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Short Communication

**DIGITAL TRANSFORMATION ON REGULATORY SUBMISSION
FOR DRUG REGISTRATION IN CHINA**

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HISTORY BACKGROUND OF REFORMS

Approximately 25 years ago, could you imagine reserving a room for holidays via clicking on several tabs of the hotel websites? could you imagine purchasing anything what you need at home? could you imagine transferring money or purchasing financial products via non-paper electronic online platforms? could you imagine being present in your virtual classes with online training courses? could the doctors imagine seeing the patients in the online clinics who live in a town within a distance of 300 miles from the hospitals? However, everything turns into realities after decades. Digital technologies are changing our lives and adoption of new internet applications was estimated to account for up to 22 percent of labor-productivity growth by 2025 [1]. The costs of global healthcare expenditures were over \$7 trillion in 2015 and were forecast to exceed \$9 trillion by 2020 as reported by the United States (US) International Trade Administration's Health IT Top Markets Report [2].

Since the beginning of the 21st century, we witnessed earth-shaking changes in the healthcare sector: in the hospitals, electronic medical health records (e-MHRs) have become a competent partner of the clinical physicians to manage the dossiers of the patients and their medical histories; in the pharmacies, the pharmacists distribute drugs with doctors' prescriptions via e-commerce channels; in the operation rooms, the surgeons and robotics guide the surgeries in collaboration with those peers who are based in other countries. Till the year of 2016, the production of healthcare-related industry in China was estimated to be 7.26 trillion RMBs, accounting for 9.76% of the gross domestic production (GDP) [3] and the revenues of the biopharmaceutical industry in 2017 was approximately 0.35 trillion RMBs with a compound annual growth rate (CAGR) of 9.07% [4]. By the end of the first half of 2018, a total of 3453 regulatory cases were submitted to the evaluation center of the local healthy authority in China and an increase of over 60% was observed as compared with the

rate that was calculated by the end of the first half of 2017 [5]. Based on the statistical data, the weight of the industry and its productions are self-explanatory, and it has already played an irreplaceable role in the local economy. In the pharmaceutical industry, as other areas of the healthcare sector, information technology (IT) is changing the steps of industrialization and pushing more innovative drugs in the markets as soon as it can. In past 40 years, the regulatory policies of drug registration experienced reforms in China as the other countries. In the 21st century, along with the market needs of digital transformation, application of IT facilities in the research and development of drugs have already been endorsed by more and more peers in the industry. As a result, non-paper electronic regulatory submission and approval systems for drug registration are on demand along with the progresses of the industry.

DEVELOPMENT OF COMMON TECHNICAL DOCUMENTS (CTDS) AND THE CURRENT STATUSES IN CHINA

In the pharmaceutical industry, the current global practice for drug registration is to evaluate the efficacy and safety of drugs, and analyze the ratios of the patients' risks and benefits before a drug can be approved by the healthy authority and be purchased in the market. According to the statistical data of US Food and Drug Agency (FDA) in 2016, the standard application review time frame for new molecular entities (NMEs), new drug applications (NDAs), and original biologics logistics applications (BLAs) was 10 months from 60-day filling time and the expenses were approximately \$2.3 millions [6]. In the European countries, the rapid and European Union (EU)-wide authorization for drugs and biologics lasted 277 days as per the requirements of the European Medicines Agency (EMA) [7]. As the data presented by the China Food and Drug Agency (CFDA) in 2016, we had 28.3-month and 30.5-month approval lags as compared to the time frames of FDA and EMA, respectively [8]. Given the time frame gaps between those developed countries and us, the local healthy authority decided to take actions on continuously shortening drug approval timeline, and simplifying regulatory submission procedures as the promises to the public. In order to be on the same page with other countries and develop public healthcare with more rapid steps, China joined the organization of the International Conference on Harmonization (ICH) in 2017 [9]. The ICH presence is a milestone for China to be an important "voice" in the big family and it means that China could share more high-quality global healthcare resources as other ICH member countries.

Back to the year of 2000, the concepts and guidelines of CTDs were launched and the standards of regulatory submission and drug registration were aligned by the member countries of the ICH [10]. The concept of CTDs is defined as an interface and global specification for exchanging regulatory information between the regulatory sponsors (e.g. the pharmaceutical companies) or agencies (e.g. clinical research organizations) and the health authority [11]. In 2003, the first version of guidelines on electronic CTDs (eCTD) was in place and the current version of guidelines was effective in a total of more than 40 countries. As the first player, eCTD is the only format for regulatory submission of drug registration in the US as proposed by the local healthy authority in 2008 and 80% of regulatory submissions followed the practices till the end of 2014 [10]. In the Europe, CTD submission was initiated from 2004 and all the regulatory procedures were requested to be compliant with the eCTD formats since the first quarter of 2018. On the eastern sphere of the earth, we have a significant lag for the CTD concepts in China as compared with US and European countries: in 2010, the CTD was used as a recommended submission format for some parts of submission dossiers that serve for the regulatory purposes of chemical agents [12]. The fact is that most of submissions can only be completed via paper works (even in local languages) following local regulations. In 2017, China was approved to join the ICH family given its burgeoning global scientific impacts. After initial attempts, the promotion of eCTD was formally decided to put on the working agenda of the local healthy authority [10]. The changes in relevant regulatory guidelines were planned to draft and were open to comments from the public and the electronic service vendors (e.g. Lorenz) were recruited for system preparation of the launches. The new eCTD systems will be firstly applied for the regulatory applications on the chemical generic drugs as announced by the local authority [10].

According to the information released by the authority, as the CTD format launched by US (Figure 1),[13] the Chinese version of CTD also consists of 5 modules after reforms: a) Administration Information; b) Summaries; c) Quality; d) Non-clinical study reports; e) Clinical study reports. The standards were developed based on the Extensible Markup Language (XML) [14]. As compared with the FDA version, the Chinese version includes more detailed backbones and guidance languages that are structured to explain what should be present in each module. In the process of regulatory dossier preparation and submission, after separate document components are completed by each contributor, the document components would be sent to the service vendors for edits and consolidations, the whole dossier of the completed documents with appendices would be transferred to the local healthy

authority following validations and publishes. In the new systems, regulatory submission statuses and non-confidential information are expected to share with the peers in the industry. With non-paper systems, it is possible for the submission sponsors or agencies to communicate with the healthy authority for approval progresses at any time that allow the sponsors to take actions on the comments from the official reviewers at the earliest convenience. As compared with traditional submission systems and work processes, the reforms of digital transformation on the regulatory submission will significantly lower the budget costs of dossier preparation since thousands of regulatory documents will be stored as virtual files when they are ready for handing over to the authority rather than printing out and submitting hundreds of kilograms of hand-copy documents to the local healthy authority. Along with the system designs, CFDA drafted a document titled with “Document structure of electronic common technical documents” and a document titled with “Document structure of electronic common technical documents for chemical drugs” in 2017. At the same year, the local healthy authority held official seminars and training courses to the public for promoting the regulations and system launches.

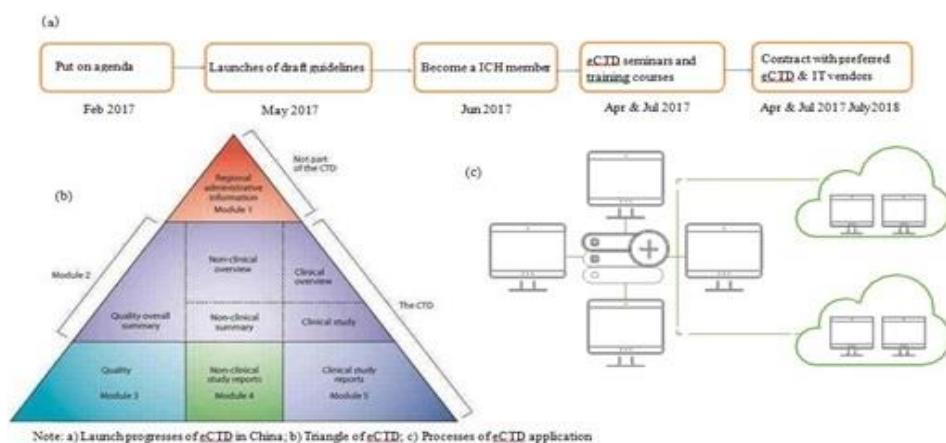


Figure 1: eCTD regulatory submission and dossier components.

The launch of our new systems and guidelines will close the epoch of regulatory paper submission, instead, the launches of eCTD in China will bridge the scientific development gaps with other ICH member countries. The non-paper system will significantly shorten timeline of communications between the submission parties and the authority given that the review and approval processes may be traced online. The reforms allow the research and development activities of drugs (especially for Chinese Traditional Medicines) in China to be

on the same page as other ICH member countries and enhance transparency and reliability of those medical researches that are conducted in China. From the perspectives of scientific talents and career markets, the reforms may offer more job opportunities and possibilities of new positions (e.g. system innovation/training manager, system monitor or subject master expert, or communication specialist of eCTD submission, etc.) that will assist to solve intractable employment problems in the country. The reforms create venture possibilities for those entrepreneurs to have own companies for developing new technologies in the areas of eCTD. On the other side of benefits, the launches of the systems may own some risks and dilemma:

- 1) Since most of the submission documents are confidential, the new systems should guarantee the security of the internets /computer terminals and privacy of the sponsors/patient information; 2) The regulatory professionals and experienced system administrators or trainers are needed at the launch time of the e-system, thus the experienced professionals who equip with eCTD knowledge would be popular in the career markets;3) System compatibility of document transitions needs to be tested with high standards to ensure information sharing and exchange security between the sponsors and the authorities who are located in the diverse places.

CONCLUSION

To summarize, in the past 10 years, we experienced the growths and developments of eCTD in China. The reform trends of digital transformation for regulatory submissions and approvals are in favor of the industry and most of the practitioners. We are confident that the reforms would bring more benefits to the industry, practitioners, and patients as compared with underlying risks and negative impacts. It would bring unimaginable valuable business opportunities, improve work efficiency, save regulatory budgets, and launch more innovative drugs as soon as we can. We are following the steps of other ICH member countries and the countries with rich experiences in eCTD, the regulatory systems in China are just like “teething toddlers” who are on the fast track of reforms and developments, thus uncertainties cannot be avoided. However, the future is promising and we believe that the grow-ups of eCTD concepts will be realized in practice even though problems and challenges are waiting for us.

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