

**Key questions:**

What animal model tests will be predictive of human outcomes for SCI?

- what are the current models, their strengths and limitations?
- when is preclinical evidence sufficient to justify human testing?
- are we using a common language for safety/tox, good lab practices, etc.?

Questions for discussion:

Given: We have no gold standard for treatment for effective treatments in SCI...

What are the significant risks that should be assessed preclinically?

How do we establish proof of principle for efficacy?

How do I sort through these tools to develop the most logical argument for my therapy?

Which factors must be tested for a given application?

Injury severity, injury level, chronicity, gender, species/strain, model of injury

Do these enable or limit inclusion criteria for trials?

(or will all trials begin testing with thoracic ASIA-A patients?)

What outcome measures can assess safety? Efficacy?

When is it appropriate for preclinical safety / toxicology to be done in SCI animals vs. normal controls?

When is SCI like / different than other neurological injury studies (TBI, Stroke, ALS, etc.)?

## Selected FDA Guidance Overviews

### Center for Drug Evaluation and Research (CDER) –

<http://www.fda.gov/cder/guidance/index.htm>

Guidance for Industry, Investigators, and Reviewers Exploratory IND Studies

<http://www.fda.gov/CDER/guidance/7086fnl.htm>

Center for Devices and Radiological Health (CDRH) – Medical Device Regulations index page (links to IDE, premarket approval, humanitarian device exemption guidances, etc.) –

<http://www.fda.gov/cdrh/devadvice/> IDE: <http://www.fda.gov/cdrh/devadvice/ide/index.shtml>

Center for Biologics Evaluation and Research (CBER) – <http://www.fda.gov/cber/faq.htm>

1) Title 21, Chapter I, Subchapter L – Part 1271.10 Human Cells, Tissues, and Cellular and Tissue-Based Products – Summary:

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?FR=1271.10>

2) Information on Submitting an Investigational New Drug Application

<http://www.fda.gov/cber/ind/ind.htm>

### Jurisdiction Guidance

1) Transfer of Therapeutic Biological Products to the Center for Drug Evaluation and Research / Combination Therapies <http://www.fda.gov/oc/combination/transfer.html>

2) How do biological products differ from conventional drugs?

<http://www.fda.gov/cber/faq.htm#4>

3) Devices Used to Process Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) - Jurisdictional Update <http://www.fda.gov/oc/combination/hct.html>

FDA Definition of Good Laboratory Practice for Non-Clinical Laboratory Studies

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=58>

## Suggested References on Preclinical Studies:

[Macleod MM, Fisher M, O'Collins V, Sena ES, Dirnagl U, Bath PM, Buchan A, van der Worp HB, Traystman R, Minematsu K, Donnan GA, Howells DW.](#)

Good Laboratory Practice. Preventing Introduction of Bias at the Bench. *Stroke*. 2008 Aug 14.

[Sena E, van der Worp HB, Howells D, Macleod M.](#)

How can we improve the pre-clinical development of drugs for stroke?

*Trends Neurosci*. 2007 Sep;30(9):433-9. Epub 2007 Aug 31. Review.

[Kleitman N.](#) Keeping promises: translating basic research into new spinal cord injury therapies. *J Spinal Cord Med*. 2004;27(4):311-8. Review, including discussion of preclinical data.

Stroke Treatment Academic Industry Roundtable <http://thestair.com/>

[Narayan RK, Michel ME, Ansell B, et al.](#)

Clinical trials in head injury.

*J Neurotrauma*. 2002 May;19(5):503-57. Review.

Are we speaking a common language?  
e.g., “Good Laboratory Practice”

From academic working groups:

Good Laboratory Practice to prevent “Bias at the Bench”

- Sample size calculation:
- Inclusion and exclusion criteria:
- Randomization:
- Allocation concealment:
- Reporting of animals excluded from analysis:
- Blinded assessment of outcome:
- Reporting potential conflicts of interest and study funding:

From FDA guidance:

Title 21CFR; Subchapter A, Part 58 “Good Laboratory Practice for Nonclinical Laboratory Studies”

- Organization and Personnel
- Facilities
- Equipment
- Testing Facilities Operation
- Test and Control Articles
- Protocol for and Conduct of a Nonclinical Laboratory Study
  - Written protocol,
  - clear objectives and methods,
  - identified test and control articles, named sponsor & test facility,
  - number, weight range, sex, supplier, species, strain (substrain), age of test system
  - identification procedure of test system
  - experimental design and methods to control bias
  - described diets, solvents and other reagents, acceptable contaminant levels
  - dosage level (mg/kg), method and frequency of administration
  - type and frequency of tests, analyses and measurement
  - records maintenance
  - protocol approvals, dates
  - statistical methods
  - any changes/revisions/reasons
- Records & Reports

[43 FR 60013, Dec. 22, 1978, as amended at 52 FR 33781, Sept. 4, 1987; 67 FR 9585, Mar. 4, 2002]

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=58.120>