development. Compared to the earlier generation, new generation ADCs come with enhanced specificity and cytotoxicity profiles, but challenges exist. Inadequate tumor targeting, complex pharmacokinetics, and issues with payload release and drug resistance can be tough to handle. The use of advanced analytical techniques, innovations in the main components (antibody, payload, and linker), and novel bioconjugation platforms can help shape the future development of ADCs.

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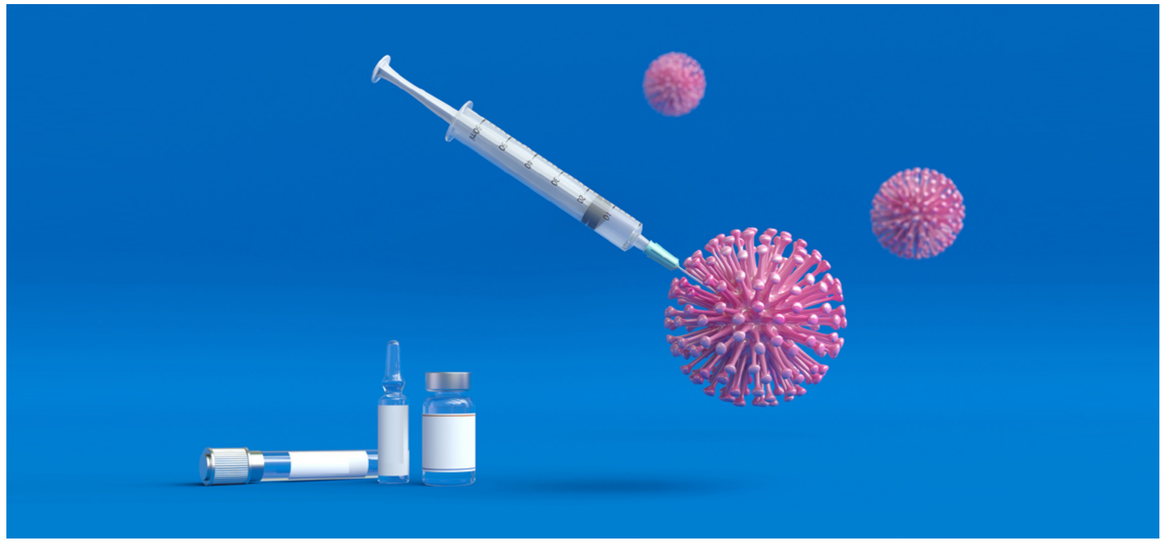
Chinese Pharmaceutical Companies Entering the DC Vaccine Market Under the Support of Tens of Millions of Financing

Which can be applied to the treatment of cancers and even the COVID-19 infection

By Yefenghong

Keywords: DC Vaccine, Solic Tumor Therapies, COVID-19 Treatments



On April 20, Zhongshan Hengsai Biotechnology Co., Ltd. ("Hengsai Bio" for short) announced that it has completed the Pre-A round of financing of tens of millions of RMB. The funding is led by Fuho Capital, with the participation of Hengyue Investment, and MedBio Capital assuming the responsibility of the exclusive financial advisor.

Founded in 2018, Hengsai Bio is a high-tech enterprise focusing on tumor immunotherapy. It is mainly engaged in the R&D and industrialization of a new generation of individualized dendritic cell tumor treatment vaccine (DC vaccine).

What is the DC vaccine? What fields can it be applied to? Which stage of research progress does it hold currently? How huge the potential market is?

Dendritic cells (DC) are the most powerful antigen-presenting cells (APC) found at present. Their antigen-presenting function is much stronger than other antigen-presenting cells, such as macrophages and B cells. They have a sharp capacity to activate CD8+ and CD4+ T cells and can secrete a variety of cytokines to participate in immune regulation and response.

DCs were identified in 1973 by Professors Zanvil Cohn and Ralph Steinman. Professor Ralph Steinman treated himself with the DC vaccine for pancreatic cancer, which substantially extended his survival time. Hence, in 2011 Professor Ralph Steinman was awarded the Nobel Prize in Medicine for his pioneering work in identifying DCs. Substantial breakthrough in the DC vaccine has been obtained in the clinical research of tumor immunotherapy at home and abroad, and now, the DC vaccine has grown to be a fascinating research area in the field of tumor immunotherapy.

The theory of the DC vaccine preparation is very simple. DC precursor cells of patients are separated and cultured in vitro. Loading with tumor antigen, they are transferred to patients. Then, DCs stimulate specific anti-tumor T cells to make the

anti-tumor effect come into play. Besides, DCs can establish a persistent anti-tumor-specific immune response, holding a critical position in anti-tumor immunity.

Since the anti-tumor properties of DCs remain consistent with the vaccine theory, DC therapy is mostly called DC vaccine clinically.

Research Progress of DC Vaccine

The first anti-cancer vaccine approved by FDA in 2010, Provenge (sipuleucel-T), was the DC vaccine. It is applied for the treatment of metastatic prostate cancer. Currently, various DC vaccines have been approved for marketing in the world, including CreaVaxRCC, Hybricell, DCVax-Brain, Provenge, and APCEDEN. The indications involve prostate cancer, malignant melanoma, renal cell carcinoma, non-Hodgkin's lymphoma, glioma, lung cancer, liver cancer, colorectal cancer, breast cancer, and nasopharyngeal carcinoma.

It deserves to be mentioned that Dendreo, which once developed Provenge, has a troubling sales condition in the later period on account of great production cost, complex operation, and marketing. In November 2014, the company declared bankruptcy because of heavy liabilities. Later, after rounds of twists and turns, SanPower Group, a private Chinese enterprise, finally acquired Provenge with US$ 819 million.

Till now, when the keyword "DC vaccine" is inputted in ClinincalTrials.gov for retrieval, a total of 256 trials on the DC vaccine can be reported. Both the ongoing clinical research and the marketing-approved DC vaccine have proved the possibility of it being innovative and effective immunotherapy for treating tumors.

Clinical Progress of DC Vaccine in Solid Tumors

Renal cell carcinoma

At the 2020 ASCO SITC Clinical Immuno-oncology Symposium, Immunicum released the latest data of Phase II clinical research MERECA of its DC vaccine, ilixadencel, on metastatic renal cell carcinoma (mRCC). The data showed that: as of December 2019, the survival rate of the ilixadencel treatment group was 54%, while that of the control group was 37%. The objective response rate (ORR) of the ilixadencel treatment group was 42% and that of the control group was 24%.

Glioblastoma

In April 2020, AIVITA analyzed the Phase II clinical trials (NCT03400917) of its candidate DC vaccine, AV-GBM-1, against glioblastoma (GBM). The results showed that: the overall survival rate of GBM patients (n=50) who received treatment with AV-GBM-1 was 76%, while that of the control group was 48%.

Small cell lung cancer

In March 2021, a randomized controlled Phase II trial of DC vaccine (Ad.p53-DC) for patients with recurrent small-cell lung cancer (SCLC) showed that the vaccine was safe, mainly with grade 1/2 toxicity and partial grade 3 toxicity. The positive immune response rates of different experimental groups ranged from 20% to 43.3%. Although the vaccine fails to enhance the objective response rates (ORRs) of patients under second-line chemotherapy, it still possesses the security and therapeutic immunity potential. As of the end of November 2021, there were 8 ongoing clinical trials of the DC vaccine for patients with lung cancer.

Prostate cancer

Another human Phase I/II trial of an adjuvant DC vaccine for high-risk prostate cancer patients after receiving radical prostatectomy presented results with great prospects. 5 of 12 patients with prostate cancer were relieved after 84 months, while the immune response of all patients was promoted. As of the end of November 2021, there were 5 ongoing clinical trials of the DC vaccine for patients with prostate cancer.

Currently, targeting solid tumors remain a critical challenge in tumor immunotherapy, and most innovative immune cell therapy technologies mainly focus on hematologic tumors. It is no doubt that the emergence of the DC vaccine shows a new direction for the immunotherapy of solid tumors.

DC Vaccine for the Treatment of COVID-19 Infection

Research has revealed that patients with coronavirus show moderate neutralizing antibody titer and T cell response falter, manifesting that it may be hard for conventional vaccine methods to produce long-term protection through a cellular immune response. As the most effective antigen-presenting cells in the human body, dendritic cells can present virus antigens to the immune system, to improve strong immune memory and offer years-lasting protection against the serious outcome of coronavirus infection.

Lineage Cell Therapeutics, a biotech enterprise that develops new cell therapies, has applied to the California Institute of Regenerative Medicine (CIRM) for funding in May 2020 to support the development of vaccines against SARS-CoV-2 with the company's allogeneic DC therapy platform, VAC.

Currently, the development of the COVID-19 vaccine at home and abroad grows vigorously. mRNA vaccines, DNA vaccines, inactivated viral vaccines, and recombinant adenovirus vaccines have been put on the market successively or are under clinical development. It is expected that the DC vaccine will become a member of the anti-pandemic arsenal as soon as possible.

Chinese DC Vaccine R&D Layout

NMPA has released such policies as Requirements for Registration Classification and Application Information of Biological Products (Trial), Guidelines for Acceptance and Examination of Registration of Therapeutic Biological Products (Trial), and Technical Guidelines for Research and Evaluation of Cell Therapy Products (Trial) to respond to the R&D trend of cell therapy including DC tumor vaccine, which indicates China's forward-looking requirements for encouraging and standardizing the overall cell therapy technology, including DC tumor vaccine.

With the implementation of policies, Chinese cancer vaccine projects have been followed up rapidly. Several enterprises have entered such a market. Among DC tumor vaccines based on tumor-associated antigens which are developed by enterprises led by HRYZ Bio Tech Co. and Shanghai Cell Therapy Group Co, Ltd., the first generation of DC vaccine takes Haixin Bio-tech as the fastest one, whose DC vaccines for colorectal cancer have entered clinical Phase III.

The second-generation DC tumor vaccine enterprises focusing on new antigens take Zskybio as a representative. Currently, Zskybio is advancing its clinical trials in China and the United States on a full scale, including the exploratory clinical research on new antigen DC vaccines for advanced malignant brain tumors, intestinal cancer, liver cancer, and pancreatic cancer. The company is expected to be the first new antigen DC tumor vaccine company in China to apply for IND.

The tumor vaccine is a hot research area in recent years, and its outstanding advantages provide new ideas for cancer treatment. Currently, most tumor vaccines are in the early clinical trial stage. Compared with other immunotherapy products, the prominent advantages of tumor vaccines are persistent anti-tumor immune response and high security, and there is no critical toxic reaction like cytokine release syndrome.

It is believed that with the R&D acceleration of the tumor vaccine and the advance in technical approaches, it is accessible to prevent and treat cancers with vaccination.

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Worth Reading:

The Oral Vaccine Market and Technology

Read More

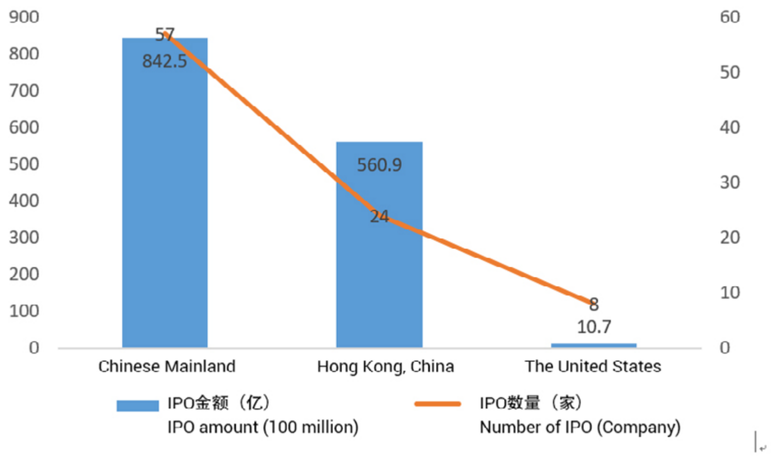
IPOs Review of Chinese Biomedical Companies in 2021

By Caicai

Keywords: Biomedicine, IPO, Captial

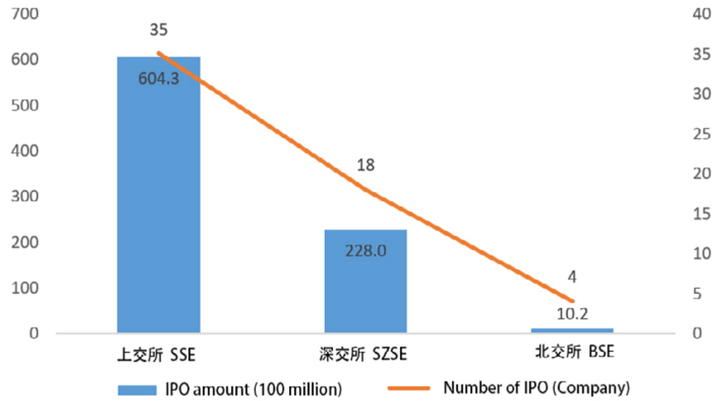
In 2021, there are 89 Chinese biomedical companies (according to the classification of "Pharmaceutical and Biological" based on the industry division method of Shenyin & Wanguo Securities) completed IPOs in the Chinese mainland, Hong Kong Region of China, and the United States in total.

Among them, 57 companies were listed on the Chinese mainland (23 on A-shares and 34 on STAR), raising RMB 84.25 billion (RMB 26.6 billion on A-shares and RMB 57.7 billion on STAR); 24 companies were listed on Hong Kong, raising HKD 56.09 billion; 8 companies were listed on the United States, raising US$ 1.07 billion.



(The data are from public sources.)

Of the 57 companies that were listed on the Chinese mainland, 35 were on the Shanghai Stock Exchange, of which 34 were on the STAR and only 1 was on the main board market; while 18 were on the Shenzhen Stock Exchange and 4 were on the Beijing Stock Exchange.



(The data are from public sources.)

SSE (STAR)

In 2021, a total of 34 Chinese biomedical companies were listed through the STAR, raising a total of approximately RMB 57.7 billion in IPO capital.

June was the month with the largest number of IPOs in a single month, with a total of 8 biomedical companies such as BCHT and Chemexpress listing on the STAR; December marked the highest single-month fundraising for the listing, totaling RMB 24.3 billion.

As the world's first Chinese biomedical company with triple listing of "US+H+A shares", BeiGene became the largest biomedical company to raise funds on the STAR in 2021, raising RMB 22.16 billion.

Order No.	Name	Code	IPO amount (RMB 100 million)	Listing time
1	BeiGene	688235.SH	221.6	December 15, 2021
2	ChengDa Biotechnology	688739.SH	45.82	October 28, 2021
3	HuiYu Pharmaceutical	688553.SH	24.72	October 26, 2021
4	Vazyme	688105.SH	22.01	November 15, 2021
5	Liferiver	688317.SH	21.04	January 18, 2021
6	Dizal	688192.SH	21.03	December 10, 2021
7	AllTest	6886O6.SH	18.05	March 25, 2021
8	BCHT	688276.SH	15.01	June 25, 2021
9	Wegortho	68816LSH	15	June 30, 2021
10	APT Medical	688617.SH	12.41	January 7, 2021
11	GDK Biotechnology	688670.SH	12.14	August 2, 2021
12	Chemexpress	68813LSH	12.09	June 8, 2021
13	Assure Tech	688075.SH	12	November 18, 2021
14	Xiangyu Medical	688626.SH	11.53	March 31, 2021
15	Yi Zhong Pharma	68809LSH	10.08	September 9, 2021
16	BiotesT	688767.SH	9.21	September 8, 2021
17	Neuftech	688076.SH	8.3	May 20, 2021
18	Kawin Technology	688687.SH	8.06	February 8, 2021

19	NovelBeam Technology	688677.SH	7.79	February 26, 2021
20	Aohua Endoscopy	688212.SH	7.5	November 15, 2021
21	Warrant Chiral Pharmaceutical	688799.SH	7.24	July 13, 2021
22	YHLO	688575.SH	6.07	May 17, 2021
23	Hob	688656.SH	5.56	January 13, 2021
24	Allgens	688613.SH	5.48	May 21, 2021
25	Sun-Novo	68862LSH	5.38	June 21, 2021
26	Novogene	688315.SH	5.13	April 13, 2021
27	Careray Digital Medical	6886O7.SH	5.11	February 1, 2021
28	Olymavx	688319.SH	4.00	June 8, 2021
29	Shengnuo Biotechnology	688117.SH	3.58	June 3, 2021
30	Nanomicrotech	68869O.SH	3.55	June 23, 2021
31	CHIVD	688468.SH	2.93	April 9, 2021
32	Righton Gene	688217.SH	2.56	May 17, 2021
33	Kontour Medica	688314.SH	2.52	May 18, 2021
34	AVE	688067.SH	2.5	June 16, 2021

(The data are from public sources.)

SEHK

In 2021, there were 24 Chinese biomedical companies listed on Hong Kong, raising HKD 56.09 billion in the capital.

February was the month with the largest amount of funds raised in a single month, with a total of HKD 13.32 billion. A-share listed Asymchem is the largest biopharmaceutical company to raise funds on the SEHK in 2021, raising HKD 7.15 billion.

Order No.	Name	Code	IPO amount (HKD 100 million)	Listing time
1	Asymchem	6821.HK	71.45	December 10, 2021
2	Joinn	6127.HK	65.48	February 26, 2021
3	Shanghai Hutchison Pharmaceuticals	0013.HK	47.96	June 30, 2021
4	Keymed-B	2162.HK	35.71	July 8, 2021
5	CARsgen Therapeutics-B	2171.HK	31.08	June 18, 2021
6	Brii Biosciences-B	2137.HK	27.89	July 13, 2021
7	Zylox-tonbridge-B	2190.HK	25.62	July 5, 2021
8	MicroPort CardioFlow-B	2160.HK	23.56	February 4, 2021
9	New Horizon Health-B	6606.HK	23.48	February 18, 2021
10	SciClone Pharmaceuticals	6600.HK	21.81	March 3, 2021
11	Zhaoke Ophthalmology-B	6622.HK	20.76	April 29, 2021
12	Basecare-B	2170.HK	20.12	February 8, 2021
13	Clover Biopharmaceuticals-B	2197.HK	20.07	November 5, 2021
14	Microtech Medical-B	2235.HK	18.15	October 19, 2021
15	Abbisko-B	2256.HK	17.55	October 13, 2021
16	Broncus Medical-B	2216.HK	16.71	September 24, 2021
17	Acotec-B	6669.HK	16.33	August 24, 2021
18	Airdoc-B	2251.HK	15.66	November 5, 2021
19	MedBot®-B	2252.HK	14.57	November 2, 2021
20	HeartCare-B	6609.HK	11.29	August 20, 2021
21	CANbridge-B	1228.HK	6.85	December 10, 2021
22	Transcenta-B	6628.HK	6.45	September 29, 2021
23	Modern Chinese Medicine Group	1643.HK	1.77	January 15, 2021
24	JBM (Healthcare)	2161.HK	0.54	February 5, 2021

(The data are from public sources.)

NASDAQ Stock Exchange

In 2021, 8 Chinese biomedical companies were listed on the NASDAQ Stock Exchange in the US, raising US$ 1.07 billion in capital.

Lianbio was the largest biomedical company to raise the most money in a U.S. IPO in 2021.

No.	Name	Code	IPO Amount (US$ 100 million)	Listing Time
1	LianBio	LIAN.O	3.25	November 1, 2021
2	Gracell Bio	GRCL.O	2.09	January 8, 2021
3	Connect Biopharma	CNTB.O	1.91	March 19, 2021
4	Adagene	ADAG.O	1.40	February 9, 2021
5	Terns Pharma	TERN.O	1.28	February 5, 2021
6	QLI	QLI.O	0.25	January 12, 2021
7	Universe Pharmaceuticals INC	UPC.O	0.25	March 23, 2021
8	Regencell Bioscience	RGC.O	0.22	July 16, 2021

(The data are from public sources.)

It can be seen that, the current STAR is the first choice for domestic biomedical companies to list, and their enthusiasm for listing on the US has waned.

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1、 *2021 China Biomedical Investment and Financing Blue Book*

About the Author:

Caicai

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.

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Standards for Integrity Testing

By Muhammad Asim Niazi

Keywords: Packaging, Integrity Testing, USP, ASTM, FDA

Packaging integrity testing is a critical process for evaluating the reliability of pharmaceutical packaging. There are various methods of ensuring the packaging integrity, which help in protecting the pharma product and, at the same time, increase the efficiency of a pharma packaging. Among many factors, standards and regulatory body regulations are essential for ensuring the integrity of a pharma product packaging.

Every pharma manufacturer is legally and morally bound to adhere to regulatory regulations. These bodies' advantages are many, but mainly, without accrediting to these bodies, pharmaceuticals manufacturers are not allowed to enter any pharma market.

Advantages of Regulatory and Standardization Compliance

Compliance with standards and regulations is often termed a daunting task, which requires continuous process improvement, resourcefulness, and monitoring practices to troubleshoot any non-compliance issues. It also requires investment in the process, resources, and technical expertise to maintain regulatory compliance.

However, compliance with regulatory bodies is a worthwhile investment that pays off in both the short and long terms. Some advantages that compliance with regulatory bodies offers include, but are not limited to

Increased Customer Trust

Regulatory agencies and standardizing bodies have a strong research background, and their regulations are backed by thorough study, efforts, and experts. This makes their regulations proven in practical operations with guaranteed results. A manufacturer that adopts their regulations have access to the latest practices, and their workforce is more prepared for disaster management and mitigating risks common in day-to-day production. If their process or product

fails, they have better arrangements and practices to tackle these issues.

The procedures mentioned above result in increased customer trust in the pharma manufacturer, which increases the customer market. Customers remain confident that they are getting the right value against their money spent, and more importantly, they remain hopeful that it will cure their diseases. Customer trust becomes more critical in the case of life-saving and biotech products, where the cost of the drug is significantly higher than ordinary pharmaceutical products.

Exposure to Latest technologies

Research and Innovation are common in the Regulatory and standardization bodies, the reason why they constantly update their regulations. The purpose of research is to deal with the latest challenges in the health sector and produce solutions that can be quickly and equally implemented across all the accredited industries.

Accrediting with these bodies gives access to the latest technologies that the regulatory bodies have invented by investing heavily in humans, processes, and products. Another advantage is the manufacturers do not have to spend as much as these bodies. Instead, they have only to follow their guidelines and gain access to the latest Innovation and technologies.

Easy access to regulated markets

Although there is a worldwide trend of making processes and products in a pharmaceutical industry compliant with regulatory bodies' guidelines, some markets, especially in third world countries, are still behind in achieving full regulatory status. However, first and second-world countries are highly regulated, and it is impossible to enter these markets without achieving total regulatory approvals.

The first and second world markets are profitable compared to third world countries. These markets give more value to a single dollar spent than other markets. Another advantage is that manufacturers that gain access to these markets are considered more credible. Their processes and products are more trusted than others. This also increases their business opportunities and profit margins compared to their competitors.

Regulations and Standardization for Packaging integrity testing

When acquiring compliance for pharma manufacturing, it is necessary for every process and product. Every pharma product process must be fully compliant, and if not, the manufacturer is not allowed to manufacture the product. The manufacturer can also face legal actions such as fines, product recalls, and even shut down of operations.

It is common in the pharmaceutical industry that one product or process is compliant while another product or process is not compliant. In that case, the product or process not compliant is not allowed for production until it is fully compliant with the regulations.

For the packaging integrity testing in the Pharmaceutical industry, the following are common regulations and standards.

USP 1207

The United States Pharmacopeia develops standards for products consumed by humans, including medicines. Pharma manufacturers and regulatory agencies use these standards to verify the processes and practices.

The USP 1207 guides are assuring the integrity of sterile packaging. According to USP 1207, integrity is defined as protecting the container's constituents from leaking out and at the same time protecting it from outside harmful contaminants.

Following leaks are risky, and container should be able to deal specifically to these types

- **Microorganisms**
  It results in failure of product sterility

- **Leaking of headspace gas of a container**
  It includes loss of inert gasses from container or vacuum leak from a container. These gasses are often utilized to protect the product from getting reaction. It results in physicochemical failure of product.

- **Leaking of product from inside or allowing external liquid or solid to go inside**
  When this leak occur, the product is said to be physicochemical failed

Further guidance is provided in the following sub-sections of USP 1207.

- **USP 1207.1:** Package Integrity Testing in the Product Life Cycle—Test Method Selection and Validation

- **USP 1207.2:** Package Integrity Leak Test Technologies

- **USP 1207.3:** Package Seal Quality Test Technologies

The standards outline in this guide apply to the following Small and large Volume Parenteral packages

- Vials or bottles which are sealed with elastomeric closures or screw threaded caps
- Form-Fill-Seal plastic or glass ampoules
- Syringes or cartridges
- Flexible bags or pouches
- Packages for drug/device combination

ASTM F2338

ASTM International, formally known as the American Society for Testing and Materials, is an international standardization organization that develops standards for various materials and processes. Its membership is voluntary and is initiated by the organization itself, not by ASTM.

Vacuum Decay Test Method

The ASTM F2338 is a specialized test called Vacuum Decay Test. This test is based on the fact that if there is a leak in a packaged product, the vacuum decays or decreases, and pressure rises.

The vacuum is created in an enclosed container containing the package, by suitable apparatus. The vacuum is monitored for any decrease in its value. A small leak in pharma packaged product will change the vacuum value, monitored by these recording devices.

The apparatus contains transducers for measuring and recording the pressure value, which directly indicates the status of packaging integrity. It also contains mechanism for creating vacuum, possibly through a motorized mechanism. The motor creates vacuum, until desired value of vacuum is achieved. All the process executes automatically through the use of main controller, without human involvement.

Following types of packaging can be subject to vacuum decay test method

- Plastic bottles with screw capped. This test can be applied container containg both Solids or Liquids
- Glass or Plastic vials, containing Solids or Liquids
- Glass or Plastic Ampoules
- Glass Pre-Filled Syringes containing liquids or solids
- Ophthalmic dropper tip bottles containing liquids
- Blow Fill Seal bottle or strip containing liquid
- Flexible and non-porous packaging such as pouches
- Sealed cups or trays containing solids

Food and Drugs Administration – FDA

The Food and Drugs Administration in the United States is the agency for ensuring the quality and safety of pharmaceutical products and medicines. Every manufacturer that intends to manufacture or sell pharma products in the United States must comply with its regulations. If any pharma product is found without appropriate regulation status, the product is confiscated, and the manufacturer is fined for not acquitting the regulatory status.

The FDA regularly inspects and monitors pharma manufacturing facilities to check whether they are complying with the regulations.

In the United States, every federal agency is represented by the Code of Federal Register – CFR, followed by its specific number. The FDA has a CFR number of 21. Every time a CFR has a number 21 attached, it represents Food and Drug Administration regulations. The FDA has regulations and guidelines for each process in a pharma environment, including the packaging processes.

Regulations for packaging integrity are mentioned in part 211 of 21CFR and are called Current Good Manufacturing Practices. Its section 94 contains guidelines for packaging integrity for finished pharma products. There are three variants of these regulations concerning packaging integrity testing, indicated by a,b and c. These are indicated as follows

21CFR211.94(a)

According to this regulation " Drug product containers and closures shall not be reactive, additive, or absorptive so as to

alter the safety, identity, strength, quality, or purity of the drug beyond the official or established requirements."

21CFR211.94(b)

According to this regulation "Container closure systems shall provide adequate protection against foreseeable external factors in storage and use that can cause deterioration or contamination of the drug product".

21CFR211.94(c)

According to this regulation "Drug product containers and closures shall be clean and, where indicated by the nature of the drug, sterilized and processed to remove pyrogenic properties to assure that they are suitable for their intended use. Such dehydrogenation processes shall be validated".

21CFR211.94(d)

According to this regulation "Standards or specifications, methods of testing, and, where indicated, methods of cleaning, sterilizing, and processing to remove pyrogenic properties shall be written and followed for drug product containers and closures."

About the Author:

Muhammad Asim Niazi

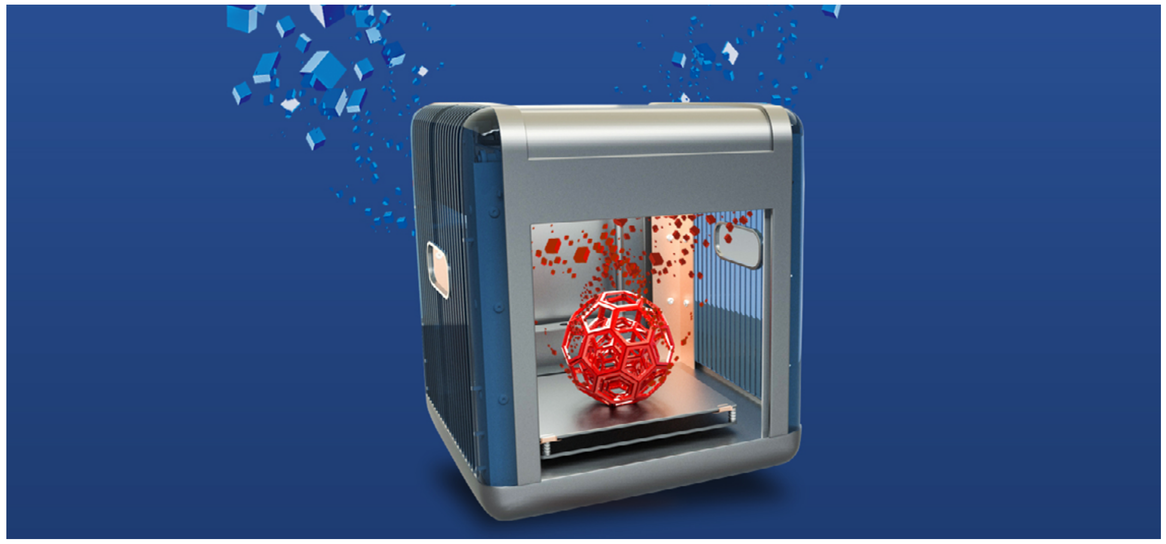
Muhammad Asim Niazi has a vast experience of about 11 years in a Pharmaceutical company. During his tenure he worked in their different departments and had been part of many initiatives within the company. He now uses his experience and skill to write interested content for audiences at PharmaSources.com.

Industry Insight JUNE 2022

3D Printing, A Perfect Storm for Pharma Industry and Regulatory Agency

By Eric Sun, Ph.D.

Keywords: 3D printing, Spritam, EHD



3D printing or additive manufacturing is a process of creating three-dimensional solid objects from a digital design. The process involves printing sequentially thin layers of the building materials until the object is created. The earliest 3D printing technologies came about in the 1980s. Over the past decades, 3D printing has proved itself to have the potential of revolutionizing the way we make almost everything. Nowadays, 3D printing has been employed in aerospace, manufacturing, construction, medicine, and biomedical engineering. Spritam®, the levetiracetam tablets made by 3D printing technology was first approved by FDA in 2015 and remains the only licensed 3D printed drug product till today, which marked a new chapter of making drugs. 3D printing is largely for oral solid medications accounting for the majority of marketed drug products. More over, 3D printing is able to print small batches for small patient populations. The patient-specific or individualized 3D-printed medicine tailors treatments to the individual characteristics of each patient. Its simple and decentralized production process enables locally controlled supply chain without security issues such as contaminations and frauds, but on the other side, brings in new compliance and regulatory challenges. The 3D-printing drug manufacture has created a perfect storm for the pharmaceutical industry and its regulatory agency.

3D-printing Technologies In Pharmaceutical Applications

Although not yet fully commercialized as the traditional formulation technologies, the following methods are widely used in making 3D-printed drugs [1]: Extrusion Molding Printing (EMP), Drop On Powder Printing (DOP), Selective Laser Sintering (SLS), Stereolithography (SLA), and Electrohydrodynamic Printing (EHD). In all techniques, the printing is executed by following the model parameters preset by a computer design. Among these established methods, DOP and EMP are well studied and have become common practices [2]. For instance, DOP is successfully employed in the production of Spritam® tablets. However, Each method has its own pros and cons, and requires further fine-tunes or big-leaps in resolving technical

incompetency.

The EMP technology has two branches based on molding materials, the fused deposition modeling (FDM) and semisolid extrusion molding (SSE). In FDM method, a semifluid state of drug-loaded polymers is formed by heating, which is then extruded from the printing nozzle. The desired product is formed after solidification. The cheap and simple operation process has made FDM the most frequently used technique. However, the high heating temperature, usually over 150 °C, is not suitable for thermal-liable APIs without adding low-melting point excipients or water in the drug-loaded filaments. In contrast, the SSE technology does not involve heating process, and can be a good surrogate technique for temperature-sensitive APIs. It extrudes semisolid paste under the pressure of screw gear rotation via a syringe-based print head, and deposits the paste in layers to form the object. One of the disadvantages of SSE is using organic solvents in preparing the paste, which can lead to the residual solvents in the printed products.

DOP is similar to wet granulation used in tablet preparation with regard to solidification mechanisms. DOP sprays droplets containing binders from the print head onto the powder bed. The API can be dispersed either in the liquid or solid phases, e.g. discharging excipient binder onto API-loaded powder. After printing one layer, the platform is lowered vertically, and the new powder layer is spread over the previous layer. The procedures are repeated until the dosage form is complete. This print-glue approach offers reduced formulation complexity, as similar binders are compatible with a broad range of APIs. The method is relatively low cost, easy to scale up and produces tablets with high porosity. The limitation of DOP is its low resolution and high fragility. Post-processing is needed to eliminate residual solvents and recovery of the unprocessed powder.

In SLS, CO2 laser beam instead of binder droplets in DOP is applied to sinter the selected regions of powders in each layer with precision. SLS offers high-resolution, solvent-free, single-step 3D printing. Its process chamber is generally kept between 40 and 50 °C, filled with inert nitrogen to protect from oxidation. While its precision enables manufacturers to greatly control the microstructures of the drug products produced, SLS process is relatively slow and prone to break down APIs and excipients with high-energy laser, thus, the SLS process needs to be verified for drug degradation and mechanical properties.

SLA uses ultraviolet lasers to polymerize photosensitive resins in layers, repeating until the desired dosage form is created. It has the best resolution of 3D printing, facilitating precise structures. There are a couple of drawbacks of SLA technique: it requires post-processing to eliminate resin toxicity, the equipment is costly, few approved resins are available for the pharmaceutical field, and efficiency is low.

EHD is an emerging 3D-printing technology that can pattern fibrous material by digitally controlled deposition to create customized geometries and well-ordered complex structures. EHD 3D printing enables micro to nano-scale fiber engineering and alignment. EHD offers small-scale manufacturing to tailor medicines to meet individual patient needs by printing a vast array of APIs of predefined amounts in a specific pattern on a porous film. EHD applications are limited by low solubility, residual solvents in the dosage form, and high requirements for solution properties.

The technical, compliance, and regulatory challenges

In spite of the unique advantages of 3D-printing drug manufacture, its process and control must comply with stringent pharmaceutical standards to assure the printed drug products meet the characteristic requirements for safety, identity, strength, quality, and purity. As the structure design of a dosage form evolves during formulation development, the modeling software must be continuously updated, in addition, mechanical adjustments to the printing equipment and control systems are required to fix and prevent instrumental malfunctions such as nozzle clogging or binder leakage, which involves computer software verification, instrument qualification, and change controls.

In 3D-printing formulation, the physicochemical properties of the excipients are extremely critical to the quality of printed dosage forms. For FDM procedures, the carrier excipients are modified to prepare low-temperature filaments to prevent drug degradation and improve drug loading. For SLA and SLS, the excipients of photopolymers and laser sinterable materials are selected, but these excipients are not included in the FDA's Generally Recognized As Safe (GRAS) list [3]. Comparing with traditional formulation processes, the availability of excipients that can be used for 3D printing is limited. These 3D-printing suitable excipients might not be certified for pharmaceutical grade, and have compatibility issues or toxic/adverse side effects. Generally speaking, more of non-toxic, stable, biodegradable, and pharmaceutically certified excipients need to be developed to support commercialized 3D printing formulation.

The inherent nature of 3D printing is stacking layer-by-layer of polymers or powders, results in rough surface or insufficient adhesion strength. The printing procedures can also affect content uniformity, hardness, and friability, which should be listed as quality control parameters in the specifications of solid dosage form with specification limits appropriate for the decentralized, small batch 3D-printing production. Removing the residual solvents and unprocessed powders in the post-processing should be handled properly accordingly to EHS policies. Overall, the 3D printer, the printing process, the operation procedures, the API and excipients, and personnel training should be validated as a complete quality system to ensure all practices meet cGMP requirements.

With respect to the regulation, on top of the aforementioned issues to be addressed, there are many other questions surrounding how 3D-printing formulation should be monitored and controlled for quality. Imagining the 3D-printed drug is customized to the patient in a hospital or in a clinic, whether this is classified as a manufacturing process or compounding will result in different regulatory requirements. In such a circumstance, healthcare specialists will have to undergo thorough training in using various 3D-printed drug formulation technologies, learn to recognize quality defects, and assess possible adverse effects in the just-made medicines. Although FDA has authorized the first 3D-printed tablets, neither guidelines nor regulations are available governing 3D-printed drug products. FDA has issued its guidance on Technical Considerations for Additive Manufactured Medical Devices in 2017 [4] to provide the Agency's initial thinking on technical considerations specific to devices using additive manufacturing, the broad category of manufacturing encompassing 3-dimensional (3D) printing; however, the guidance states “Not all considerations described will be applicable to every device, given the variety of AM technologies, materials, and devices made with additive manufacturing”, thus, it should not be applied to 3D-printed medicines, as its safety, effectiveness or efficacy have to be assessed separately. FDA's thinking towards 3D-printed drugs is currently being shaped and is yet to be publicized in a similar manner [2].

The development trend towards a mature technology

The capability of 3D printing in fabricating personalized medicines based on clinical needs has gained interests across pharmaceutical industry as its opportunities, benefits and successes become more and more apparent. It is estimated by a market report that the global healthcare additive manufacturing market size was $1.34 billion in 2020 and is growing at a rapid compound annual growth rate of 21.8% [5]. After obtained FDA's approval on Spritam®, Aprecia Pharmaceuticals forged a long-term collaboration with R&D firm Battelle to further advance its 3D printing equipment. FabRx has also been active on the printed drug development front - having produced personalized medicine for children with rare metabolic disorder maple syrup urine disease (MSUD), and launched its M3DIMAKER 3D printer in 2020. Merck has become a major player in the pharmaceutical 3D printing arena. Merck is taking plans to establish 3D printing for clinical trial supply including scale up to commercial production. In early 2021, a Chinese 3D printing pharmaceutical company Triastek has received IND clearance from FDA for its first 3D-printed rheumatoid arthritis tablets.

The flexibility of dosage and format changes by 3D printing has made it a perfect tactic for readily finish early-phase formulation and reformulation in providing small batches of clinical trial materials through computer modeling and printing instead of implementing new mechanical tools. In 3D printing, less excipients and APIs are required, and it is very likely that the formulation development can be warped up via a single formulation with no needs to change the drug formula and alter manufacturing process for each clinical trial. Comparing with the conventional tablet manufacturing process typically involving blending, granulation, lubrication, tablet compression, and coating, the 3D-printing tablets can be produced in two steps as simple as blending & printing. The flexibility and simplicity of 3D printing has the potential to cut the amount of APIs used in Phases 1 to 3 combined by 50%, and shorten the formulation development timelines by 60% [6]. Given the global COVID-19 pandemic attack on and post-pandemic disruption of pharmaceutical supply chain, the cost and timeline savings plus the decentralized production offered by 3D-printing has a much superior outlooks over the conventional tablet-making process.

3D printing has revealed its potential in transforming the way pharmaceuticals are manufactured and turn the personalized

medicine into reality. To shift from the traditional batch production to continuous additive manufacture, installing a reliable and robust process analytical technologies (PATs) and implementing quality by design (QbD) principles are essential to monitor and ensure the critical quality attributes (CQAs) of each single personalized drug product continuously and at all times [7]. The applications of PAT and QbD in 3D-printing formulation and manufacture will make the technology more mature, robust, and comply with the stringent pharmaceutical standard and regulatory requirements. The adoption of 3D printing in pharmaceutical industry will become ever more widespread. With the collaborations between industry, academia, and regulatory agency, it is highly anticipated that combining this innovative 3D printing technology with PAT and QbD will deliver high-quality, regulatory-compliant, customized therapeutics to the specific patient populations.

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Eric Sun, Ph.D., a seasoned pharmaceutical professional, has diverse experiences in both U.S. and China pharmaceutical industry. He has led research and development, clinical supplies, compliance, and regulatory filing activities at big pharmas, startups, and CROs/CDMOs. His recent interest has been channeled to improve the overall R&D productivity and success rate ensuring the delivery of the beneficial therapeutics to the clinic in an optimum timescale with minimum safety concerns.

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