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Adapt and Survive: Implementing the new ICH Development Safety Update Report (DSUR)

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ABSTRACT

In 2010, the International Conference on Harmonization (ICH) rolled out its E2F Development Safety Update Report (DSUR) guideline. The DSUR is similar to the US's Investigational New Drug Annual Report (IND-AR) and the EU's Annual Safety Report (ASR) in that its purpose is to provide a brief overview of safety for a project on an annual basis so health authorities can better make decisions to protect the safety of patients. However, there are some significant differences in content between DSUR and previous annual reports.

Since DSUR implementation is new to all companies, getting a handle on best practices is a wide-spread challenge. This paper will address the major highlights of DSUR content and suggest some ways of producing these reports efficiently within a company.

INTRODUCTION

For decades, health authorities (HAs) across the globe have been requiring periodic safety reports on Investigational Medicinal Products (IMPs) that are marketed or under development. The intent is to keep HAs appraised of the safety profile for a compound, which enables them to better protect the public. These reports tend to require both cumulative and interval cuts of data, to involve primarily adverse event, exposure, and demographic information, and to be high-level as opposed to very detailed. Companies doing business with the United States are familiar with the IND Annual Report (IND-AR), which has been required by the Food and Drug Administration (FDA), and those doing business with the European Union are familiar with the Annual Safety Report (ASR), which has been required by the European Medicines Agency (EMA).

The International Conference on harmonization (ICH) is involved in standardizing regulatory reporting requirements across the regions of the US, Europe, and Japan. Their contributions include the Common Technical Document (CTD) and the Guidelines for Safety, Efficacy, Quality, and Multi-Disciplinary drug development activities. In 2010, ICH rolled out a new guideline for producing annual safety reports called the Development Safety Update Report (DSUR), labeled E2F. This report is now expected annually by the EMA and is accepted annually by the FDA (FDA still accepts IND-ARs). Note that Japan has not required an annual safety report.

The ICH E2F DSUR guideline can be found at this link:
http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/development-safety-update-report.html

The corresponding sample DSUR produced by ICH is located here:
http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2F/Examples_DSUR/E2F_Example_Commercial_DSUR.pdf

COMPARISON OF DSUR, THE US IND ANNUAL REPORT, AND THE EU ANNUAL SAFETY REPORT

There are numerous similarities among the DSUR, IND-AR, and ASR since they share a common purpose. However, some of the ways in which they achieve that purpose differ in the details. Major features of the DSUR are that it covers an entire IMP, rather than just an indication, and that much of its information is cumulative from inception of the project.

Please see below for a summary of the similarities and differences in various areas.

	DSUR	**IND-AR**	**ASR**
Scope	Molecule	Indication (IND)	Molecule
Time Period Covered	Cumulative mostly	Annual mostly	Annual
Data Lock Point	DIBD* or IBD**	IND anniversary date	DIBD* or IBD**
AE Summaries	Serious	Non-Serious and Serious	Serious
Serious AE Listings	Yes	Yes	Yes
Death Listings	Yes	Yes	No
AE Dropout Listings	Yes	Yes	No
PK-PD, Manufacturing, Microbiology, Investigation Plan, Phase I Protocol Changes	No	Yes	No
Investigator Brochure	No	Yes	Yes
Non-Clinical Results	Yes	Yes	Yes
Literature, Marketing Developments	Yes	Yes	No
Summary of Important Risks	Yes	No	Yes
Regulatory Limitations	Yes	No	No
Specifications	ICH E2F	21 CFR 312.33	EU Directive 2001/20/EC, ENTR/CT3

*DIBD is the Development International Birth Date: the date on which the product was first authorized for testing in humans anywhere in the world

** IBD is the International Birth Date: the date on which the product was first approved for market anywhere in the world

The intent of the DSUR is to cover similar bases to those covered by the IND-AR and ASR but to do so in a consistent manner that decreases the number of reports needed by a sponsor and increases the focus on risk-benefit of products.

ROLES AND RESPONSIBILITIES

Since the DSUR requires information from many different areas within a company, coordination across these functional areas is warranted. Required tasks include scheduling, preparation, writing, review, approval, publication, distribution, submission, archiving, and tracking.

Every institution is organized a bit differently, but below is a generic outline of roles and responsibilities that cover DSUR production:

- Regulatory Affairs: Develop cross-functional SOP and/or process guide; maintain schedule of all DSURs for the company; coordinate overall effort; identify studies to be included in the report; possibly obtain demography and exposure numbers from completed clinical study reports (CSRs).

- Clinical Operations: Identify planned enrollment numbers for ongoing studies.
- Drug Safety and/or Clinical Science: Produce outputs of serious AEs, medical literature searches, high-level discussions of safety issues, status update on investigational program.
- Biostatistics: Provide input into demographic and treatment groupings; review draft outputs.
- Programming: Produce outputs of exposure, demography, discontinuations, deaths, and possibly AEs; optionally automate production of outputs.
- Medical Writing: Compile text and tables; possibly obtain demography and exposure numbers from completed CSRs.
- Quality: Review report.

PROCESS DEFINITION

For a frequent, common report such as the DSUR, a company should have an SOP or other process guide to instruct functional areas on what is expected and when. Development of this process guide should include all functional areas impacted by the task and should be as general as is reasonable; this ensures that it can be applicable to as many projects as possible and accommodate standardization and automation of approaches, which have accompanying quality and cost benefits. For global companies, a process guide is even more important than for local ones due to the complexity of interactions.

In addition to a process guide, it is advisable to maintain a list of all projects with their IDBDs and DSUR due dates. This ensures all involved parties are on the same page regarding timing expectations.

Companies should anticipate that process guides, including roles and responsibilities as well as specific decisions about data handling, may change somewhat after their initial use as the company gains experience at producing DSURs.

There are several specific issues that a process guide can address to help avoid confusion and wasted time for project teams when developing their DSUR:

Obtaining Patient Counts for Old Studies

One potentially contentious issue in assigning roles and responsibilities for DSUR is deciding which functional area must research completed CSRs to obtain demography and exposure counts. For old and/or large projects, this can be a tedious, time-consuming, and sometimes frustrating task. Candidate functional areas generally include Regulatory Affairs, Medical Writing, and Biometrics. Regardless of which department is chosen, at least this must only be done for the first DSUR for a molecule; in subsequent years, the company need only update the list with studies that were ongoing during the DSUR reporting interval.

Studies Conducted Externally

The DSUR process guide should include a section on how to handle studies that are done externally, such as those performed by a contract research organization or cooperative group. Options are to have the external party follow the company's processes or to follow their own. If a project is shared across companies, only one company need produce the DSUR, and it is best to use that company's processes.

Study Periods

Another important and potentially confusing issue that should be addressed generically is which study periods to include in the DSUR. Studies may have survival follow-up or other periods that do not have direct bearing on the product's safety profile. The ICH DSUR guidance should be examined thoroughly and study periods identified that support its requirements. It would be difficult to fully identify all study periods in a generic process guide, so some project-specific customization on this issue may be needed.

Analysis Considerations

Analysis considerations that can be addressed in the process guide include which populations to use for the outputs (safety, intent-to-treat), how to handle studies in which patients received more than one

treatment (recommend counting them in every treatment they received), how to identify patients that died or discontinued during the reporting interval, and whether/how to standardize race values.

STANDARD PROGRAMMER INVOLVEMENT

There is some ongoing, healthy debate about whether or not automating production of demography and exposure outputs would be cost-effective. Most companies have software that produces summary tables for this kind of information as well as producing standard listings of deaths and discontinuations, but production of the study-by-study listings of demography and exposure that the DSUR expects is typically not already automated. It is possible to produce these outputs using web page data entry or template or custom SAS ® software programs, and it is also possible to manually generate them in Excel. Once the initial DSUR year has passed, these lists only need to be updated in subsequent years with information on studies that were ongoing during that year, which may not be a time-consuming task. The sponsor company needs to weigh the cost of developing standard software versus custom programming and/or hand entry.

BIOMETRICS PROJECT PROGRAMMER INVOLVEMENT

Once generic roles and responsibilities have been worked out, a given project team can settle into getting the DSUR produced for their molecule. The following information will be needed by the Biometrics Project Programmer to accomplish their part of this task:

- List of studies to include
- Assignment of status category to each study on the list:
    - completed
    - completed during reporting interval
    - ongoing at end of reporting interval
- Data cut-off date (this may be the DIBD, but note that once a product is marketed, the International Birth Date (IBD) generally replaces the DIBD as the data cut-off date of the DSUR
- Due date for programmed output
- Due date for DSUR submission (generally 60 days after DIBD/IBD)
- Project-customized decisions of roles and responsibilities, if needed
- Project-customized decisions for study periods to include, populations to use, datasets and variables to use, if needed

The following items may be produced by the project programmer, depending on their company's process guide:

- Cumulative list of all studies ever done on the molecule with number of patients assigned to each drug (some of this information can be obtained from other functional areas, depending on the company's process guide)
- Cumulative list of all studies ever done on the molecule by age, sex, and race for patients who took the IMP (as noted above, some of this information can be obtained from other departments)
- For studies that had more than one dose for any given treatment, a cumulative list of all treatment arms for these studies and the patient count in each arm (this is not necessarily required and if produced, can be limited to studies ongoing during the reporting interval)
- For each study ongoing at any time during the reporting period:
    - A list of patients that received the IMP who died
    - A list of patients that received the IMP who dropped out due to an adverse event

SAMPLE OUTPUT TEMPLATES

The following templates represent examples of the information needed from the Biometrics Project Programmer.

Table 1

Cumulative Exposure to IMP, Placebo, and Comparator
All Studies
Reporting Period: Cumulative through ddmmmyyyy

Study	Study Status	Data Source	Analysis Population	Patient Exposure (N)			Comments
				IMP	**Placebo**	**Comparator**	
ZZ1234	Completed	CSR	All Patients	239	240	242	
ZZ2345	Completed	CSR	Safety	50	0	0	
Completed Sub-Total	**Completed**			**289**	**240**	**242**	
ZZ3456	Ongoing	Estimate	Safety	81	40	0	Randomization scheme=1:1:1 IMP (1mg, 2mg), placebo; 121 patients enrolled at DLP
ZZ4567	Ongoing	Clinical DB	Safety	168	162	0	
Ongoing Sub-Total	**Ongoing**			**249**	**202**	**0**	
Total Cumulative Exposure				**538**	**442**	**242**	

It may be helpful to generate the following preliminary table by study to help determine the summary numbers needed for the table being submitted to the HAs.

Preliminary Table 2

Cumulative Exposure to IMP by Demography by Study
All Studies
Reporting Period: Cumulative through ddmmmyyyy

Study	Age				Sex			Race							
	<18	>=18 – <= 65	> 65	Unk	Female	Male	Unk	American Indian or Alaska Native	Asian	Black or African American	Multiple	Native Hawaiian or Other Pacific Islander	Other	White	Unknown
Non-Blinded															
ZZ1234	27	202	10	0	122	117	0	2	60	29	23	5	47	71	2
ZZ2345	0	50	0	0	26	24	0	0	10	8	3	0	5	24	0
ZZ4567	2	161	5	0	87	81	0	0	32	15	5	1	3	112	0
Sub-Total	**29**	**413**	**15**	**0**	**235**	**222**	**0**	**2**	**102**	**52**	**31**	**6**	**55**	**207**	**2**
Blinded															
ZZ3456	0	108	13	0	61	60	0	0	21	17	19	0	7	56	1
Sub-Total	**0**	**108**	**13**	**0**	**61**	**60**	**0**	**0**	**21**	**17**	**19**	**0**	**7**	**56**	**1**

Table 2

Cumulative Exposure to IMP by Demography
All Studies
Reporting Period: Cumulative through ddmmmyyyy

Exposure by Age, Sex, Race	Completed and Ongoing, Non-Blinded Studies	Ongoing, Blinded Studies
Age		
<18	29	0
>=18 - <= 65	413	108
> 65	15	13
N	457	121
Sex		
Female	235	61
Male	222	60
N	457	121
Race		
American Indian or Alaska Native	2	0
Asian	102	21
Black or African American	52	17
Multiple	31	19
Native Hawaiian or Other Pacific Islander	6	0
Other	55	7
White	207	56
Unknown	2	1
N	457	121

Table 3

Cumulative Exposure by Treatment Arm
Studies Completed or Ongoing during Reporting Period
Reporting Period: Cumulative through ddmmmyyyy

Treatment Arm	ZZ2345	ZZ3456	ZZ4567	Treatment Arm Total
IMP 0.1 mg	10			10
IMP 0.3 mg	9		83	92
IMP 0.5 mg	11		85	96
IMP 0.75 mg	12			12
IMP 1.0 mg	8			8
IMP Sub-Total	**50**		**168**	**218**
Placebo			162	162
Placebo Sub-Total			**162**	**162**
Blinded IMP 1mg		41		41
Blinded IMP 2mg		40		40
Blinded Placebo		40		40
Blinded Sub-Total		**121**		**121**

Listing 1

List of Subjects Who Died during Reporting Period: Study ZZ2345
Reporting Period: ddmmmyyyy through ddmmmyyyy

Treatment	Patient ID	Date or Study Day of Death	Age	Sex	Race	Cause of Death
IMP	2389	11-AUG-2011	52	Male	White	Stroke
IMP	5490	13-MAR-2011	68	Female	Asian	Myocardial Infarction

Listing 2

List of Subjects Who Dropped Out during Reporting Period: Study ZZ2345
Reporting Period: ddmmmyyyy through ddmmmyyyy

Treatment	Patient ID	Age	Sex	Race	Reason for Withdrawal
IMP	2389	52	Male	White	Hypertension
					Intracranial Hemorrhage
	5490	68	Female	Asian	Myocardial Infarction
	8339	29	Female	Black or African American	Ulcerative Colitis

CONCLUSION

Developing processes and tools for a new regulatory requirement can be challenging, but the challenges can be abated by proactively identifying generic roles and responsibilities, study handling decisions, and analysis decisions and officially documenting these for broad consumption across the company.

The DSUR expects more information than its predecessors -- IND-ARs and ASRs -- including patient data from the inception of a project, and could thus take more time for a company to prepare. As with most things, once a process is put in place and becomes familiar, subsequent reports will become smoother to produce. A company would be wise to resource this work more heavily in the first DSUR year than in later years.

REFERENCES

International Conference on Harmonization Development Safety Update Report Guideline: http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/development-safety-update-report.html

International Conference on Harmonization Development Safety Update Report Guideline Sample: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2F/Examples_DSUR/E2F_Example_Commercial_DSUR.pdf

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