Quick Guide to Creating an SD File for eCTD Submissions

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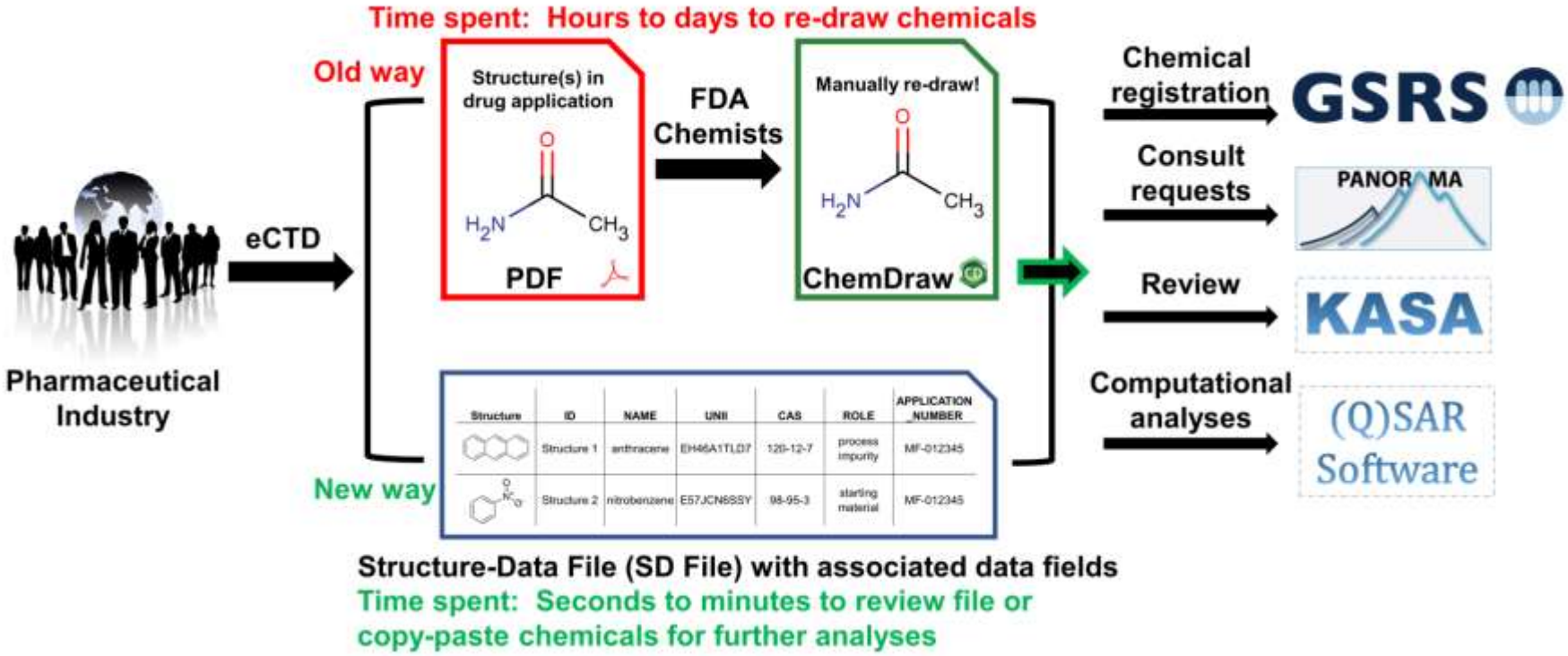
Creating and submitting a structure-data file (SD File)

- Define an SD File
- Format
- File locations in electronic common technical document (eCTD)
- Available software
- Special chemical structure scenarios
- Additional Support

What happens to the chemical structure at FDA?



Structure-Data File from Sponsors' Submissions Promotes Rapid Chemical Registration and Computational Analyses, Scientific Computing Days 2021, https://www.fda.gov/media/151913/download

Moving forward

- In 2021, SD Files became an acceptable file format in the eCTD.
- As of October 21, 2022, FDA received 65 SD files with an average of 30 structures per file.

What is an SD File?

- SD File – chemical-data file format that can associate data with a chemical structure
- The chemical structure uses the MOLfile[1] format, which describes the atoms, bonds, connectivity, coordinates, and properties of the structure using strings of text
- File extension is “.sdf”
- Also known as SDF

[1]Chemical table file – Molfile. https://en.wikipedia.org/wiki/Chemical_table_file#Molfile

The *computer* interprets the file and translates the string/text into a graphical structure and table.

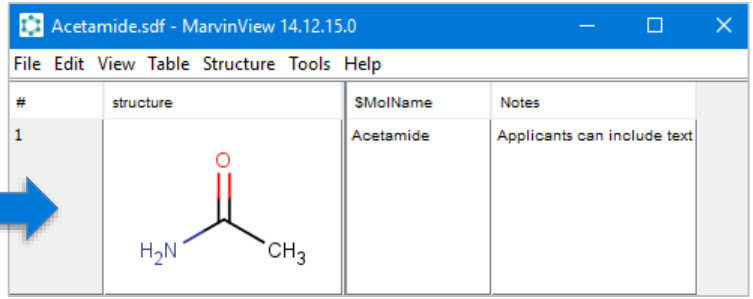
SD File text contents

```
Acetamide


  4  3  0  0  0  0  0  0  0  0999 V2000
    0.0000   -0.2062    0.0000 C   0  0  0  0  0  0  0  0  0  0  0  0
    0.0000    0.6188    0.0000 O   0  0  0  0  0  0  0  0  0  0  0  0
   -0.7145   -0.6188    0.0000 N   0  0  0  0  0  0  0  0  0  0  0  0
    0.7145   -0.6188    0.0000 C   0  0  0  0  0  0  0  0  0  0  0  0
  1  2  2  0  0  0  0
  1  3  1  0  0  0  0
  1  4  1  0  0  0  0
M  END
>  <Notes> (Acetamide)
Sponsors can include text

$$$$
```

Graphical chemical structure and data table



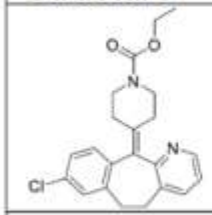
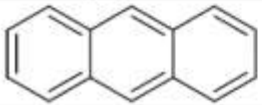
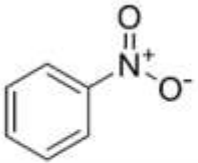
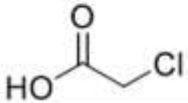
Suggested file type and name

- Please use V2000 format
- One SD file containing more than one chemical structure will be expected
- File name - SDF_DMF_012345_Loratidine.sdf
  - Application type and number (i.e., DMF 012345, ANDA 012345)
  - Name of the Active Pharmaceutical Ingredient (API)

Columns/data items linked to each chemical structure

- **NAME** - Name(s) of the chemical as referenced in the application
- **APPLICATION_NUMBER** - Application type prefix (e.g., DMF, ANDA, NDA, IND, or BLA) before the number (e.g., DMF 012345 or DMF 12345)
- **ID** - Unique identifier for cross-references
- **ROLE** – e.g., active ingredient, process impurity, intermediate, degradant, metabolite, and/or starting material
- **UNII** - Unique Ingredient Identifier, if available from https://precision.fda.gov/uniisearch and https://gsrs.ncats.nih.gov/ginas/app/beta/
- **CAS** - If available, from SciFinder - https://scifinder.cas.org
- **NOTES** – if needed. Notes specify/qualify something about the substance that is not easily discernable from the structure alone

Sample SD File with columns/data items and associated data

Structure	ID	NAME	UNII	CAS	ROLE	APPLICATION_NUMBER
	Structure 4	loratadine	7AJO3BO7QN	79794-75-5	active ingredient	DMF-012345
	Structure 1	anthracene	EH46A1TLD7	120-12-7	process impurity	DMF-012345
	Structure 2	nitrobenzene	E57JCN6SSY	98-95-3	starting material	DMF-012345
	Structure 3	2-chloroacetic acid	5GD84Y125G	79-11-8	starting material	DMF-012345

Note – Helpful if the active ingredient is the first record

Types of chemicals to include

- Impurities of drug substance and drug product
- Leachables exceeding the analytical evaluation threshold (AET) (calculated from the safety concern threshold (SCT))
- Impurities evaluated by (Q)SAR to support selection of a surrogate molecule or predict potential mutagenicity

Place SD File(s) in appropriate section of eCTD

- Module 3 has several sections which may contain information relating to drug substance (3.2.S) or drug product (3.2.P)
- Impurities evaluated by (Q)SAR
  - 3.2.S.3.2 for drug substance
  - 3.2.P.5.5 for drug product

Place SD File(s) in appropriate section of eCTD

(continued)

- 3.2.R Supportive files placed here for any of the sections above should be properly hyperlinked. One SD File may be suitable when substances pertain to multiple sections
- Nonclinical study reports submitted in Module 4 may include hyperlink(s) to SD Files submitted in Module 3 to assist cross-references
- May also submit to other sections, if needed, e.g., 3.2.S.6 and 3.2.P.7 Container Closure System

Software available

Commercial

- ChemAxon Marvin
- Microsoft Excel with ChemDraw Add-in from ChemOffice
- Instem Leadscope SDF Editor
- Molecular Operating Environment

Publicly available and free

- Open Babel
- DataWarrior
- KNIME SDF Writer
- RDKit
- CDK

Special chemical structure scenarios

- Salts, mixtures, 3-D configurations, isotopes, or stereochemistry, please use the SD File Guide

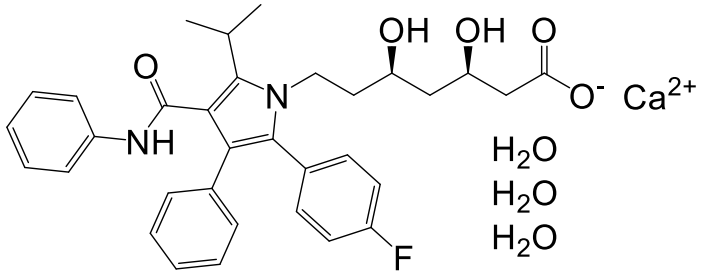
- For complex substances other than small molecules (e.g., proteins, nucleic acids) please contact FDA-SRS@fda.hhs.gov for a UNII

Include stoichiometry explicitly

Magnesium chloride ($MgCl_2$)

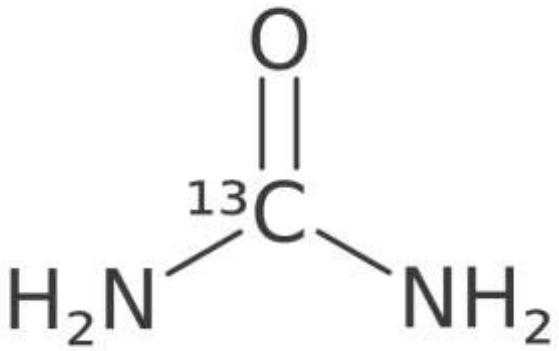
Cl^- Mg^{2+} Cl^-

Atorvastatin calcium trihydrate

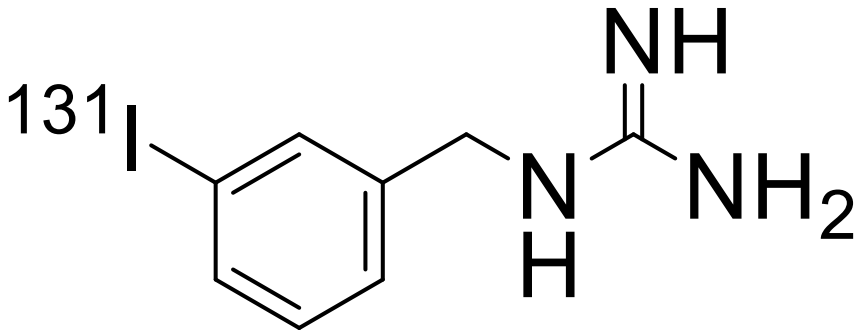


Specify isotopes

Urea C^{13}

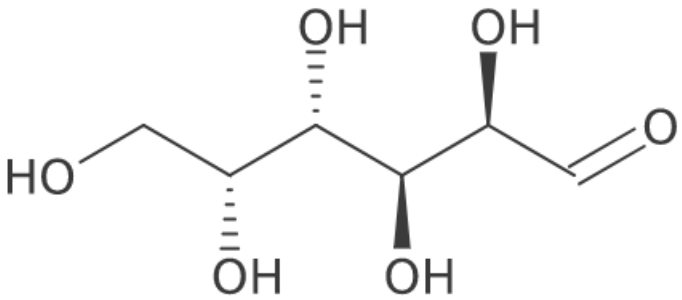


Iobenguane I-131

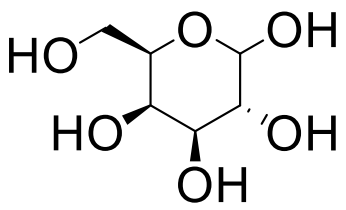


Use planar drawings for cyclic structures and ring systems

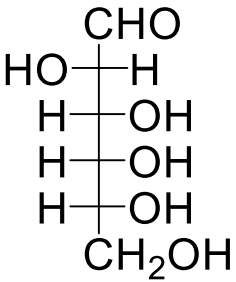
D-Galactose



Preferred drawing

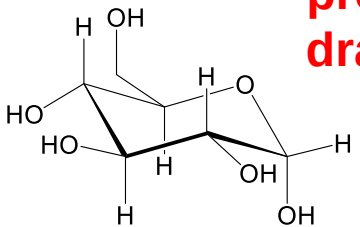


Haworth



Fischer

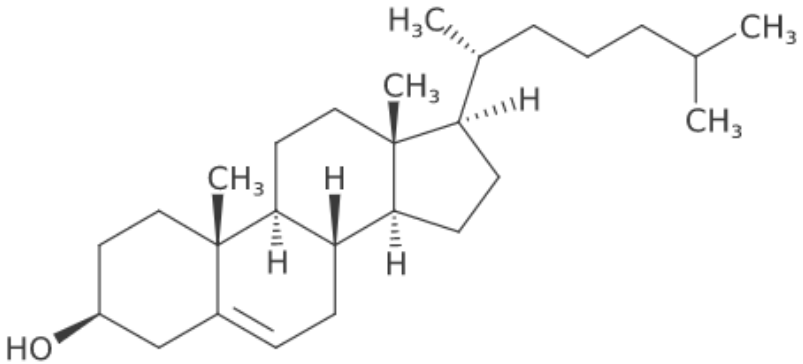
NOT preferred drawings



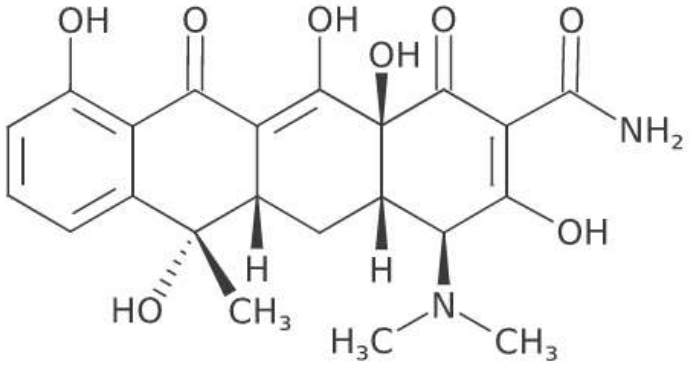
Chair

Use wedge and dash bonds to indicate stereochemistry

Cholesterol



Tetracycline



Additional support

- FDA-SRS@fda.hhs.gov -Requesting UNII, formatting SD Files, drawing complex structures
- DMFOGD@fda.hhs.gov - DMF submissions
- esub@fda.hhs.gov - CDER related to eCTD submissions
- esubprep@fda.hhs.gov - CBER related to eCTD submissions

We've come a long way

- Standardized data fields meets FDA's cheminformatics needs
- Errors associated with redrawing structures are eliminated
- Process increases accuracy, quality review efficiency, and eliminates redundancy
- Impacts drug substance and drug product reviews, (Q)SAR analyses, and GSRS registration efforts

Submit a comprehensive SD File with your submission!

Resources

- Dalby A, et al. Description of several chemical structure file formats used by computer programs developed at Molecular Design Limited. J. Chem. Inf. Comput. Sci. 1992, 32, 3, 244–255.
- SD File Quick Guides
  - DMF submissions
  - Other types of submissions (ANDA, NDA, BLA)
- Electronic Common Technical Document (eCTD) | FDA
- Study Data Standards Resources | FDA

Thank you!

SD File Implementation Team

Tyler Peryea

Barbara Scott

David Green

Naomi Kruhlak

GSRS Staff and Collaborators

Frank Switzer

Larry Callahan

Elaine Johanson

Dammika Amugoda

Marian Nkeng

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Charles Robertson

Andre Raw

Geoffrey Wu

Extractables and Leachables Subcommittee

Data Standards Board

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Ray Wang