USDA-APHIS Biotechnology Regulatory Services
User's Guide

General Document Preparation Guidelines For Submission to BRS

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Biotechnology Regulatory Services
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The information contained in this document is intended solely as guidance, and reflects APHIS' current interpretation of applicable statues and regulations. Except where noted, persons may choose to follow APHIS guidance or follow different procedures, practices, or protocols that meet applicable statutes and regulations.

Language implying that guidance is mandatory (e.g. "shall," "must," "required," or "requirement") should not be construed as binding unless the terms are used to refer to a statutory or regulatory requirement. Throughout the document, sections from applicable statutes and regulations are clearly identified in grey-shaded text boxes.

Conversely, following the guidelines contained in this document should not be construed as a guarantee of compliance with applicable statutes and regulations.

General Document Preparation Guidelines For Submission to BRS

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Quick Guide to BRS Submissions

Documents submitted to BRS are primarily related to four types of regulatory procedures that are discussed in detail in other guidance documents:

- Permits for the introduction of regulated articles
- Notification of the introduction of regulated articles
- Petitions to grant non-regulated status to a regulated article
- Extension of non-regulated status to a regulated article

Although the specific content of individual documents will vary based upon the type of submission, all documents submitted to BRS have some features in common.

- General formatting (p. 3-5)
    - Documents submitted to BRS should be of professional, publication quality.
    - Specific document preparation guidelines are provided in this document.
- Presentation of data and statistical analysis (p. 5-8)
    - Data and statistical analysis included in submissions must be of a sufficient caliber as for publication in a scientific peer reviewed journal.
    - Specific guidelines for presentation of data and statistical analysis are provided in this document.
    - Particular care must be taken in selecting statistical methods to demonstrate *equivalence*.
- Confidential business information (p. 8-10)
    - All documents submitted to BRS may be released to the public pursuant to a request under the Freedom of Information Act (FOIA).
    - Information determined to be "confidential business information" (CBI) is protected from public disclosure.
    - Applicants must submit a letter justifying any claims of CBI in submitted documents.
    - Submissions to BRS that include CBI must be formatted to protect this information from public disclosure by preparing an additional CBI-deleted version.

General Document Preparation Guidelines for Submission to BRS

Most documents submitted to BRS are associated with one of the four types of regulatory procedures discussed in detail other guidance documents:

- Permits for the introduction of regulated articles
- Notification of the introduction of certain regulated articles
- Petitions to grant non-regulated status to a regulated article
- Extension of non-regulated status to a regulated article

Each guidance document above includes sample documents related to a particular type of submission. Although the specific content of individual documents will vary based upon the submission type, all documents submitted to BRS have some features in common. This guidance document details basic guidelines for document preparation and formatting, presentation of statistical information, and handling of confidential business information.

Document Preparation Guidelines

All documents submitted to BRS should be of professional, publication quality, as if for submission to a peer reviewed scholarly journal. Language should be clear, well organized, and free of typographical and grammatical errors. Documents should generally follow standard formatting guidelines similar to those provided by most scientific journals.

Please use the following specific guidelines, where appropriate, for preparation of all documents submitted to BRS.

General Text Formatting

Format text in the body of the document for printing on standard U.S. letter-sized paper in portrait orientation. Use at least 1" margins on all sides of the text. Line spacing may be single or double. Use a 12-point font (for proportionally spaced type) or 10 characters/inch (4 characters/cm) if the letter spacing is uniform. Number all pages in the document sequentially beginning with the first page.

Divide long documents (such as petitions) into sections, and include Table of Contents, and Lists of Tables, Figures, etc.

Scientific Names and Terminology

Spell out all symbols, abbreviations and acronyms the first time they are used. Avoid use of abbreviations for gene, protein or other specialized names. Define (or avoid) all technical terms that may be familiar only to specialists.

The species name is required for all donor and recipient organisms. *Italicize* scientific names. Species name must be fully spelled out the first time it is mentioned in the text (e.g. *Lycopersicon esculentum*), but may be abbreviated with the single-letter generic name thereafter (e.g. *L. esculentum*) as long as no confusion with other species results. Also, cite sub-species, cultivar, etc., where relevant. Do not use common and species names interchangeably, but common names may be used after scientific names are provided.

The first time an organism is introduced in the text, provide a brief description to clearly identify the organism; e.g. "*Cornus florida* L. (flowering dogwood), a small deciduous tree."

References

If references are cited in the text of a submission, presenting them in the text as (Author, Year) is preferable. The submission should also include a reference list that details reference author(s), date, article title, journal title, volume, and page number. Do not abbreviate journal titles. When conference proceedings or other books are cited, provide the publisher's name and location. See the American Medical Association for an example of an acceptable citation style:

http://www2.liu.edu/cwis/cwp/library/workshop/citama.htm

Copies of literature cited need not be included with the submission. However, APHIS may request copies of literature cited if necessary.

Tables

Tables should supplement, not duplicate, the text. Number tables in the order of their citation in the text. Provide a short descriptive title at the top of each table; rather than simply repeating the labels on columns and rows of the table, the title should reveal the point of grouping certain data in the table. Statistical and other details should be provided as footnotes rather than appearing in the title. Tables should have footnotes for any abbreviations used in the table. Do not add vertical or horizontal lines to tables unless essential to avoid ambiguity. Do not repeat the same material in figures and tables; when either is equally clear, a figure is preferable. Do not include any class of information in tables that is not discussed in the text of the document.

Small tables may be embedded in the text. Larger tables should be presented on a separate page either following the first citation in the text, or at the end of the document or major section. If presented on separate page, a table may be in either portrait or landscape orientation.

Figures

Figures should be numbered sequentially, titled, and legends should be brief, self-sufficient explanations. The figure title (i.e., Figure 1) should be given as the first two words of the legend. Label graph axes with the parameter or variable measured, the units of measure, and the scale. Definitions of symbols should usually appear in the figure legend. Avoid the use of light lines and screen shading, instead use black-and-white, hatched and/or crosshatched designs for

emphasis. Before submitting figures, please photocopy each one to verify that photocopied versions of the figures are as clear as the originals.

Include figures in the document following the guidelines for tables (see above).

Equations

Equations set separately from the text should be broken into two or more lines if they exceed the width of one column. Use leading zeroes with all numbers less than one, including probability values (e.g., $P < 0.001$).

Sequence Data

In general, nucleotide and amino acid sequences should be submitted only when the sequences are not already available in a public database. Short sequences should be included in the body of submissions only when necessary to illustrate a specific point. For example, amino acid sequence might be included in a figure to illustrate similarity to other amino acid sequences. Attach long stretches of sequence (greater than ~100 nucleotides or amino acids) as separate files in a standard sequence format. Applicants are encouraged to submit sequence data to public databases, such as those maintained by the National Center for Biotechnology Information (NCBI), and provide APHIS with accession numbers.

Color Printing

The use of color in submissions is discouraged, unless color is an integral part of the image's meaning. Submissions are commonly reproduced in black and white, particularly when distributed to the public. In many cases, the use of color may be unavoidable (i.e. photographs). If color images are necessary, submit original full-color copies of the image with all required copies of the document. Color images should be clear and understandable when printed in black and white (e.g. when photocopied or printed in grayscale).

Media Type and Number of Copies

Acceptable media type (printed vs. electronic) and required number of copies varies depending upon the type of submission. See other guidance documents for information specific to each submission type. When printed documents are accepted, the original document should be printed on one side of U.S. letter-sized paper. Any required copies should be of a quality and clarity comparable to the original.

Where electronic media are accepted, submit all files on a single CD (if possible) formatted to be accessible on a computer with a Microsoft Windows operating system. In some cases, files may be submitted via e-mail. Acceptable file formats include Microsoft Word, Word Perfect, and Adobe pdf. See other guidance documents for information specific to each submission type.

Data Quality Guidelines

Any experiments performed by the submitter must follow certain guidelines in order to be used as supporting data in submissions to BRS. The amount of detailed information given is critical, especially for petitions and extensions. Supporting data provided to APHIS is expected to be of the same scientific caliber as that published in peer reviewed journals.

In all submissions, fully describe experimental design, use of controls, and appropriate statistical methodology, in addition to concurring published data. Acknowledgement of opposing data and logical arguments against it should also be included. Note that for most submissions to BRS, federal regulations require disclosure of unfavorable evidence.

Data Collection and Experimental Design

Clearly describe sampling designs, experimental designs, data collection protocols, precision of measurements, sampling units, experimental units, and sample sizes. Where possible, include some measure of the precision of estimates— standard errors or confidence intervals— although this may not be necessary or possible in all instances, especially for unusual statistics.

Graphical data presentation is encouraged. Carefully composed graphs often permit the reader to decide at a glance if data are in danger of violating statistical assumptions.

Statistical Methodology

Authors are free to interpret statistical analyses as they see fit; however, documents must include information sufficient for an independent assessment of the author's analysis. Clearly state the assumptions and the model underlying any statistical analysis, and provide sufficient detail in the presentation of results.

Assumptions. Assumptions behind any statistical analysis must be articulated and well justified. Where unusual assumptions are made, unusual procedures are used, or unusual types of data are involved, provide sufficient information for an assessor to judge whether any departures from assumptions are severe enough to invalidate the conclusions. The amount of detail provided in any particular instance will depend on the centrality of the statistical test to the conclusions.

Reporting of analyses. Always state the specific statistical procedure used. If a statistics program or program package was used, a complete citation (including version number) should be given. If necessary, the author should indicate which procedure within a package was used, and which method within a procedure was chosen. Explain unusual statistical procedures in sufficient detail, including references if appropriate, for the reader to reconstruct the analysis. To denote levels of significance, actual P values are generally more informative than symbols such as * and **.

If conclusions are based on an analysis of variance or regression, information sufficient to permit the construction of the full analysis of variance table (at least degrees of freedom, the

structure of F-ratios, and P values) must be presented or be clearly implicit. Where ambiguity is possible, the authors must indicate which effects were considered fixed or random and why.

Use of controls. In all experimental designs, use appropriate positive and negative control groups. Include control groups in tables and figures for comparison.

Statistically Valid Demonstration of Equivalence

Much of the data submitted to BRS is used to argue the *equivalence* of a transgenic variety and a non-transgenic comparator. This is particularly true for petitions to grant non-regulated status, in which the petitioner presents evidence that a transgenic organism is no more likely to pose a plant pest risk than the unmodified organism from which it was derived.

In support of this, many applicants submit data that, in their view, demonstrates that the agronomic and compositional properties of a transgenic line are statistically similar to a non-transgenic line. Applicants often base a conclusion of equivalence upon statistical methods designed to detect statistical *differences*, using an argument as follows:

- The null hypothesis is that there is no difference between two lines.
- The statistical test evaluates the probability of finding the observed difference between the lines by chance alone, given that the null hypothesis is true.
- If the difference *is* statistically significant—that is, the difference is unlikely to have been observed by chance— then it seems clear that the two lines *are not* equivalent.
- If the difference *is not* statistically significant, it seems to make sense to conclude that the two lines *are* equivalent.

This last conclusion is often used to support the interpretation the variable measured is equivalent between the transgenic and non-transgenic lines.

This approach, however, is **statistically invalid** and leads to invalid conclusions. If this kind of test reaches the conclusion of "no statistically significant difference," it means the current evidence is not strong enough to demonstrate that the two lines are different; this is not the same as demonstrating that the two lines are the same. The procedure establishes evidence against the null hypothesis only, not for it. In other words, the absence of evidence is not evidence of absence.

A small sample size, for example, can make it difficult to detect statistical significance of a difference. If the goal is to establish equivalence, following the flawed methodology above one would just run the experiment with few samples or replicates. Furthermore, problems with the data itself (e.g. outliers), may hamper the ability to find a result at the specified significance level, and so again one could come to a conclusion of equivalence as a result of poor data.

Statistical methods are readily available to determine whether two groups are *statistically equivalent*, and should be used accordingly. Equivalence tests begin with the null hypothesis

that two samples are *different*, and seek evidence to reject that hypothesis. For more information on statistical methods of equivalence testing, see:

- M. Clark (2005) *Equivalence Tests*, available online at http://www.unt.edu/benchmarks/archives/2005/february05/rss.htm
- *Statistical Tests for Equivalence*, online at http://www.graphpad.com/library/BiostatsSpecial/article_182.htm

Confidential Business Information (CBI) in Submissions to BRS

All documents submitted to BRS are subject to the Freedom of Information Act (FOIA), which requires that records submitted to federal agencies be made available to the public. BRS provides the public with documents it receives when formally requested through the APHIS FOIA office. Additionally, BRS voluntarily makes many submitted documents freely available on its website (http://www.aphis.usda.gov/biotechnology/status.shtml). Section (b)(4) of the FOIA, however, exempts from disclosure certain types of information related to trade secrets and commercial or financial information, collectively referred to as *confidential business information* (CBI). Documents submitted to BRS that contain CBI require special handling.

What is confidential business information (CBI)?

Information that would be protected from disclosure under section (b)(4) of the FOIA is classified as confidential business information (CBI). This includes trade secrets and commercial or financial information found to be confidential.

A *trade secret* is information relating to the production process, including production data, formulas, and processes, and quality control tests and data, as well as research methodology and data generated in the development of the production process. Such information must be (1) commercially valuable, (2) used in one's business and (3) maintained in secrecy.

Commercial or financial information may be deemed confidential if review establishes that the applicant faces active competition in the area to which the information relates and that substantial competitive harm would result from disclosure. Information such as safety data, efficacy or potency data, and environmental data may be such confidential information.

If an applicant believes a document to be submitted to BRS contains confidential business information, upon submission the applicant must:

1) provide a detailed letter justifying any claims of CBI found in the document, and
2) include both CBI-containing and CBI-deleted versions of the document.

Letter of justification for claims of CBI

If an applicant believes that a document to be submitted to BRS contains confidential business information, the applicant must include a letter justifying all claims of CBI. The letter must be

detailed enough to demonstrate that *each piece of information claimed as CBI* meets the definitions of trade secret or commercial or financial information, as described above. Claims of CBI must be justified in terms related to competitive harm due to its release. Information is not protected from disclosure simply because the applicant does not want the information to be made public.

The following are examples of information often reasonably justified as CBI in submissions to BRS:

- donor organism
- gene name and description
- phenotype
- transformation method
- amount shipped or acreage planted
- specific addresses of field sites
- names and institutions of collaborators

The following kinds of information are not typically considered CBI, but in exceptional cases might be claimed as CBI with a strong and legitimate justification:

- names and addresses of responsible parties
- organization
- recipient organism
- phenotypic category
- county
- state

Additionally, information which is published or otherwise publicly available may not be claimed as CBI. BRS reserves the right to accept, challenge, or request further information on each claim of CBI.

Preparation of documents containing CBI

If a document to be submitted to BRS contains information that the applicant claims as CBI, the applicant must submit two versions of the document: a complete version containing CBI (the "CBI Copy") and an edited version with the CBI redacted (the 'CBI-deleted Copy"). Use the following guidelines to prepare these two documents.

- Each page of a document containing CBI must have "CBI Copy" marked in the upper right corner. Each page of a CBI-redacted document must have "CBI-deleted Copy" marked in the upper right corner.
- In a document containing CBI, mark with square brackets only the specific words or phrases claimed as CBI, and in the right margin for each set of brackets write "CBI." In the CBI-deleted version, replace with blank spaces the words or phrases marked in the

CBI version, mark the spaces with square brackets, and in the right margin for each set of brackets write "CBI-deleted."

- The CBI-deleted version should be identical to the CBI version, except 1) blank spaces surrounded by square brackets occurring in the text where the CBI text has been redacted and 2) "CBI-deleted Copy" should appear in the upper right corner of each page instead of "CBI Copy."
- The CBI-deleted version must be paginated identically to the CBI copy. The CBI-deleted version should be made directly from the same document which originally contained CBI.
- If several consecutive pages are CBI-deleted, a single page designating the numbers of deleted pages may be substituted for those pages (for example, "Pages 7 through 10 have been CBI-deleted.").
- Do not insert additional text (transitions, paraphrasing, or generic substitutions, etc.) into the spaces of the CBI-deleted version.
- All published references that appear in the CBI copy should be included in the reference list of the CBI-deleted copy.

How to Find More Information

For information related to submission of specific documents to BRS, please refer to the contact information listed within the corresponding guidance document:

- Permits for the introduction of regulated articles
- Notification of the introduction of certain regulated articles
- Petition to grant non-regulated status to a regulated article
- Extension of non-regulated status to a regulated article

If you would like more information about confidential business information in BRS submissions, please contact:

Document Control Officer
USDA-APHIS-BRS
4700 River Road, Unit 91
Riverdale, Maryland 20737
(301) 851-3892 or (301) 851-3877

To request a copy of BRS documents under the Freedom of Information Act, please contact:

FOIA Officer
USDA-APHIS
4700 River Road, Unit 50
Riverdale, MD 20737-1232
(301) 851-4102

Version History

01/16/2007	Original draft.
11/20/2007	Reformatting to remove references to chapter organization of *BRS User's Guide*
02/05/2008	Removal of word "draft" from document.
2/22/2011	Added table of contents and updated hyperlinks.