Provisional Translation (as of March 22, 2011)[*]

Administrative Notice
January 17, 2011

To: Division of Pharmaceutical Affairs,
Prefectural Health Department (Bureau)

From: Evaluation and Licensing Division,
Pharmaceutical and Food Safety Bureau,
Ministry of Health, Labour and Welfare

Format for Preparing the Common Technical Document for Submission of New Drug Applications to Reduce Total Review Time

With respect to the preparation of documents to be submitted in new drug applications, the "Guidance on Preparation of Documents to be Submitted in New Drug Applications" (PFSB/ELD Notification No.899 of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated June 21, 2001) has been issued. Also, to provide the procedural guidance for submission of new drug applications to reduce the total review time, the "Points to Consider for Reducing Total Review Time for New Drug Applications" (Administrative Notice from the Evaluation and Licensing Division and the Compliance and Narcotics Division, PFSB, MHLW, dated June 9, 2010) has been issued. To reduce the total review time for new drug applications, especially from the standpoint of reducing the applicants' time, we have formulated the guidance document titled "The Recommended Format for Preparing the Common Technical Document," which provides recommendations when preparing new drug applications using the Common Technical Document, as shown in the Attachment. Please inform the relevant organizations under your jurisdiction of this Administrative Notice to ensure that the guidance is followed.

[*] This English version of the Japanese Administrative Notice is provided for reference purposes only. In the event of any inconsistency between the Japanese original and the English translation, the former shall prevail.

The Recommended Format for Preparing the Common Technical Document*

1. Objective

The objective of this document is, by providing a format for preparing the quality section and clinical safety section in the Common Technical Document (CTD) that the Pharmaceuticals and Medical Devices Agency (PMDA) recommends, to prevent major corrections or changes to the CTD after submitting a new drug application, thereby making the review process more efficient.

The recommendations in this document apply to all new drug applications using the CTD for marketing approval. In principle, PMDA will not request major changes after submission for the areas discussed in this document, as long as they are prepared in accordance with these recommendations. However, if PMDA considers that post-submission changes are necessary, it may make a request, with justification, that the applicant take appropriate actions to amend the submission.

If the applicant considers that a departure from these recommendations is appropriate because of the nature or properties of the new drug seeking approval, it is recommended to consult in advance with the review team of PMDA for the product (for example, through a face-to-face consultation).

2. Data Relating to Quality

- **Listing of parameters/acceptable ranges around target values/set values described in the manufacturing methods section of the application form**

The operating procedures in the manufacturing process which are essential to ensure constant quality of the drug product should appropriately be selected and described in the manufacturing method field of the product application form. To ensure that the reviewers effectively understand the CTD during the regulatory review process, enabling faster review and smooth GMP inspection, the applicant of a new marketing application or the applicant of a partial change application requiring the description in the manufacturing method field of the application form should prepare lists of the acceptable ranges for parameters and operational conditions as mentioned below, and attach the data to the CTD 1.13 to support the information in the manufacturing method field on the application form. This requirement does not apply to biological products.

For matters in the product application form subject to minor change notification if changed (excluding batch size) or typical manufacturing process parameters not provided in the application form, the applicant should present the following listings in accordance with the examples below: descriptions in the product application form, control ranges established in the product master formula currently used at the manufacturing site, proven acceptable ranges, and rationales for establishing the values in the application form. In the column “rationale for establishing values in the application form,” if the ranges for parameters

* This English version of the Japanese Administrative Notice is provided for reference purposes only. In the event of any inconsistency between the Japanese original and the English translation, the former shall prevail.

or operational conditions have been proven to be acceptable, the ranges should be described, and if the acceptable ranges have not been particularly examined, the fact should be mentioned. If further information is available, the impact on the quality of the product manufactured under conditions out of the range should also be described briefly.

The production scale in which these examinations were conducted should also be described. If results of validation in a commercial production scale is not obtained and the product master formula has not been established, the fact should be described (e.g., “Production validation in a commercial production scale has not been implemented, and the acceptable ranges have not been particularly examined. The product master formula has not been established. The descriptions in the product application form are based on data accumulated in a small to pilot scale production.”). In this case, revised lists should be submitted additionally to the review team after validation in a commercial production is completed and confirmed.

The manufacturing method field in Drug Master Files should be handled in a similar manner. The lists of acceptable ranges for parameters and operational conditions should be submitted to PMDA together with the CTD Module 2 data during regulatory review of a drug using the Drug Master Files.

Example 1 **Matters subject to minor change notification if changed**

No.	Process	Product application form	Product master formula, etc.	Proven acceptable range	Rationale for establishing values in application form
		Matters subject to a minor change notification if changed	Control range	Edge of failure if it is confirmed	
001	Step	『20°C』	xx°C - xx°C	xx°C - xx°C	

Example 2 **Typical manufacturing process parameters not provided in the product application form**

No.	Process		Product master formula, etc.	Proven acceptable range	Rationale for establishing values in application form
		Manufacturing process with no parameters presented in application form	Control range	Edge of failure if it is confirmed	
001	Step	Put A 『×kg』 and B 『×kg』 into the fluid bed granulator and mix them.	xx rpm, xx - xx minutes	xx - xx rpm, xx - xx minutes	

3. Clinical Safety Data

3.(1) General considerations

- Generally, appendices to CTD sections 2.7.3 and 2.7.4 should be attached only to the original and the duplicate copies of the CTD; they are not to be included in the copies for the reviewers.
- Generally, clinical safety data in the new drug application (except for those presented as Reference Data) should be described according to sections 3.(2) to 3.(4) below. However, if there are reasonable grounds and if the review team agrees in advance, the data may be presented in a different manner or in a different part of the CTD.
- The tables shown in this document are presented for illustrative purpose only, which describe what the tables should contain and how the contents should be presented. The size and type of lines, the order of information, footnotes, etc., may be different from the examples. If tables are to be used for comparison of data, however, the tables should be arranged so as to facilitate the comparison.
- If the contents and tables as recommended in this guidance are presented in the Module 5 in an eCTD submission, hyperlinks to those in Module 5 may substitute for those in the Module 2. In this case, when the CTD Module 2 is made publicly available after approval, the corresponding part of Module 5 should be also available to the public.

3.(2) Descriptions of adverse events

3.(2).1) General considerations

- Adverse events (AEs) to be presented in the CTD Module 2 should be organized by applying the same rule to both Japanese and foreign studies for the purpose of increasing review efficiency. All AE terms should be preferably written in Japanese. If there are major differences in MedDRA term selection between Japanese and foreign studies, the differences should be explained in section 2.7.4, etc. of the CTD.
- Even if the explanation and tables on the number of subjects who experienced AEs are presented using a combined analysis based on results from several studies, the results of individual studies to be submitted as the Evaluation Data should be presented separately. If the results of individual studies are described in section 2.7.6, it is acceptable to cite the relevant parts in a way that allows easy reference instead of giving a full description in 2.7.4.
- The tables presented in section 2.7.4 of the CTD may contain only AEs with an incidence of greater than a certain threshold value. However, since a suitable threshold value may vary according to the disease category, the threshold percentage should be defined with justification. Typically this threshold might be “2% or higher” in the case of certain disease areas with lower incidence of AEs, while “10% or higher” in the case of certain disease areas with higher incidence of AEs (for example, oncology area), and if other threshold values are used in such areas, the percentage should be justified in the CTD. For other disease areas, it is desirable that the threshold value be agreed in advance between the applicant and the review team.
- Section 2.7.6 of the CTD should summarize all AEs occurring in the studies to be submitted as the Evaluation Data regardless of the threshold percentage above, in the tables of “all AEs” (regardless of causal relationship to treatment) and “treatment-related AEs” (causal relationship

cannot be ruled out), unless agreed in advance with the review team.

- The causality assessment criteria (classification of degrees of causality and their definitions) and which degree(s) were summarized as “No causality exists” should clearly be presented. If different methods for causality assessment are used in Japanese and foreign studies, each of them should be described. Also, if an individual causality assessment was not carried out, that should clearly be mentioned.
- If it is difficult to summarize AEs in one table, for example, when there are many treatment arms in a study, separate tables may be used to summarize “all AEs” and “treatment-related AEs”. The format of these tables should be suitable to enable appropriate comparison between treatment arms.
- AE summaries should be provided by System Organ Class (SOC) and Preferred Term (PT) of MedDRA. It is preferred that SOCs and PTs are presented in the same table, but separate tables are also acceptable.
- Subjects who discontinued due to AEs should be described in such a manner that other AEs that occurred in the same subject can be identified.
- If results from a multi-regional study(ies) including Japanese subjects are presented as the Evaluation Data, then tables etc. should be prepared to enable comparison of the AE profile between Japanese and non-Japanese subjects. If many Asian subjects other than Japanese are included in the study, ensure that comparison of AEs between Japanese and non-Japanese Asian population can be made.
- The table footnotes should include the section number and the relevant table number in the CTD Module 5 from which the information is cited. This requirement does not apply if a hyperlink to the relevant section is created in the eCTD or the tables are prepared independently in Module 2.

Example of descriptions of AEs

Regarding the safety of the investigational drug, all AEs regardless of causality were observed in xx% of subjects (xx/xx subjects), and the most common AEs observed in xx% or more subjects in any group are summarized in Table xx. Those AEs include nasopharyngitis, …etc.

AEs for which the causal relationship to the drug cannot be ruled out were observed in xx% of subjects (xx/xx subjects), and the most common AEs observed in xx% or more subjects in any group are summarized in Table xx. Those AEs include nasopharyngitis, …etc.

Table xx Number of subjects with AEs (%) (Study xxxx)

	All-causality AEs			Treatment-related AEs		
	Group A (n=150)	Group B (n=148)	Group C (n=151)	Group A (n=150)	Group B (n=148)	Group C (n=151)
Number of subjects with AEs (%)	132 (88.0)	135 (91.2)	140 (92.7)			
Infections and infestations	32 (21.3)	40 (27.0)	50 (33.1)			
Nasopharyngitis	23 (15.3)	25 (16.9)	30 (19.9)			
.....						
.....						
Upper respiratory tract infection	0 (0)	3 (2.0)	4 (2.6)			
Dizziness postural	1 (0.6)	2 (1.3)	0 (0)			
....						

Adverse event terms: MedDRA/J ver xx.0

Causality assessment: Causal relationship is assessed using the following six-degree scale: “not related,” “probably not related,” “possibly related,” “probably related,” “related,” and “unknown.” If an AE is assessed as “possibly related,” “probably related,” “related” or “unknown,” it was summarized as a treatment-related AE.

Source: Clinical Study Report - Table 20 (5.3.5.1.1)

3.(3) Descriptions of deaths and serious adverse events

3.(3).1) General considerations

- All subjects of deaths and serious adverse events (SAEs) submitted in the clinical data package (Evaluation Data and Reference Data), regardless of causality, should be summarized in a table in 2.7.4.2.1.2 (Deaths) or 2.7.4.2.1.3 (other SAEs). If the table extends to tens of pages, it may be presented separately in a different location following a consultation with the review team.
- In CTD section 2.7.4, a case listing should be presented according to the requirements below:
  - Japanese subjects should be distinguished from non-Japanese subjects in all studies. The race of non-Japanese subjects should be clearly mentioned, e.g., Japanese, non-Japanese Asians, Caucasians, etc.
  - The Evaluation Data should be clearly distinguished from the Reference Data.
  - The case listing should be sorted by study.
  - The following information should be provided in the case listing: study number, treatment group, subject ID, race, sex, age, dose (in the case of dose-escalation study, the dose at the AE onset), AE (PT), severity, seriousness (serious/not serious), the day of AE onset with specifying whether

or not the day of the first dose is included in the day count, duration or the day of resolution of the AE, causality, action taken (the drug administration was continued or discontinued, etc.) and outcome. All AEs observed in the subject, in addition to those that led to death or SAE, should be described as necessary.

- The table footnote should include the section number in the CTD where the clinical study report describing the details of the subject is located and the relevant table number. This requirement does not apply if a hyperlink to the relevant section is created in the eCTD or the tables are prepared independently in Module 2.

3.(3).2) Details of individual subject

- Narratives describing the clinical course of events for each subject who experienced an SAE or death as part of the Evaluation Data should be presented in CTD section 2.7.6. Narratives for those subjects experiencing SAEs or death as part of the Reference Data are not required. If details for a single study extend to tens of pages then, depending on the study size and target disease, they may be presented separately following a consultation with the review team.
- The details of individual subjects in CTD section 2.7.6 should be described with clear presentation of the following information: subject ID, race, sex, age, treatment group (including dose), AE (PT), causality, action taken, cause of death, sponsor's opinion on rationale for determining causality (investigator's opinion as necessary; if opinions of the sponsor and the investigator differ, the investigator's opinion should always be presented), medical history (anamnesis), and concomitant medication (drugs that had been used up to the AE onset). The AEs to be described in this section should include not only the AE that led to death or the SAE, but all AEs observed for the subject.
- For deaths where causal relationship to the drug cannot be ruled out, in addition to the information above, the following more detailed information should be provided in a table or in the text in CTD section 2.7.6: subject background, the clinical course of events leading up to death, actions taken, the investigator's opinion, concomitant medication, rationale for determining causality, etc.
- When describing details of individual subjects in CTD section 2.7.6, the corresponding section number in Module 5 should also be provided so that the relevant section in Module 5 is easily identified. This requirement does not apply if a hyperlink to the relevant section is created in the eCTD or the descriptions are made independently in Module 2.

Example of listing of deaths

In the phase III, double blind, placebo-controlled trial (5.3.5.1.1, Study 0085642), xx deaths were observed in the group A, xx in the group B, and xx in the group C, and the details are shown in the table below.

Listing of deaths (Study xxxx)

Treatment group	Subject ID	Race	Dose	Sex	Age	Adverse event	Day of onset (Day xx of administration)	Duration	Causality	Severity	Serious/ not serious	Action taken	Outcome
Group A (n=150)	0001	Japanese	100mg/ day	Female	74	Ventricular fibrillation	5	6	None	Moderate	Serious	Discontin-ued	Not recovered
						Myocardial infarction	5	10	None	Severe	Serious	Discontin-ued	Death
	0006	Caucasian	200mg/ day	Male	78	Pyrexia	5	2	None	Mild	Not serious	None	Recov-ered
						Acute P.E.	30	32	Probably not related	Severe	Serious	Discontin-ued	Death
Group B (n=148)	0018	Japanese	300mg/ day	Male	64	...	7	7	None				
	0030	Asian	300mg/ day	Female	68	...	26	30	Probably related				
	0053	Black	400mg/ day	Female	82	Cardiac failure	80	81					Death
Group C (n=151)	00065	Asian	0 mg/ day	Male	65	Deterioration of cancer	14	14	None				Death

Adverse event terms: MedDRA/J ver xx.0
Source: Clinical Study Report - Table 28（5.3.5.1.1）
Day of onset is counted from the day of the first administration inclusive.

Example of listing of SAEs

In the phase III, double blind, placebo-controlled trial (5.3.5.1.1: Study 0085642), xx serious adverse events were observed in the group A, xx in the group B, and xx in the group C, and the details are shown in the table below.

Listing of serious adverse events (Study xxxx)

Treatment group	Subject ID	Race	Dose	Sex	Age	Adverse event	Day of onset (Day xx of administration)	Duration	Causality	Severity	Serious/ not serious	Action taken	Outcome
Group A（n=150）	0003	Caucasian	100mg/ day	Female	78	Atrial fibrillation	10		None	Mild	Not serious	None	Recov-ered
						Fractures	34		None	Moderate	Serious	Discontin-ued	Recov-ered
	0008	Asian	100mg/ day	Male	69	...	25		Probably not related			Continued after medication	Recov-ered
Group B（n=148）	0031	Japanese	300mg/ day	Male	54	...	4		None			None	Not recov-ered
	0045	Japanese	300mg/ day	Female	47	Pelvic fracture	35		None			Discontin-ued	Recov-ered
	0068	Caucasian	300mg/ day	Female	58	Pneumonia	80		Probably related			Discontin-ued	Recov-ered
Group C（n=151）	00070	Black	0 mg/ day	Male	65	...	14		None			None	Recov-ered
		Japanese											

Adverse event terms: MedDRA/J ver xx.0
Source: Clinical Study Report - Table 32 (5.3.5.1.1)
Day of onset is counted from the day of the first administration inclusive.

3.(4) Descriptions specific to diseases

3.(4).1) Table of AEs in an anticancer drug study by severity

In the CTD for an anticancer drug, summaries of AEs by severity (if an AE was observed at more than one severity in one subject, classify it as the severity of the most severe case) should be presented by study in CTD section 2.7.4 as shown in the table below. In the summary, it is acceptable to include only AEs with an incidence above a specified threshold, but the rationale for that threshold should be provided. Generally, AEs with an incidence of "10% or higher" in any group should be presented. However, depending on the circumstances, the review team may make a request, in advance or during the review process, that AEs with an incidence above a different threshold percentage be summarized. In such cases, the revised table may be included in the response to the PMDA's inquiry.

Example of AEs of anticancer drug

SAEs by severity (incidence of 10% or higher) (Study xxxx)

	Group xx (N=XX)			Group yy (N=YY)		
	n, (%)			n, (%)		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
●●	●(●)	●(●)	●(●)	●(●)	●(●)	●(●)
●●	●(●)	●(●)	●(●)	●(●)	●(●)	●(●)
・・・	●(●)	●(●)	●(●)	●(●)	●(●)	●(●)
・・・	●(●)	●(●)	●(●)	●(●)	●(●)	●(●)
・・・	●(●)	●(●)	●(●)	●(●)	●(●)	●(●)

3.(4).2) AEs summary in long-term clinical trial(s)

If a long-term study of a new drug intended for long-term treatment of non-life-threatening diseases has been conducted, AEs should be summarized so that the time of onset is made clear in CTD section 2.7.4, with attention to the points described below.

- The AEs should be grouped according to the time of onset post the start of drug administration. Generally, these groups will partition the data into periods of 3 months in duration. The duration of these periods may, however, be adjusted depending upon the nature and properties of the new drug and any observed occurrence pattern of AEs.
- If a long-term study is conducted as an extension of a double-blind study, the time of onset from the start of the double-blind study also should be summarized. Therefore, it is recommended to consult the review team in advance regarding matters requiring additional determinations, including the choice of starting point and the lengths of the partitioned periods.
- The day of onset should be identified as, in principle, the time point when the AE was first observed in a subject.
- If results of multiple studies are pooled, provide a justification of why pooling is appropriate for comparisons (taking into account the heterogeneity in study design: duration of administration, dose,

etc.), and specify the pooled studies.

- In general, the AEs observed at an incidence of 2% or higher during the entire study period should be summarized. However, the review team may make a request in advance or during the review process that AEs with an incidence above a different threshold percentage be summarized. In such cases, the revised table may be included in the response to the PMDA's inquiry.
- The number of subjects evaluated should be presented for each period partitioned.
- If AEs of special interest are specified in advance, it is useful to present a Kaplan-Meier plot for days of onset of the event.
- It may be useful to add the median day of onset (and the shortest value, the longest value) for each AE.

Example of AEs by period in a long-term clinical study

AEs observed at an incidence of 2.0% or higher in the entire study period

		The investigational product				
Day of onset	Total	To Month 3	Month 4 to 6	Month 7 to 9	Month 10 to 12	Month 13 or later
Number of subjects evaluated	100	100	92	85	80	76
All AEs	68 (6.8 %)	13	xx	xx	xx	xx
Number of deaths	xx (xx%)	xx	xx	xx	xx	xx
Number of subjects with SAEs other than deaths	xx (xx%)	xx	xx	xx	xx	xx
Number of subjects who discontinued	xx (xx%)	xx	xx	xx	xx	xx
Nasopharyngitis	xx (xx%)	xx	xx	xx	xx	xx
Headache	xx (xx%)	xx	xx	xx	xx	xx
……						
…….						