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Reporting of Deaths During Pre-Approval Clinical Trials for Advanced HIV-Infected Populations

Rosemary Johann-Liang, Andrea N. James, Virginia L. Behr, Kimberly Struble and *Debra B. Birnkrant*

Division of Antiviral Drug Products, Center for Drug Evaluation and Research, The US Food and Drug Administration, Rockville, Maryland, USA

Abstract

The Division of Antiviral Drug Products of the US FDA has regulatory authority over the investigational new drugs under development by various sponsors to treat HIV-infected populations. The FDA and the sponsors of investigational new drugs use the Code of Federal Regulations to guide the entire drug development process, in order to ensure that safe and efficacious drugs are brought to market. To achieve this goal, diligent monitoring for safety during the pre-approval phase of new drug development is particularly crucial. When deciding what adverse experiences on clinical trials should be expeditiously reported, the Division recommends a conservative interpretation of the Code of Federal Regulations, where an adverse experience in a clinical trial of advanced HIV-infected patients is considered to be 'associated with the use of the drug' when the relationship cannot be ruled out with objective evidence. Fatal adverse experiences for subjects on clinical trials should be especially scrutinised. Safety reporting should be expedited when death occurs during clinical trials of advanced HIV-infected populations. The three components of an expedited reportable death occurrence, namely 'serious', 'unexpected' and 'associated with the drug use' as they relate to advanced HIV-infected populations, are discussed in this article. An occurrence of death is by definition serious. Unexpected experiences are unlisted adverse experiences, but need to be put into the context of specificity and severity. 'Associated with the drug use' has been clarified as 'relationship to the drug cannot be ruled out'. Because death in the advanced HIV-infected/AIDS population is usually a complex event, the possible contribution of the study drug is difficult to rule out. Thus, if the three components of the reporting requirement are met or insufficient information is available to make a firm determination of causality by the seventh day of the reporting period, the Division of Antiviral Drug Products expects expedited death reports on subjects participating in investigational new drug clinical studies.

Advanced HIV-infected/AIDS patients often die of an intricately related and complex myriad of problems.[1,2] The death certificate may list 'cardiopulmonary arrest', 'AIDS-complex disease' or simply 'AIDS', but frequently multi-organ system failure and numerous concomitant medications underlie the abbreviated listed cause of death. The exact cause of death is often difficult to determine with certainty. After an analysis of 260 HIV-related deaths, the authors of a recent article[1] concluded

that their observations "underscore the need to monitor the aetiologies of HIV-associated mortality and to better our understanding of the relationships among immune defences, treatment-related toxicities, and end-organ failure in patients with HIV disease". Particularly in the setting of investigational new drug (IND) clinical trials, the aetiology of fatal adverse events in HIV-infected study subjects should be scrutinised more carefully. The relationship of the death on study to the investigational drug should be considered a possibility until this relationship can be ruled out beyond a reasonable possibility.[3]

The Division of Antiviral Drug Products (DAVDP) of the US FDA has regulatory authority over the investigational new drugs under development by various sponsors to treat HIV-infected populations. The FDA and the sponsors of INDs use the Code of Federal Regulations (CFR) to guide the entire drug development process in order to ensure that safe and efficacious drugs are brought to market. Recently, the DAVDP has become aware that drug sponsors interpret, quite variably, the section of the CFR addressing IND-expedited safety reporting and that the drug sponsors' interpretations sometimes differ considerably from that of the drug reviewers in the DAVDP. This has resulted in a number of sponsors not expeditiously reporting deaths on investigational study under the 21 CFR 312.32 IND safety reports;[4] that is, reporting deaths as they occur in real time (as soon as possible, but no later than 7 calendar days after the sponsor's initial receipt of the information). Rather, sponsors have been reporting deaths on investigational study under the 21 CFR 312.33,[5] which is reporting as part of an once-yearly collective annual safety report. Furthermore, the DAVDP's evaluation of these deaths that were not expeditiously reported in HIV drug trials showed that a more conservative approach (i.e. reporting deaths in real time when the exact reason for the deaths is not readily clear) to the interpretation of IND-expedited safety reporting procedures was warranted from the sponsors.

According to the 21 CFR 312.32, sponsors are required to report deaths during clinical trials conducted under an IND. The CFR states that the sponsor shall notify the FDA of "any adverse experience associated with the use of the drug that is both serious and unexpected".[4] All three components of this code, namely any adverse experience that is: (i) serious; (ii) unexpected; and (iii) associated with the use of the drug, need to be met for the sponsor to report the adverse experience under the IND-expedited safety reporting requirement. Herein, we examine the three components of the 21 CFR 312.32 (requirements of IND safety reporting) in the context of clinical trials in advanced HIV-infected populations and strive to clarify the DAVDP's regulatory expectations of expedited safety reporting of deaths on study. The DAVDP's expectations parallel the International Conference on Harmonisation (ICH) guidance.[3] This explanation is followed by several examples and DAVDP's comments.

1. Serious

Seriousness is the clearest of the three components to interpret. The CFR[4] states that a serious adverse drug experience is any adverse drug experience occurring at any dose that results in any of the 'serious' outcomes. Serious outcomes include death, followed by life-threatening adverse drug experiences, inpatient hospitalisation, disability or required intervention. The ICH guidance[3] further clarifies that 'serious' is based on subject/event outcome or action criteria, which is usually associated with events that pose a threat to a subject's life or functioning. Hence, any event of death on a clinical trial is considered to be 'serious' and automatically meets the first of the three components for IND-expedited safety reporting.

2. Unexpected

The definition of 'unexpected' from the 21 CFR 312.32 is as follows: "an unexpected adverse drug experience is any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure; or if an investigator brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended".

Three elements make up this second component for IND-expedited safety reporting. First, an unex-

pected experience is an experience not previously observed in a concrete way. This does not mean that an adverse experience is a predicted experience that is based upon the pharmacological properties of the investigational product. Practically, an unexpected experience translates into an unlisted experience in the drug trials' current investigator's brochure (or similar). For example, if under the laboratory abnormalities section of the investigator's brochure, anaemia and neutropenia are listed, but not thrombocytopenia, then the development of thrombocytopenia in a patient under clinical study is considered to be 'unexpected'.

Second, if the listed experience does not specifically describe the adverse experience that has occurred, the occurring adverse experience can still be considered to be 'unexpected', even though the experience is listed in the investigator brochure. For example, although anaemia is listed as an adverse experience in the investigator's brochure, if the occurring adverse experience is specifically 'megaloblastic anaemia', this may be considered to be an 'unexpected experience'.

Third, an adverse experience may be listed (and may be even specifically listed), but if the occurring adverse experience is more severe than is expected from what is listed, it can be considered to be 'unexpected'. For example, diarrhoea may be an already observed and listed adverse experience. However, if only mild to moderate diarrhoea is expected and the occurring adverse experience is considered severe in nature, then the adverse experience is 'unexpected'. Of note, 'severity' is not the same as 'serious'. As discussed previously, serious experiences with regard to safety assessments are related to outcomes that pose a threat to a patient's life or functioning. Severity relates to the intensity of the experience. Hence, the adverse experience of severe dyspepsia may be considered to be an 'unexpected' experience if only mild dyspepsia was previously observed and listed. The 'unexpected' classification may be relevant even though the actual experience of severe dyspepsia poses no serious medical sequelae.

3. Associated with the Use of the Drug

The third component of the IND safety reporting requirement is where most interpretative liberties have been taken. The CFR definition[4] states that "associated with the use of the drug" means "there is a reasonable possibility that the experience may have been caused by the drug". The DAVDP interprets this definition to mean that the sponsor should adopt a conservative approach when determining the potential association of a serious and unexpected adverse experience to the use of an investigational drug, particularly during early drug development. The conservative approach means that the serious and unexpected adverse experience (i.e. death in this case) should be considered as possibly related and thus reportable, unless an association has been reasonably ruled out using objective evidence. This definition as it pertains to pre-approval IND clinical experience is further clarified in the ICH 2EA document under section II: definitions and terminology associated with clinical safety experience.[3] The guidance states that "in the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established, all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions". The ICH guidance further clarifies that "the phrase, responses to a medicinal product, means that a causal relationship between a medicinal product and an adverse experience is at least a reasonable possibility, i.e. the relationship cannot be ruled out".

For example, in certain situations a serious adverse experience probably occurred as a result of the underlying disease and not as a result of the test drug or biological product. However, it may not be possible to determine with certainty that the investigational product did not contribute to the serious adverse experience. In pre-approval clinical trials conducted in the advanced HIV-population, such an adverse experience should be noted and reported as a serious adverse drug experience with a 'reasonable possibility' that the drug or biological product may have caused the serious adverse experience. Of course, this classification would not establish causality (attributability) by itself; it would only indicate that causality could not be ruled out with certainty.

Thus, a conservative interpretation is recommended when deciding what adverse experience should be reported under the 21 CFR 312.32. A

definitive causal relationship between the drug and the adverse experience ('ruled in') is not needed to determine the association of the adverse experience with the drug. Rather, if a causal relationship between the adverse experience and the use of the investigational drug cannot be eliminated ('ruled out'), then a 'reasonable possibility' exists that the adverse experience and the use of the investigational drug are associated.

The DAVDP defines an adverse experience in a clinical trial of advanced HIV-infected subjects to be 'associated with the use of the drug' when the relationship cannot be ruled out with objective evidence. For example, unless the serious and unexpected adverse experience of death on study is attributable to something specific (i.e. pneumococcal meningitis), the relationship of the drug to the death will be challenging to rule out. This is especially true if the cause of death is 'unknown', as is the case in many instances at the early investigative stage of the death occurrence or vague, as in 'AIDS', 'AIDS-complex', or 'cardiopulmonary arrest'. Moreover, in a medically complex population, such as patients with advanced HIV infections or AIDS, it is difficult to attribute any one specific cause to the death occurrence. Add in a long list of concomitant medications that may have potential or unknown interactions with the investigational drug and it becomes even more difficult, if not impossible, to rule out the relationship of the investigational drug to the death occurrence during the investigational stage of a new drug.

A corollary to this discussion is how the clinical trial database adverse experiences are displayed in the recent drug approvals to treat HIV infection.[6,7] All treatment-emergent adverse experiences are shown. Adverse experiences are no longer listed as 'drug-related' because in this population, it is very difficult to attribute specific adverse experiences to a drug or not to a drug. Likewise, in another study population that is medically complex (cancer patients with fungal infection), all-cause mortality (not fungus-related or drug-related mortality) is what should be determined when examining adverse experiences that are associated with clinical trials, since the exact cause of death is difficult to assess and attribute to a specific cause.[8]

4. Reporting Procedures

When a death (automatically 'serious') on study has been deemed 'unexpected' (unlisted or listed, but not specific enough or severe) and a relationship to the trial drug cannot be ruled out ('associated with the use of the drug'), then according to the 21 CFR 312.32, the "sponsor shall also (in addition to written report) notify the FDA by telephone or by facsimile transmission as soon as possible but in no event later than 7 calendar days after the sponsor's initial receipt of the information. Each telephone call or facsimile transmission to FDA shall be transmitted to the FDA new drug review division in the Center for Drug Evaluation and Research or the product review division in the Center for Biologics Evaluation and Research that has responsibility for review of the IND." In the current case of drug products to treat HIV-infected patients, the review division to be contacted in the Center for Drug Evaluation and Research is the Division of Antiviral Drugs.

If the death occurrence is being investigated by the sponsor and all the results of the investigation to 'rule out' the drug's association to the death occurrence are not available by the seventh calendar day, that death occurrence should be reported as an expedited report as outlined in the CFR. A follow-up report can be submitted as the information becomes updated and the causality of death is clearer.

Another vital piece of information that should be submitted to the FDA with the death report (or any other expedited reportable experience) is a 'like analysis' of similar experiences that have been previously reported in relation to the IND. The CFR states that "in each written IND safety report, the sponsor shall identify all safety reports previously filed with the IND concerning a similar adverse experience, and shall analyse the significance of the adverse experience in light of the previous, similar reports". When 'like analysis' is not submitted with the expedited report, valuable time may be lost as the FDA works to put the fatal (or other serious and unexpected experience) into perspective and make appropriate regulatory actions.

5. Specific Examples

In this section, all three components of the IND safety reporting requirements are brought together (remembering that the CFR states that all three components should be met for expedited reporting) and discussed through two hypothetical illustrative examples. These examples are specific to clinical studies in patients with advanced HIV disease. The necessary IND safety reporting procedures are also discussed.

5.1 Example 1

This case was not reported as an expedited report by a sponsor. A 45-year-old White patient with HIV enrolled in a randomised, double-blind, comparative safety and efficacy trial of a trial drug versus comparator in patients who had previously received multiple antiretroviral drug regimens. The patient was started on the trial drug on 23 June 2003; however, on 15 September 2003, he developed diarrhoea (4–5 times/day) and also noted mental status changes (memory lapses). On 18 September 2003, the patient was hospitalised after being taken to the hospital by co-workers. On 20 September 2003, the patient developed hypokalaemia for which he received treatment and recovered on 22 September 2003, at which time he developed hypophosphataemia. The patient recovered from the hypophosphataemia on 23 September 2003. On 24 September 2003, he recovered from the diarrhoea and mental status changes. On 15 October 2003, the patient died.

The reported cause of death was 'acquired immunodeficiency syndrome'. The concomitant medications included efaviranz, tenofovir, atovaquone and azithromycin. The trial drug, as well as the concomitant drugs, were continued until death. The investigator judged that there was no reasonable possibility that the events were related to the trial drug. The death report was received by the sponsor on 23 October 2003. The clinical monitor judged that there was a reasonable possibility that the diarrhoea was related to the trial drug and also judged tenofovir to be the alternate suspect drug in causing the diarrhoea. However, the clinical monitor judged that there was no reasonable possibility that the remaining events (mental status changes, hypokalaemia, AIDS and, therefore, death) were related to the trial drug.

The DAVDP reviewer's assessment

Serious: Yes.

Unexpected: Yes. Death was unexpected in a patient who was apparently well enough to be working just a month prior to death and enrolled in a randomised, controlled clinical trial. Also, no information regarding the circumstances of his death was given. Insufficient information was available to make an assessment.

Relationship to drug cannot be ruled out: Yes. The investigator and the clinical monitor made statements about the relationship of diarrhoea to the electrolyte abnormalities, but did not give statements about the relationship to the death occurrence on study. Again, insufficient information was available to make an assessment.

Reporting requirement: As there was no information provided regarding the circumstances surrounding the patient's death, nor any indication that the patient's condition was deteriorating in general or after recent hospital discharge, there was no obvious aetiology for the fatality.

Overall assessment: This case should have reported to the DAVDP as an expedited IND safety report followed by further information reports.

5.2 Example 2

This case was reported as an expedited report by a sponsor. An HIV-positive woman (age unknown) enrolled in a long-term, open-label, rollover trial that assessed the safety and tolerability of combination antiretroviral drug use in HIV-1 infected subjects and began taking the trial drug on 15 March 2003. Significant relevant medical history included end-stage AIDS, wasting, fever of 104°C (date not specified), shingles, anaemia, low potassium levels, cryptococcus infection, anxiety, depression, hypertension, allergies and steatohepatitis. On 4 August 2003, the patient developed liver failure and on 5 August 2003, the patient died of multiple organ failure in the emergency room, as was reported by the investigative site. Her laboratory deteriorations showed hyponatraemia with hyperkalaemia and renal failure, in addition to acidosis, increased transaminase levels and increased bilirubin levels. The

concomitant medications reported included lamivudine, enfuvirtide, epoetin alfa, iron, acyclovir, potassium, dapsone, fluconazole, ibuprofen and oxycodone. The investigator judged that the liver failure was aggravated by the study medication and triggered the multiorgan failure. No further details were reported. The investigator and clinical monitor judged that there was a reasonable possibility that the hepatic failure, but not the multiorgan failure, was related to the trial drug.

The DAVDP reviewer's assessment

Serious: Yes.

Unexpected: Yes (because of the severity of the liver failure).

Relationship to drug cannot be ruled out: Yes (trial drug could have caused progression of the steatohepatitis, inducing liver failure, which in turn led to multiorgan failure).

Reporting requirements: Since all three components of the reporting requirement were met, this event should have been (and was) reported as an IND-expedited safety report.

Overall assessment: The DAVDP agreed with the sponsor's reporting of this fatal event as an IND-expedited safety report. However, a like analysis with previous hepatic adverse events in the drug development programme should have been submitted with this expedited report.

6. Conclusions

Safety reporting should be expedited when death occurs during clinical trials of advanced HIV-infected populations. This article discussed the three components of an expedited reportable death occurrence, namely what constitutes 'serious', 'unexpected' and 'associated with the drug use' as they relate to the population of patients with advanced HIV-infection. An occurrence of death is by definition serious. Unexpected experiences are unlisted adverse experiences, but need to be put into the context of specificity and severity. Associated with the drug use has been clarified as 'relationship to the drug cannot be ruled out'. Because death in this patient population is usually a complex event, the possible contribution of the study drug is difficult to rule out. Thus, if the three components of the reporting requirement are met or insufficient information is available to make a firm determination of causality by the seventh day of the reporting period, the DAVDP expects death reports of subjects participating in IND clinical studies to be submitted as expedited reports.

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Correspondence and offprints: Dr *Rosemary Johann-Liang*, Division of Antiviral Drug Products (HFD-530), Center for Drug Evaluation and Research, The US Food and Drug Administration, Rockville, 9201 Corporate Boulevard, MD 20850, USA.
E-mail: johannliangr@cder.fda.gov