Medical Writing: The Backbone of Clinical Development

Medical Writing for Submission to Asia-Pacific Regulatory Authorities

The need for quality medical writing services is growing in Asia. While some Asian countries follow the ICH guidelines, sometimes with additional local requirements, others have their own specific regulations. Medical writers are being called upon to help guide teams in navigating the different regulations during document preparation. This article reviews the current landscape for key regulatory documents for submission to major health authorities in Asia, and describes how seasoned writers with local knowledge can contribute to successful submission.

The pharmaceutical market in Asia-Pacific is expanding. Japan is the largest pharmaceutical market in the region, at $116 billion, and China is rapidly catching up ($99 billion, and 18.7% compound annual growth rate projected for 2015-2017). The growth of other Asia-Pacific countries is also projected at 9-13% over the same period. There is increasing demand for studies to launch new medicinal products in the Asia-Pacific region, especially in China and Japan where regulatory changes are speeding up the drug review and approval process. Consequently, the need for medical writing support for the regulatory documents that make up the marketing approval application is growing in parallel.

While the documentation required by some Asian regulatory authorities is largely harmonised with ICH, there are also some local variations or additional requirements. For economic and practical reasons, most multinational companies do not have a medical writing function in each country within Asia. Instead, they may establish medical writing functions in one or two hub locations in the region. Medical writers in these teams may therefore need to be familiar with the regulations for marketing applications across multiple countries in Asia.

The clinical regulatory documents most frequently prepared by medical writers in Asia are:

- Protocol and informed consent form (ICF)
- Development safety update report (DSUR)
- Clinical study report (CSR)
- Clinical sections of the marketing application dossier
- Periodic safety update report (PSUR)
- Risk management plan (RMP)

There are many considerations and requirements, some different from ICH, which medical writers must keep in mind when preparing these types of documents for key regulatory authorities in the Asia-Pacific region.

China Food and Drug Administration

The Chinese pharmaceutical market is dynamic and increasingly complex. In the past two years, the Center for Drug Evaluation (CDE) affiliated to China Food and Drug Administration (CFDA) has released more than one guideline or draft guideline seeking public opinion almost every month. Recent changes include the prioritisation of approval of certain drug classes in order to accelerate approval times. Priority drugs include new drugs not yet marketed in China or overseas, products undergoing simultaneous marketing application in the US or Europe, products showing clinically significant superiority for certain diseases (HIV, viral hepatitis, tuberculosis, oncology, rare diseases), and products intended for paediatric use.

Medical writers are increasingly involved in writing protocols for studies run in China. The protocol, together with the ICF, generally follows the content outlined in the ICH E6 guideline.

A pre-approval safety update report such as the DSUR is not mandatory unless requested by the sponsor or CFDA. However, this may soon change because the draft Administrative Provisions for Drug Registration (Revision) includes a requirement for an annual report during clinical studies, which will periodically summarise data relating to drug manufacturing and safety and efficacy data for preclinical and clinical studies, and will evaluate the actions taken or to be taken.

A CSR guideline was issued by the CFDA in 2005 defining three types of CSR structure (3): for Phase I tolerability studies, Phase I pharmacokinetic studies and Phase II/III studies. The elements of the CFDA CSR guideline are very similar to ICH E3, but it does have some unique requirements regarding CSR appendices that are not covered by the ICH guideline, including individual by-site summaries, and a statistical analysis report. Some
companies strictly follow the CFDA guideline for CSRs. In practice, the CFDA also accepts the CSR body in the ICH E3 format, if the CSR appendices are supplemented by the additional documents required to comply with the CFDA guideline. Data in Chinese patients are required to obtain marketing approval from the CFDA. These data may be obtained from a stand-alone China study or by including Chinese sites within a multi-country study. A recent CFDA draft guideline clarifies that for a multinational clinical trial, comparisons between Asian versus non-Asian, and Chinese versus non-Chinese data must be included in the CSR (4). A skilled medical writer will be able to help the team determine how best to present these data.

The format of the CFDA marketing application dossier is changing. The following new guideline was issued in May 2016, and is already being followed although it is still in draft stage: Requirement on Registration Dossier under the New Categorization for Chemical Drug Registration (Tentative) (5). This regulation requires inclusion of additional documents not previously specified, such as a data management plan and data management report. The draft guideline also refers to The Guideline of the Structure and Content of Summary Documents for Chemical Drug – Summary of Clinical Studies (6), the content of which is similar to Module 2.5 of ICH M4, Common Technical Document (CTD). For Chinese marketing applications for drugs already marketed outside of China (category 5), the CTD modules including the comparisons of Chinese to non-Chinese data may be submitted instead of the CFDA dossier format, if supplemented by Module 1(administrative and summary section) from the CFDA guideline. If the company does not have a global CTD to use as the starting point, the clinical summary guidance may be followed but the actual structure of the documents may need to be determined depending on the data to be presented (6).

PSURs are required for marketed drugs, and these follow ICH E2C. At present there is no requirement for an RMP in China.
The recent CFDA requirement for sponsors to conduct self-inspection activities places an increasing focus on data quality, and by implication, the quality of the marketing application dossier. Overall, there is a general trend towards aligning quality with international standards, as illustrated by a recent CFDA decision to accept regulatory and technical guidance from ICH, EMA, FDA and WHO, to facilitate dual registration of new drugs. An experienced medical writer can assist not just in the writing of the documents required in the pre- and post-approval phases, but increasingly in providing guidance to the responsible teams to align the strategy with both local and international standards.

At present, the marketing application in China may be one of the last in a multinational company’s global development plan, in part due to the long investigational new drug (IND) and new drug application (NDA) approval times. The prioritisation of applications for specific drug classes, as well as plans to increase the numbers of CFDA reviewers will serve to shorten approval times in the long term. For now, however, medical writers can contribute to global submissions by anticipating presentation formats, resource and timelines for the additional data displays required by CFDA. A medical writer with local knowledge can also help the team ensure their approach is up to date, as the regulations continue to evolve.

Although the eCTD is expected to be implemented at some point, the clinical dossier is currently required as a paper submission, and timelines must be planned accordingly. In addition, the study report and submission documents may be prepared in English if a global team will be involved in the review, then translated into simplified Chinese for CFDA submission. Writers with excellent verbal and written English skills, in addition to Chinese, will be able to ensure this process runs smoothly.

**Pharmaceuticals and Medical Devices Agency (PMDA) – Japan**

Japan has a Good Clinical Practice (GCP) guideline that follows the ICH GCP requirements, with some Japan-specific additions. These include emphasis of the role of the head of the hospital/institution, in addition to those of the investigators. To conduct a clinical study, an approval letter from the head of the investigational site based on Ethics Committee (EC) approval is required.
Protocols are accepted by PMDA in English although a Japanese language version is needed for the site personnel. An appendix of the study organisation, including by-site listing of clinical sites, with address and name of investigator, and list of study-related vendors, should be submitted together with the protocol.

The ICF generally complies with ICH E6, but general background about clinical trials must be included, as well as more detailed information on the study procedures and inclusion/exclusion criteria. In addition, use of visual components is considered to be important, such as tables, pictures or certain font types.

DSUR submission is mandatory for clinical trials using pre-approval (not marketed) study drug (7). Submission of the global DSUR in English is accepted if accompanied by Japan-specific cover letters including an executive summary in Japanese and separate assessments of Japanese cases in a specified format (Form 1, Form 2).

The CSR is accepted in English in ICH E3 format. Separate assessments of data in Japanese subjects are required (8).

The marketing application dossier follows ICH M4 CTD format. Module 1 is prepared in Japanese and includes the local regulatory requirements. Module 2 is also prepared in Japanese, but Modules 3, 4, and 5, may be submitted in English. The Japanese CTD requires a separate assessment of Japan data in the clinical modules (Modules 2.5 and 2.7), inclusion of a listing of Serious Adverse Events (SAE) and death cases in Module 2.7.4, and safety narratives in Japanese for pivotal studies in Module 2.7.6 (9).

A Post-Marketing Safety Periodic Report is required. It includes the post-marketing safety survey reports, and the PSUR is appended. A PSUR in Periodic Benefit Risk Evaluation Report (PBRER) format is accepted in English for global studies. For local studies, a PMDA-compliant PSUR format in Japanese should be used (10).

The RMP is required for new drugs and for biosimilars/follow-on biologics for applications submitted on or after 1 April 2013, and follows ICH E2E.

In Japan, writing in local language is very important, as many documents must be submitted in Japanese, or require a Japanese cover letter. This typically includes a summary of the document and will specifically highlight the separate assessment of Japanese subjects.
PSUR

<table>
<thead>
<tr>
<th>Country</th>
<th>Notes</th>
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<tbody>
<tr>
<td>China</td>
<td>Post-Marketing Safety Periodic Report is required every 6 months for the first 2 years, then annually until re-examination (drug re-examination system: part of the PMS to examine safety and efficacy data collected during a certain period of time) (10). The report includes post-marketing survey reports: overview and analysis of the survey, ADRs reported, individual case report of ADRs, actions taken for safety reasons including any changes to the drug labelling, the package insert, and an analysis of safety. The PSUR is attached to the Post-Marketing Safety Periodic Report. PBRER format is accepted in English for global studies. For local studies, a PMDA-compliant PSUR format in Japanese should be used. For non-marketed products, a 6-month periodic report of serious ADRs is to be submitted, including all serious ADRs reported in and outside Japan.</td>
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<tr>
<td>Japan</td>
<td>Periodic PMS report is required every 6 months for the first 2 years, then annually until the end of the surveillance period. The report must summarise the results of use-result surveillance and special surveillance studies, local and foreign safety data, and sales data (14).</td>
</tr>
<tr>
<td>Korea</td>
<td>PBRER format plus local appendices (package insert, domestic sales information and analysis of domestic ADRs). Required every 6 months for the first 2 years, then annually for next 3 years.</td>
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<tr>
<td>Taiwan</td>
<td>PBRER format. For drugs under regular registration: every 6 months for the first 3 years, annually for the next 2 years, thereafter every 2 years.</td>
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<td>Malaysia</td>
<td>PSUR guidelines are mainly based on ICH E2C. Major differences are: • Must be submitted in Chinese or with Chinese translation, except for line listings and summary tabulations • Any differences between China and other countries, such as drug indications, formulations and dosages, and any safety information, need to be addressed and explained • Required annually in new drug monitoring period (3-5 years); thereafter every 5 years</td>
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<tr>
<td>Thailand</td>
<td>Not required unless requested by Thai FDA</td>
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Ministry of Food and Drug Safety (MFDS) – Korea

ICH guidelines are generally accepted by MFDS for the protocol, investigator brochure, CSR, CTD, periodic safety report, etc. However, there are some local requirements, listed below:

- In addition to the ICF, Ministry of Health (MOH) ICF (Form #34), is applicable for clinical studies that require storage of human-derived material or its usage apart from the purpose of the clinical trial (11).
- The DSUR is not mandatory but is accepted if submitted.
- The CSR follows ICH E3. In addition, bridging data from Korean patients is usually required to obtain marketing approval, obtained from a stand-alone Korea study, or by including Korean sites within a global study. The bridging data report must be included in the marketing authorisation application. MFDS has published a guideline for the required content and format (12).
- The marketing application dossier is accepted in ICH M4 (CTD) format, but additional Korea-specific documents are required, according to MFDS guidelines (13). The local requirements mostly concern the chemistry, manufacturing and controls sections in Module 3. Submission in eCTD format is mandatory.
- A periodic post-marketing surveillance (PMS) report must be submitted every six months for the first two years, then annually until the end of the surveillance period. The report must summarise the results of use-result surveillance and special surveillance studies, local and foreign safety data, and sales data (14).
- The RMP has been implemented since 2015 and must be submitted as part of the marketing authorisation application for new or orphan drugs. Local regulation and guidelines apply to the RMP format (15).

The Korean regulatory environment is continuously evolving and medical writers need to keep up to date with the frequent changes in regulations. As of October 2016, a new regulation on safety of pharmaceuticals has been announced (16). The impact is under assessment; however, it does include updates on requirements for clinical trials.

Taiwan Food and Drug Administration (TFDA)

The regulatory infrastructure is well developed in Taiwan. Although Taiwan follows most of the global standards, the medical writer needs to understand the specific local requirements relating to clinical documents.

ICH guidelines are followed for most documents, eg protocol, investigator brochure, CSR, and other global standards, eg US FDA guidance, are accepted. There are additional local requirements for certain documents:

- The ICF generally complies with ICH E6, although certain specific terms or template text must be used.
- The DSUR is not mandatory. However, according to GCP, the sponsor should submit all safety updates and periodic reports to the regulatory authorities, and the ICH E2F format is accepted.
- ICH E3 is followed for the CSR, supplemented with a summary of the data in Taiwanese patients. The Taiwan data should generally be compared to non-Taiwan or global population.
- The marketing application dossier follows ICH M4 CTD. If there are sufficient data to demonstrate ethnic insensitivity, a bridging study evaluation (BSE) report may be submitted to request waiver of the bridging study requirement (17). If a waiver is not approved, the bridging study will need to be conducted, and the bridging study report submitted to support the marketing application.
- A PSUR in PBRER format is required every six months for the first two years, then annually for next three years.
• There is a TFDA specific guideline for RMPs. In addition, depending on the risk of the product, use of product-specific templates, eg for tumour necrosis factor (TNF)-alpha products, may be required

Malaysia MOH

The Malaysia regulatory environment is well structured and a guideline is available for submission of clinical trials in Malaysia (18).

In general, Malaysia has adopted the ICH and EMA guidelines.

• The ICF follows ICH E6 but country-specific customisation is required and a standard checklist is provided by the central EC
• The DSUR is not mandatory; however, its submission is encouraged
• The CSR is mandatory and follows ICH E3
• The marketing authorisation application follows the ASEAN Common Technical Dossier/Requirement (ACTD/ACTR) guidelines. The structure is similar to ICH M4, however there are four parts instead of five modules. A Clinical Overview and Clinical Summary are required
• A PSUR in PBRER format is required every six months for the first two years, then annually for next three years
• The RMP will normally be required for an application involving new drug products or new biologics or for any significant change to an existing registered product, as specified in the guidelines

Philippines Food and Drug Administration (PFDA)

The regulatory environment in the Philippines is changing in line with global standards. The PFDA follows global guidelines such as ICH guidelines, and a Bureau Circular has been published on the process of evaluating clinical trials (19).

• There are country-specific requirements for the ICF, and local templates are provided
• A DSUR is required, and should comply with ICH E2F
• Submission of the CSR is not mandatory but it is best practice to submit it when available
• The marketing authorisation application follows the ACTD/ACTR guidelines
• A PSUR is required in PBRER format. For drugs under regular registration, the PBRER is required every six months for the first three years, annually for next two years, thereafter every two years
• A RMP guideline is in development and will be implemented once available

Thailand Food and Drug Administration (Thai FDA)

The regulatory environment is evolving in Thailand. Guidance for clinical trial applications was announced and implemented in August 2015, with further guidance implemented in October 2016 (20). A new guidance implementing electronic submission for pharmaceutical product registrations for New Chemical Entity, New Biologicals and Human Vaccines came into effect in January 2016. Nevertheless, ICH guidelines and other
ICH guidelines are widely adopted in Asia-Pacific, and there is increasing alignment with other global standards. However, each country generally has its own local requirements in addition to global standards, e.g., US FDA guidance, which are recognised by the Thailand FDA. Most of the core documents such as protocol and investigator brochure follow the global standards and structure.

- The ICF must comply with ICH E6, however several country- and site-specific requirements apply
- The CSR is not a mandatory document, although an end-of-study safety report is required within six months of end of study
- There is a local format for the annual safety report; however, a DSUR in ICH E2F format will also be accepted
- For the marketing authorisation application, a dossier in either M4 CTD or ACTD format may be required, depending on the type of application
- The RMP is not mandatory

Conclusion

ICH guidelines are widely adopted in Asia-Pacific, and there is increasing alignment with other global standards. However, each country generally has its own local requirements in addition to global standards. Furthermore, the regulatory environment is evolving in some parts of Asia-Pacific, and it is important to keep up to date with local requirements to avoid delays in the submission approval process.

The quality of the data presentation is important, in addition to regulatory compliance. Separate analysis of local patient data is required for some countries, and the writer’s skills are needed to understand how best to present and discuss this data. Bi- or even trilingual written and verbal communication skills can be essential. The value of the medical writer is achieving increasing recognition in Asia, and experienced writers with the ability to contribute local regulatory and writing knowledge are in demand to assure the success of local submissions as well as the overall global submission strategy.

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12. Visit: www.mfds.go.kr/index.do?mid=1161&searchClass=&searchDivision=&searchSubDivision=&searchkey=title%3Acontents&searchword=%B0%A1%B1%B3&x=0&y=0
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16. Visit: www.law.go.kr/lsSc.do?menuId=01&subMenu=1&navigation=1&sectionNo=10&query=EC%9D%98%EC%95%88%EB%99%B5%EC%95%88%EC%9D%98%20%EC%95%88%EC%A0%84%EC%97%9D%9C%EA%84%8D-%ED%95%9C%20%EC%89%99%18%80
17. Visit: www2.cde.org.tw/FAQ/NDLA/sublink%EB%8A%A1%98%8D%82%EB%97%A5%9D%97%EC%AC%9B%80%93%9D%89%95%8B%8C%9F%80
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