108

Guidance for Industry

How to Submit Information in Electronic Format by E-Mail

(THIS VERSION OF THE GUIDANCE REPLACES THE VERSION MADE AVAILABLE IN MAY 2004)

This guidance document is intended to provide instructions on how to submit information in electronic format by e-mail to the Center for Veterinary Medicine (CVM or the Center). The guidance was revised to update the web links and the contact email and phone number.

Comments and suggestions regarding this document should be sent to Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. Submit electronic comments to http://www.fda.gov/dockets/ecomments. All comments should be identified with the exact title of the document.

E-mail submissions that follow this guidance will be compatible with CVM's current information technology capabilities. This will help ensure the confidentiality, integrity, security, and authenticity of data submitted to the Center. If a regulated sponsor or person wishes to use an electronic approach other than that set forth in this guidance document, the Center will, on request, discuss alternative methods of submitting information.

For questions regarding this document, contact Margaret Zabriski, Center for Veterinary Medicine (HFV-016), Food and Drug Administration, 7519 Standish Place, Rockville, MD 20855, 240-276-9143, e-mail: margaret.zabriski@fda.hhs.gov.

According to the Paperwork Reduction Act of 1995, a collection of information should display a valid OMB control number. The valid OMB control number for this information collection is 0910-0454. The time required to complete this information collection is estimated to vary between 5 and 20 minutes per response, including the time to review instructions, search existing data resources, gather the necessary data, and complete and review the information collection.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Veterinary Medicine
January 17, 2006

Table of Contents

CONTAINS NON-BINDING RECOMMENDATIONS

GUIDANCE FOR INDUSTRY[1]

HOW TO SUBMIT INFORMATION IN ELECTRONIC FORMAT BY E-MAIL

This guidance represents the Agency's current thinking on how to submit information in electronic format by e-mail to the Center for Veterinary Medicine. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statue and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance provides general standards which should be used for the submission of any information in electronic format to the Center for Veterinary Medicine (CVM) by e-mail.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word "should" in Agency guidances means that something is suggested or recommended, but not required.

CVM's ability to receive and process information submitted electronically is limited by its current information technology capabilities and the requirements of the Electronic Records; Electronic Signatures regulation, 21 CFR 11. The Center will accept certain types of submissions by e-mail with no requirement for a paper copy. The list of these submissions is published in the Electronic Submissions Docket No. 92S-0251 (available on the FDA Home Page, http://www.fda.gov).

The Electronic Records; Electronic Signatures regulation (21 CFR 11) requires that the Agency identify in the Electronic Submissions Docket the types of documents or parts of documents acceptable for official electronic submission.

[1] This guidance has been prepared by CVM at FDA. For additional copies, access the document on the Internet at the CVM Home Page (http://www.fda.gov/cvm/default.html) or send a request to the Communications Staff, HFV-12, 7519 Standish Place, Rockville, MD 20855.

This guidance implements provisions of the Government Paperwork Elimination Act, Pub. L. No. 105-277, 112 Stat. 2681 (1998), which requires that executive agencies, by October 21, 2003, provide: (1) for the option of the electronic maintenance, submission, or disclosure of information, if practicable, as a substitute for paper; and (2) for the use and acceptance of electronic signatures when practicable.

II. COMMUNICATION BETWEEN CVM AND INDUSTRY

Successful electronic submission of information for review and evaluation by e-mail requires a successful partnership between CVM and regulated industry. Information needs to be exchanged and errors need to be resolved. The Center has set up a hotline to resolve any problems and questions (301-827-8277). The sponsor should identify one person to be the Sponsor Coordinator who will be responsible for communication with the Center.

III. REGISTRATION TO SEND ELECTRONIC SUBMISSIONS LISTED IN ELECTRONIC SUBMISSIONS DOCKET

Agency Certification:

To participate in CVM's electronic submissions by e-mail, the sponsor provides certification to the Agency's Office of Regional Operations that the sponsor's electronic signature is the legally binding equivalent of the signer's handwritten signature as required by 21 CFR 11.100(c).

The suggested certification statement to provide is:

"Pursuant to Section 11.100 of Title 21 of the Code of Federal Regulations, this is to certify that [Company Name] of [Company Address] intends that all electronic signatures executed by our employees, agents, or representatives, located anywhere in the world, are the binding legal equivalent of traditional handwritten signatures."

Center Registration:

In addition, CVM needs other information to ensure the confidentiality, integrity, security, and authenticity of data submitted to the Center in electronic format by e-mail. This information includes the password that will be used by individuals to submit information electronically on the sponsor's behalf. Use of the password to encrypt information sent by e-mail will help assure the security of submissions and together with an individual e-mail address will constitute an electronic signature (21 CFR 11.200(a)).

Sponsors wishing to provide regulatory submissions in electronic format to CVM register once for all types of submissions listed for CVM in the Electronic Submissions Docket. If a regulated sponsor or person wishes to use an electronic

approach other than that set forth in this guidance document, the Center will, on request, discuss alternative methods of submitting information.

A. Sponsor Registration and Password Initialization

Sponsors wishing to submit information electronically should send a single, original, signed paper registration letter to CVM. In an attachment to this letter, the sponsor should identify:

- The name, mailing address, phone number, and e-mail address of the Sponsor Coordinator;
- The name, mailing address, phone number, and e-mail address for each person who will be submitting information electronically;
- The password used to encrypt the electronic registration letter that will be submitted by e-mail. This password will be used by CVM to encrypt the response to the registration letter; and
- The subject of the letter should be **Registration Letter for Electronic Submission to CVM** to clearly identify the purpose of the letter.

An encrypted, identical electronic copy of the registration letter should be sent by e-mail to cvmdcu@fda.hhs.gov with the subject line of the e-mail reading **REGISTER**. CVM will decrypt the electronic registration letter with the password identified in the paper copy of the registration letter.

The Center will send two acknowledgements to the sponsor: (1) a paper letter acknowledging receipt of the registration and stating that the sponsor appears to be able to make electronic submissions that are compatible with CVM's current technology, (2) after CVM successfully accesses the electronic registration letter, an electronic receipt for the registration letter, by e-mail, to the Sponsor Coordinator as an encrypted Portable Document Format (PDF) file (compatible with Adobe® Acrobat® version 5.05)[2].

[2] FDA use of specific products does not constitute an endorsement of that product.

Example of Registration Letter

HFV-199
Attention: Lesley Groves
Office of New Animal Drug Evaluation
Center for Veterinary Medicine
7500 Standish Place
Rockville, Maryland 20855

Subject: Registration Letter for Electronic Submission to CVM

To Whom It May Concern:

This letter notifies the Center for Veterinary Medicine (CVM) of our intent to use e-mail to submit documents listed in the Electronic Submissions Docket No. 92S-0251. An attachment to this registration letter contains the name of the person who will serve as our Sponsor Coordinator and the names of the persons who will be submitting electronic information, along with their mailing addresses, phone numbers, e-mail addresses, and a password for initializing the Electronic Submission System.

We have certified to the Food and Drug Administration, Office of Regional Operations, that the electronic signatures used to submit information on our behalf are intended to be the legally binding equivalent of traditional handwritten signatures.

We are submitting an electronic copy of this request to cvmdcu@fda.gov encrypted with our password.

We look forward to receipt of CVM's letter acknowledging our intent to submit information by e-mail and stating that we appear to be able to make electronic submissions that are compatible with CVM's current technology.

Sincerely yours,

Attachment

B. Creating Individual Passwords and Using the Electronic Submission System (ESS)

After receiving the paper and electronic acknowledgements, the Sponsor Coordinator and each person submitting electronic submissions should choose an individual password and notify CVM ESS of the new password using FORM FDA 3538 (Electronic Submission System Participant Password or Addition) by an e-mail message sent to cvmdcu@fda.hhs.gov.

- Each person should fill out part I of FORM FDA 3538.
- The subject line of this e-mail message should be **MANAGE**.
- Passwords should be changed prior to sending your first electronic submission to the ESS. The new password should not be used until the acknowledgment has been received from CVM of a successful password change

Passwords should be changed after an appropriate period of time to assure security. CVM will monitor the aging of passwords and suggest re-initialization periodically. Changes to passwords follow the same process used to establish the initial password change using FORM FDA 3538.

Any registered user can send a blank e-mail message with the subject line of **ECHO** to confirm that they are recognized by the ESS. The system will respond with basic information confirming the identity of the sender and that the ESS is functioning.

C. Adding New Participants to a Registered Sponsor

The Sponsor Coordinator may add participants to the ESS by using FORM FDA 3538 sent to cvmdcu@fda.hhs.gov.

- The Sponsor Coordinator should fill out all fields in part II of FORM FDA 3538.
- The subject line of this e-mail message should be **MANAGE**.

D. Other Changes to the Sponsor Registration

The Sponsor Coordinator may request changes in electronic submission registration. These changes may include, but are not limited to, removing an authorized sender, adding or removing a Sponsor Coordinator, changes to e-mail addresses, changes to sponsor names, etc.

To request a change, the Sponsor Coordinator should send an e-mail message to cvmdcu@fda.hhs.gov with the subject line of **CHANGE**. The e-mail message should have a PDF file attached that has been encrypted by the Sponsor Coordinator's password. The attached PDF file should contain the specified change(s) that the Sponsor Coordinator is requesting.

This does not include any changes to an individual password. See Section III.B of this document for those changes.

IV. PROCESSING PROCEDURES FOR ELECTRONIC SUBMISSIONS

Information transmitted to CVM by e-mail should adhere to minimum standards to ensure confidentiality, integrity, security and authenticity. CVM can process only submissions that comply with the Electronic Records; Electronic Signatures regulation. In addition, procedures described in this guidance take into consideration the current information technology capabilities of CVM. Adherence to these standards is verified by the Center's e-mail processing, and generally only submissions in full compliance can be successfully processed as electronic submissions. If sponsors wish to use a different approach, they should discuss it first with CVM.

Sponsors should send each electronic submission as a PDF file (compatible with Adobe® Acrobat® version 5.05) attached to an e-mail. Each e-mail with the attached submission should be sent to cvmdcu@fda.hhs.gov. Submissions are acknowledged with a receipt issued within two working days from CVM confirming the submission was successfully processed.

A. Gateway Information and Communication

The configuration of a sponsor's e-mail software or Internet gateway is critical to the successful interchange of electronic information with CVM over the Internet. Electronic mail formats are not completely standardized, however, most gateways can be configured to accommodate the more recent and reliable formats. Many gateways limit the size of attachments allowed. Therefore, for the purpose of interchange with CVM, the attachment size should be limited to no more than 50 Megabytes (50 MB).

The CVM gateway should have a MIME type e-mail encoding of the level that allows 8-bit or binary attachments for sending e-mail with an attachment.

The sponsor's e-mail software or Internet gateway should be configured to generate "MIME-Version: 1.0" in the header field and recognize the Content-Transfer-Encoding header field in the e-mail message. It should be able to decode all received data encoded by either quoted-printable or Base64 implementation and be able to encode and label 8-bit or binary data using a Content-Transfer-Encoding type of either quoted-printable or Base64 as appropriate. This will allow attached password-encrypted PDF files to be transmitted as part of the transmission package.

The sponsor’s e-mail software or Internet gateway should explicitly handle the following media type values:

Text:

- It should recognize and display "text" mail with the character set US-ASCII.

- It should recognize other character sets at least to the extent of being able to inform the user about what character set the message uses.
- It should recognize the ISO-8859 character sets to the extent of being able to display those characters that are common to the ISO-8859 and US-ASCII, namely all characters represented by octet values 1-127.

Multi-part and application:

- It should at a minimum provide facilities to treat any unrecognized subtypes as if they were "application/octet-stream."
- It should offer the ability to remove either of the quoted-printable or Base64 encoding defined in this document if they were used and put the resulting information in a user file.
- It should recognize a mixed subtype and display all relevant information on the message level and the body part header level and then display or offer to display each of the body parts individually.

The following is an example of the items in an Internet e-mail header that CVM uses to identify the sender, the function, or the type of the e-mail.

The table below shows most of the fields in a typical RFC822 header.

Field	**Example**
From:	Sponsorcontact@sponsor.com
To:	Cvmdcu@fda.hhs.gov
Cc:	Sponsorcoordinator@sponsor.com
Subject:	Email Configuration
Date:	11 May 1998 16:11:43 –0400
Importance:	Normal
Mime-Version:	1.0
Content-Type:	Multipart/mixed; boundary="__NextPart__11:05:1998_(27624)"
Content-Transfer-Encoding:	7bit

When a multipart MIME message is assembled, the text will have a set of lines such as this in front of it, including the part boundary string that was specified in the header.

The example immediately below uses the ISO-8859-1 character set rather than US-ASCII, but limits the characters to 7-bit, that is octets ranging from 1-127:

__NextPart__11:05:1998_(27624)
Content-Type: text/plain; charset=iso-8859-1
Content-Transfer-Encoding: 7bit

The lines in the example below might precede an attached file called cvmform.pdf:

__NextPart__11:05:1998_(27624)
Content-Type: application/octet-stream; name=cvmform.pdf
Content-Transfer-Encoding: base64

Note that the content is identified simply as "application/octet-stream". If PDF had been defined to the originating e-mail agent, it might have been identified as "application/pdf". If PDF was defined to the receiving agent as a type that should be processed by Adobe® Acrobat®, the agent would launch Acrobat® to view the file. When the receiving agent does not recognize the Content-Type, it should treat it as "application/octet-stream," decode it, and offer the recipient the option to save it as a user file.

B. E-mail Address

Sponsors should register their e-mail addresses with CVM as outlined in Section III. This will allow CVM to process the sponsors' submissions. The e-mail address registered with CVM should match exactly the e-mail address of the received submission.

C. Subject Line of E-mail

The subject line is an integral part of CVM's processing of electronic information submitted by e-mail. Each electronic submission of information is identified, checked, and processed based on the subject line of the e-mail message. The subject line for an e-mail message containing an attached submission should be the single word identified in the appropriate guidance. It should be only the single word, capitalized, non-quoted, and should contain no special characters. Any additional information in the subject line will cause a fatal error and CVM will not be able to process the submission.

The following are subject lines which should be used for electronic submission to CVM.

Subject Line	**Type of Electronic Submission**
REGISTER	Electronic copy of registration letter specifying sponsor's intent to submit information electronically
CHANGE	Electronic notification of changes in conditions of registration
MANAGE	Electronic request to change an individual password or add new participants to registered sponsors using FORM FDA 3538
ECHO	No submission – blank e-mail will respond with electronic acknowledgement to registered sender

D. PDF File of Electronic Submission

For purposes of any electronic submission, the sponsor should use the appropriate format provided by CVM, which should be submitted to CVM as an encrypted PDF file (compatible with Adobe® Acrobat® version 5.05) attached to an e-mail message. Forms for electronic submissions are available on CVM's Home Page, http://www.fda.gov/cvm.

There should be only one PDF attachment per e-mail, and it should be no larger than 50 Megabytes (50 MB) in size. It should conform to the format and standards for the specific type of electronic submission as detailed in the appropriate guidance. The Center's automated processing performs a check of the number of attachments and will not process an electronic submission with more than one attachment.

Sponsors should use ISO 9660 Interchange Level 1 file naming convention, i.e., up to 8 characters (A-Z, 0-9, and _) for the file name and PDF for the file extension (8.3 naming convention); an example using this convention would be filename.PDF.

E. Electronic Signature

Each person who intends to submit electronic submissions will have a unique electronic signature to verify the sender's identity. The unique electronic signature will consist of the sender's e-mail address and the individual's password.

This password should consist of **12** case-sensitive alphanumeric characters. The sender uses the password to encrypt the file before transmitting it to CVM. Only CVM's electronic submission system and the person who submits the electronic submission should know the password and be able to open the file.

CVM will acknowledge each electronic submission by creating a new e-mail message (i.e., not by using a "Reply" feature) and sending the acknowledgement to the sender. CVM's acknowledgement will be a password-encrypted message attached to an e-mail message. CVM will use the individual's password to encrypt the file.

Individuals who submit information electronically must follow the electronic signature requirements described in 21 CFR 11.100-11.300. These requirements must be followed for CVM to accept electronic submissions as the official copy, instead of paper. If sponsors are not capable of meeting these requirements sponsors must submit information on paper.

V. SECURITY MEASURES FOR ELECTRONIC SUBMISSIONS

Corporations have used the Internet as an expeditious vehicle for the exchange of information for several years. However, many corporations and government agencies

have avoided using the Internet for the exchange of sensitive and/or confidential information because of concerns about security. In developing an electronic submission project using the Internet as the message-carrying vehicle, four areas of security should be addressed adequately by all participants prior to its adoption.

A. Disclosure/Non-Disclosure

Information submitted to CVM is subject to the Freedom of Information Act and FDA's regulations on public information at 21 CFR Parts 20 and 514. Some information, such as trade secrets, certain commercial and financial information is confidential in nature and is non-disclosable. Therefore, using the Internet to submit confidential information can be done only with adequate encryption. CVM currently recommends that this encryption be in the form of a password-protected PDF file. CVM will continue to monitor and assess the adequacy of this level of security and determine whether or not a different encryption method is necessary.

Protecting the Confidentiality of the Information in Electronic Submissions

The ESS will only accept encrypted PDF files to protect the confidentiality of submitted information. The person submitting the electronic information should encrypt the file with his/her password.

Authentication Verification

Currently, CVM receives paper submissions from sponsors by US Postal Service, Federal Express, United Parcel Service, etc. With these submissions, there is a cover letter on sponsor letterhead signed by an authorized sponsor official. This information allows CVM to authenticate that the submission is from the stated sponsor. Any electronic submission should also provide a means by which CVM can authenticate the origin of the electronic document, such as the unique two-part electronic signature.

Unique Two-Part Electronic Signature

The registration letter should contain the name and e-mail address for each authorized sender. Subsequent to the receipt of CVM's acknowledgment letter for the registration, each sender should submit to CVM ESS a password change using FORM FDA 3538 as described in Section III.B of this guidance. The unique combination of the e-mail address and the password will serve as the electronic signature under 21 CFR 11.200(a)(1) and will authenticate the identity of the sender. CVM will maintain a database of electronic signatures and will automatically reject any electronic submission received that does not match the unique combination of e-mail address and password.

Verification of the Sender's Identity

An additional precaution will be taken to ensure that the e-mail message received at CVM did indeed come from the sender designated. CVM will acknowledge receipt of the electronic submission as described in section IV. If a sender receives an acknowledgment but has not sent an e-mail to CVM, he/she should immediately report this to CVM by telephone to 301-827-8277.

B. Verification of Date of Submission

Currently, time-sensitive information is submitted by certified mail so that the sponsor has a record verifying the date and name of an individual who received the information at CVM. This also provides a legal basis by which drug sponsors can assert their compliance with laws and regulations.

Currently, CVM uses the date on the cover letter to determine whether information was submitted within the time required by statute or regulation. If CVM is able to open and read the file, the date within the file will serve as the date of submission.

C. Submission Integrity

The integrity of the content of a submission to CVM is the responsibility of the sponsor. If sections of a paper submission are missing or illegible, CVM requires the sponsor to provide copies of the missing or illegible information. A remote possibility exists that intentional or unintentional changes could be made to an electronic submission that could not be made to a paper submission. For example, unintentional "scrambling" of the submission may occur during transmission so that CVM receives a corrupted, unusable file. Further, a submission could be intentionally changed if a message is intercepted en route, changes are made to the content and then the message is sent on as if from the original sender.

CVM will rely on the password encryption of the PDF file to ensure the integrity of the electronic submission. If the file is received by CVM intact and can be decrypted and opened by Adobe® Acrobat®, then CVM will assume no changes occurred to the submission once it was e-mailed from the sponsor. If CVM receives a corrupted file and can identify who the sender is, CVM will notify the sender that its file was corrupted and the sender should resubmit the file.

VI. CHECKLIST FOR ELECTRONIC SUBMISSIONS

To make electronic submissions, sponsors should:

- Have MIME (base64) compliant access to the Internet. See Section IV.A for details.
- Use the appropriate form provided by CVM.

- Conform to an ISO 9660 Interchange Level 1 compatible naming convention for PDF files e-mailed to CVM. The name of the attached file should be 8 characters or less with the letters PDF as an extension, i.e., xxxxxxxx.PDF. See Section IV.D for details.
- Register with CVM once for all types of submissions listed in the Electronic Submissions Docket.

REGISTRATION PROCESS (See Section III for details.):

1. Send a single, original, signed registration letter to CVM. See Section III.A. for an example of the registration letter. The letter should contain:
   a) the name, mailing address, phone number, and e-mail address of the Sponsor Coordinator;
   b) the names, mailing addresses, phone numbers, and e-mail addresses for each person who will submit electronic submissions;
   c) a 12 character, case-sensitive alphanumeric character sponsor password. See Section III.A for details; and
   d) the subject of letter should be **Registration Letter for Electronic Submission to CVM** to clearly identify the purpose of the letter.
2. Create a PDF copy of the registration letter. Encrypt the PDF file with the sponsor password, attach it to an e-mail message, and send it to cvmdcu@fda.hhs.gov. The subject line of the e-mail message should be the word **REGISTER**.
3. CVM will send an e-mail to the Sponsor Coordinator named in the registration letter. The message will have an encrypted PDF file attached containing an acknowledgment of receipt of the registration letter. The password necessary to decrypt the PDF file receipt will be the sponsor password sent in the registration letter. A paper response will also be sent. If the sponsor has not received both of these acknowledgments within 30 days contact CVM by calling the electronic Document Control Unit at 301-827-8277.
4. The Sponsor Coordinator and each identified contact should choose an individual password before sending an electronic submission. Directions for informing CVM of the new individual password will be included in the Center's response to the registration letter. The subject line of the e-mail message should be **MANAGE**. See Section III.B of this guidance for details.
5. The sponsor should not send an electronic submission until CVM acknowledges the receipt of an individual password by e-mail.