Therapeutic Development in Academia and the Challenges of FDA-Regulated Research

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DISCLOSURES:

• I personally have no financial interests in the material presented
• NCH and the DDD has received funding in the form of grants and contracts from the following:
  • AveXis Inc.
  • Abeona Therapeutics
  • Prevail Therapeutics
  • Myonexus Therapeutics
  • Aduentes Therapeutics
OUTLINE

• Summarize the regulations governing development of investigational drugs using the AVX-101 as an example
• Define the role of FDA in review of drugs
• Understand what to expect during FDA inspections of clinical trials
• Identify key resources for academic researchers embarking on their therapeutic development odyssey
From discovery…

… to market

IND

NDA
WHAT IS AN IND?

Investigational New Drug

*Originally* provided permission to ship experimental drugs across state lines prior to market approval

An IND is a request for FDA authorization to administer an investigational new drug to humans.

FDA reviews for safety to unreasonable risk.
PURPOSE OF THE IND

It affirms manufacturing, pharmacology, and toxicology for human testing.

Requires trials be performed in accordance with Good Clinical Practice (GCP)

Provides FDA oversight

FDA’s review focuses on safety of human subjects and ensuring that the studies will produce useful information to assess safety and efficacy of the test product.
TRANSLATIONAL VALLEY OF DEATH
BALANCE BETWEEN RESEARCH AND COMMERCIALIZATION
THE BEGINNING
PROOF OF CONCEPT

LETTERS

Rescue of the spinal muscular atrophy phenotype in a mouse model by early postnatal delivery of SMN

Kevin D Foust1, Xueyong Wang2,3, Vicki L McGovern1,4, Lyndsey Braun1, Adam K Bevan1,4, Amanda M Haidet1,4, Thanh T Le5, Pablo R Morales6, Mark M Rich4, Arthur H M Burghes1,4 & Brian K Kaspar1,4

Spinal muscular atrophy (SMA), the most common autosomal recessive neurodegenerative disease affecting children, results in impaired motor neuron function1. Despite knowledge of the pathogenic role of decreased survival motor neuron (SMN) protein levels, efforts to increase SMN have not resulted in a treatment for patients. We recently demonstrated that self-complementary adeno-associated virus 9 (scAAV9) can infect ~60% of motor neurons when injected intravenously into neonatal mice2-4. Here we use scAAV9-mediated postnatal day 1 vascular gene delivery to replace SMN in SMA pups and rescue motor function, neuroanatomical physiology and life span. Treatment on postnatal day 5 results in partial correction, whereas postnatal day 10 treatment has little effect, suggesting a developmental period in which scAAV9 therapy has maximal benefit. Notably, we also show extensive scAAV9-mediated motor neuron transduction after injection into a newborn cynomolgus macaque. This demonstration that scAAV9 traverses the blood-brain barrier in a nonhuman primate emphasizes the clinical potential of scAAV9 gene therapy for SMA.

To determine transduction levels in SMA mice (SMMN2f/f; SMNΔ7-11; Smn−/−), we injected 5 × 10^{11} genomes of scAAV9-GFP or scAAV9-3SMN (n = 4/group) under control of the chicken-β-actin hybrid promoter into the facial vein on P1. We found that 42 ± 2% of lumbar spinal motor neurons expressed GFP (Fig. 1a and Supplementary Table 1) 10 d after injection. The levels of SMN in the brain, spinal cord and muscle in scAAV9-SMN-treated animals are shown in Figure 1b. SMN levels were increased in brain, spinal cord and muscle in treated animals, but were still lower than controls (SMMN2f/f; SMNΔ7-11; Smn−/−) in neural tissue (Supplementary Fig. 1). Spinal cord immunohistochemistry demonstrated expression of SMN within choline acetyltransferase (ChAT)-positive cells after scAAV9-SMN injection (Supplementary Fig. 2).

We next evaluated whether scAAV9-SMN treatment of SMA animals improved motor function5. SMA animals treated with scAAV9-SMN or scAAV9-GFP on P1 were assessed for the ability to right themselves compared to control and untreated animals (n = 10/group). Control animals could right themselves quickly, whereas the SMN- and GFP-treated SMA animals showed difficulty at P10. However, by P13, 80% of SMN-treated animals could right themselves compared with
AAV MEDIATED GENE THERAPY
SPINAL MUSCULAR ATROPHY

Leading Genetic Cause of Infant Mortality ~1 in 10,000 live births

SMA INDIVIDUAL

- SMN genes
  - SMN1
  - SMN2
- C to T creates ESS
- Multiple Copies of SMN2 modify Phenotype

Functional SMN Protein
Not-functional SMN Protein
NATURAL HISTORY OF SMA TYPE 1

90% of SMA Type 1 patients will not survive to the age of 2

*Survival = no death, or no need for ≥16-hr/day ventilation continuously for ≥2 weeks

Adapted from Finkel RS, et al. PNMCRN Neurology 2014;83:810–7

50% survival*
10.5 mos

25% survival*
13.6 mos

8% survival*
20 mos

% Event-free survival*

0 25 50 75 100

0 2 4 6 8 10 12 14 16 18 20 22 24

Onset of SMA Type 1 by 6 months
Symptoms may present

Holds head steady alone; brings hands to mouth
Rolls over in both directions
Sits alone; crawls
Cruises; may stand alone
Walks alone; may run and walk up stairs; eats with a spoon
Climb furniture alone; kicks and throws a ball

Milestone for a healthy infant
SMA Type 1 survival rates
AVX-101 OBD AND TIME DEPENDENCE

\[ \Delta 7 \text{ SMA Mouse} \]
- High Dose prolongs survival >400 days
- Low Dose reduces survival to 35 days

ASSESS GAPS IN DEVELOPMENT
RISK VS BENEFIT RATIO

Potential Harm          Potential Benefit

Potential Benefit          Potential Harm

Potential Benefit          Potential Harm
HOW MUCH PRECLINICAL DATA IS NEEDED?

*It depends:*

Influenced by

- Disease severity
- Disease population (rare vs prevalent)
- Alternative therapies
HOW MUCH PRECLINICAL DATA IS NEEDED?

1. Mild disease
2. Prevalent disease population
3. "Less" severe disease
4. "More" severe disease
5. "Less" effective therapies
6. Effective controls for phase I trials
7. Severe / lethal disease
8. No alternative therapy
9. Rare disease population

Amount of Data

HIGH

LOW
EARLY CONSULTATION WITH FDA

Proof Of Concept

Gap Analysis

Is a Pre-PreIND meeting Justified?
EARLY CONSULTATION

Come early, come often

Pre-preIND Meetings with FDA scheduled within 60 - 75 days following receipt of written request

Must provide Briefing Dossier (data packages) at time of submission of written request
PRODUCT DEVELOPMENT TEAM

Preclinical/POC  
(Material Experts)

Manufacturing

Pharmacology/Toxicology

Clinical

Charles River

Nationwide Children's Hospital
When your child needs a hospital, everything matters.

Ohio State University
College of Medicine
FIRST FDA INTERACTION

- Pre-preIND Meeting held in 2011 by teleconference
- Held within 2 mos of written request
- Questions on preclinical data, toxicology study design, animal models, target patient population of phase I trail.
- 14 pages of data plus copy of the Nature paper.
- Three Pharm/Tox Reviewers,
- One CMC/Product Reviewer, and
- One Clinical/Medical reviewer
- Received written minutes approx. 45 Days following
AGREEMENT ON IND DEVELOPMENT

Proof Of Concept

Gap Analysis ➔ PreIND Meeting

Is a Pre-PreIND meeting Justified?
PRE-IND MEETINGS

Formal meeting held prior to initiating pivotal P/T studies or scaled drug product manufacture. Extensive Briefing Dossier

- Aimed to finalize product development plan leading to successful IND
- Comprehensive Briefing Dossier submitted 30 days prior to meeting
- Meeting Scheduled within 60 days of receipt of written request
SECOND FDA INTERACTION

• Pre-IND meeting held late 2011 by teleconference
• Held within 60 days of written request
• Pre-IND briefing dossier submitted 30 days before mtg
• Presented safety observation data:
  • Mouse non-GLP studies
  • Rhesus macaque non-GLP studies
• Minutes provided on within 60 days of meeting
MEETING ATTENDED BY:

- Regulatory Project Manager
- Clinical, P/T, and Product Reviewers
- OTAT Branch Chief
- Pharm/Tox Director
- Pharm/Tox Branch Chief
- General Medicine Branch Chief
- Senior Pediatric Ethicist
- Office of Ped Therapies Health Scientist
- Fellows of the Commissioner's Office
The IND Track

preIND meeting minutes
  – Road map to IND
IND-enabling pharmacology and toxicology studies (GLP)
Produce product for clinical use (GMP)
Significant inflection point for “investors”
INITIATION OF PIVOTAL/IND-ENABLING PROGRAMS

Proof Of Concept

Gap Analysis → PreIND Meeting

Is a Pre-PreIND meeting Justified?

Value to Investing Partners

cGMP Production

IND-Enabling Toxicology Studies
NON-CLINICAL PHARMACOLOGY & TOXICOLOGY

Compliance with Good Laboratory Practices (GLP) – 21 CFR Part 58.

Typically outsourced – Contract Research Organizations (CROs)

Final Audited Study Report included as part of IND application
PHARMACOLOGY & TOXICOLOGY

Pharm/Tox Studies initiated shortly after preIND in 2012
Included observations out to 6 months post-injection
Took roughly 12 months to complete all analyses and issue final Study Report
cGMP MANUFACTURING

- Optimized harvest and transfection process
- Recovery and stabilization of crude virus from cell-culture systems
- Concentration, formulation, and filling of vectors

- Cell Expansion
  - Master cell bank and cell expansion in adherent cell culture
  - Transfection with 2-4 plasmid vectors

- Plasmid Transfection
  - Virus production phase post-transfection

- Virus Recovery
  - Virus extraction, clarification, and concentration
  - 1- or 2-Step purification process ahead of DS formulation

- Purification
  - 0.2μm filtration and vial filling

- Drug Product Production

- Purification on affinity, charge, and size-based processes

Hitchcock T. GeneticEngineering & Biotechnology News. 2017
WHEN TO SUBMIT IND

Addressed all preIND concerns raised by FDA
  • Review preIND minutes
Established Safe Dose Range (NOAEL)
Finalized plans for manufacturing (GMP)
Finalized plans for clinical trial
  • Established MED
IND APPLICATION

1. FDA Forms 1571
2. Table of Contents
3. Introductory Statement
4. General Information
   - Intended indication and future development plan
5. Investigators’ Brochure
IND APPLICATION

6. Protocol – Phase 1 trial
7. Chemistry, Manufacturing, and Control Data (CMC)
8. Pharmacology and Toxicology Information
9. Previous Human Experience
10. Additional Information
NEED FOR STUDY REPORTS

Provide FDA evidence product is “reasonably safe to conduct the proposed clinical investigation”
Inform design and stage of clinical trials (starting dose, escalation, regimen, and route)
Inform patient eligibility criteria and monitoring procedures
Identify risks that may be delayed or not resolved during human trials
ELEMENTS OF STUDY REPORTS

Detailed prospectively designed protocol
Recorded amendments to protocol
Recorded deviations from protocol
Results for all parameters (regardless if good or bad) for each individual animal on study

TRANSPARENCY
TRACEABILITY
SUBMISSION OF THE IND APPLICATION

Proof Of Concept

Gap Analysis → PreIND Meeting

Is a Pre-PreIND meeting Justified?

PreIND Meeting → cGMP Production

IND-Enabling Toxicology Studies → IND Application

Value to Investing Partners
IND SUBMISSION

Presented complete data packet on all preclinical studies
Detailed manufacturing plans, critical reagents and quality controls
Clinical Protocol for Phase 1/2a Open Label, Dose Escalation Study in SMA type 1 infants
Tabulated responses to all of FDA’s comments included in the 12-page meeting minutes from preIND meeting
FDA REVIEW OF IND

FDA will issue decision within **30 days** following receipt of IND

“May proceed” notice or “no news is good news,” your IND is now Active

*INDs are not “approved”*

“Clinical Hold” – order issued by FDA to delay or suspending clinical investigation
INITIATION OF CLINICAL TRIAL

Proof Of Concept → Gap Analysis → PreIND Meeting

Is a Pre-PreIND meeting Justified?

PreIND Meeting → cGMP Production → IND-Enabling Toxicology Studies

IBC Application → RAC Registration → IND Application

IRB Application → First Patient Dose

Value to Investing Partners
PHASE 1 SMA GENE THERAPY TRIAL

- 15 SMA patients have been enrolled
  - Ages 0.9 to 7.9 months
  - 9 patients in original IND with amendment for an additional 6

- IV infusion (AAV9) in peripheral vein
  - Cohort 1: $6.7 \times 10^{13}$ vg/kg, n=3
  - Cohort 2: $2.0 \times 10^{14}$ vg/kg, n=12

- Prednisolone for immune suppression one day prior to gene transfer
  - 1 mg/kg (modified after Pt 1)
90% of SMA Type 1 patients will not survive to the age of 2

*Survival = no death, or no need for ≥16-hr/day ventilation continuously for ≥2 weeks

Adapted from Finkel RS, et al. PNMCRN Neurology 2014;83:810–7

Onset of SMA Type 1 by 6 months
Symptoms may present

Milestone for a healthy infant
SMA Type 1 survival rates
Single-Dose Gene-Replacement Therapy for Spinal Muscular Atrophy


ABSTRACT
EVENT-FREE SURVIVAL DATA

Mendell JR et al. NEJM 2017

Results of Historical Study

<table>
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<tr>
<th>Event-free</th>
<th>75%</th>
<th>50%</th>
<th>25%</th>
<th>8%</th>
</tr>
</thead>
</table>

Age (mo)
IMPROVED MOTOR FUNCTION

Mendell JR et al. NEJM 2017
CURRENT DEVELOPMENT

Program licensed to AveXis Inc.

IND/Regulatory Responsibility transferred to AveXis in 2015

Currently in Pivotal Trials
Ongoing pre-BLA meetings

PRESS RELEASE

AveXis Announces Alignment with FDA on Next Steps Toward a BLA Submission for AVXS-101 in SMA Type 1

– Company to submit information requested by FDA to the IND on an ongoing basis –

– AveXis plans to request a pre-BLA meeting in Q2 2018 –

– Conference call and webcast today at 4:30 pm EST –
Our STN: BL 125610/0

Spark Therapeutics, Inc.
Attention: Jim Wang, MBA, PhD
3737 Market Street, Suite 1500
Philadelphia, PA 19104

Dear Dr. Wang:

Please refer to your Biologies License Application (BLA) for voretigene neparvovec-rzyl dated April 26, 2017, and received May 16, 2017, submitted under section 351(a) of the Public Health Service Act (PHS Act).

 LICENSING

We are issuing Department of Health and Human Services U.S. License No. 2056 to Spark Therapeutics, Inc., Philadelphia, PA, under the provisions of section 351(a) of the PHS Act controlling the manufacture and sale of biological products. The license authorizes you to introduce or deliver for introduction into interstate commerce, those products for which your company has demonstrated compliance with establishment and product standards.

December 19, 2017
BLA APPROVAL
OUTLINE

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• Define the role of FDA in review of drugs
• Understand what to expect during FDA inspections of clinical trials
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WHO DOES FDA INSPECT?

Sponsor-Investigator
Clinical Investigator
Sponsor
Facilities (GMP, GLP, GCP)
Institutional Review Board
Contract Research Organizations (CROs)
WHY DOES FDA INSPECT?

Clinical sites inspections:

• Pre-approval inspections
• Routine inspections (BIMO)
• Compliance follow-up inspections (post 483)
• “For Cause” inspections
SCENARIO: FDA CRIMINAL INVESTIGATIONS

Paul Kornak, Study Coordinator
Guilty of criminally negligent homicide
Falsely representing results of blood chemistry analyses in a chemotherapy drug trial.
SCENARIO: FDA CRIMINAL INVESTIGATIONS

Carl M. Steubing
WWII Veteran
Was not eligible for the clinical trial
Received multiple treatments
Died due study treatment shortly after
PHONE TREE NOTIFICATION

Key stake holders
  • Compliance office
  • Clinical trials office, nurses/coordinators
  • Pharmacy
  • Department heads
  • Contributing laboratories
  • Study Sponsor for Industry trials
Verify key stake holders availability
Arrange for a private conference room
INSPECTIONS

Primarily review of documents

• Not an interview with personnel
• May ask clarification questions

Includes but not limited to:

• Regulatory Records
• Subject Data
• Procedures to assure adherence to FDA and GCP requirements
INSPECTIONS

May have implications for investigator if misconduct is found
If not documented, it didn’t happen
Investigator-oriented inspection:
  • Typically occur after complaints of known or suspected misconduct
DAY OF INSPECTION

Inspector will arrive at front desk/lobby.
Display FDA credentials
Present Form FDA 482
• Notice of Inspection
• Authority to enter and inspect premises per Section 704 of FD&C Act

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INVESTIGATIONS OPERATIONS MANUAL 2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

2. NAME AND TITLE OF INDIVIDUAL
4. FIRM NAME
6. NUMBER AND STREET
7. CITY AND STATE & ZIP CODE
3. DATE
5. PHONE # & AREA CODE

Notice of Inspection is hereby given pursuant to Section 704(a)(1) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 374(a)(1)). Written request is hereby given to access and/or copy the records described below, pursuant to the Federal Food, Drug and Cosmetic Act, Section 414(a) [21 U.S.C. 351c] and Title 21 Code of Federal Regulations, Section 1.361.

Applicable portions of Sections 704 and 414 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 374 and 351c) and Title 21 of the Code of Federal Regulations, are quoted below:

Sec. 704 (a)(1) For purposes of enforcement of this Act, officers or employees duly designated by the Secretary, upon presenting appropriate credentials and a written notice to the owner, operator, or agent in charge, are authorized (A) to enter, at reasonable times, any factory, warehouse, establishment in which food, drugs, devices, or cosmetics are manufactured, processed, packed, or held, for introduction into interstate commerce or after such introduction, or to enter any vehicle being used to transport or hold such food, drugs, devices, or cosmetics in interstate commerce; and (B) to inspect, at reasonable times and within reasonable limits and in a reasonable manner, such factory, warehouse, establishment, or vehicle and all pertinent equipment, finished and unfinished materials, containers and labeling therein, in the case of any person (excluding farms and restaurants) who manufactures, process, packs, transports, distributes, holds, or imports food, the inspection shall extend to all records and other information described in section 414, when the standard for records under paragraph (1) or (2) of section 414(a) applies, subject to the limitations established in section 414(d), in the case of any factory, warehouse, establishment, or consulting
INSPECTION “DO’s”

Present business card
Be prepared, organized, calm (refresh your memory about the protocol requirements and your role if uncertain)
Be professional, confident
Have note-taker present at all times during the interview
Leave as soon as the interview is over
Listen carefully and repeat a question or ask it to be repeated if necessary
Channel all requests for documents through the escort or other designee
Answer completely, directly, honestly
INSPECTION “DO NOT’s”

Guess, make up an answer or LIE

Do not volunteer more information than necessary to completely answer the question

Don’t speculate! It is okay to say you will find the information and give it to the investigator later.

Don’t conduct the inspection for the investigator

Never question the investigator’s authority, argue or raise your voice

Don’t provide documents with post-it notes, etc

Do not agree or volunteer to change a procedure or practice without first discussing with Management or conferring with Compliance.
EXIT INTERVIEW

At end of Inspection

• Form FDA 483
• Inspectional Observations (if applicable)
• Provide feedback about observations
COMMON DEFICIENCIES

• Failure to follow protocol or investigator statement on 1572
• Protocol Deviations
• Inadequate recordkeeping
• Inadequate accountability of the investigational product
• Inadequate subject protections
  • Including informed consent issues
AFTER THE INSPECTION

Clinical Investigator responds to Form 483 within 15 business days

- Describe corrective actions, present additional information (CAPA!!)

FDA Investigator prepares Establishment Inspection Report (EIR)

- Filed to FDA along with 483 and all materials
- FDA will send letter to Clinical Investigator
AFTER THE INSPECTION

Letter to Clinical Investigator:

• Basic compliance and no violations
  • Letter not always sent when no significant deviations are found

• Information or Untitled Letter:
  • Deviations noted but do not meet threshold of regulatory significance

• Warning Letter:
  • Identifies serious deviations. Includes a request for correction and written response
  • Note: warning letters are posted on FDA website
OTHER POSSIBLE ACTIONS BY FDA

Serious violations may result in:

- Initiation of investigator disqualification process
- Rejection of study data
- Deficiency Letters
- Withdrawal of market application
- Civil penalties
- Seizure of product
- Injection
- Prosecution
OUTLINE

• Summarize the regulations governing development of investigational drugs using the AVX-101 as an example
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RESOURCES

FDA Learning Portal for Students, Academia, and Industry

Welcome to FDA’s learning portal, which provides education and resources related to FDA’s regulatory, product quality, and safety responsibilities. In each section you’ll find educational materials such as lectures and courses as well as web pages related to the particular topic.

Education and Resources by Subject
RESOURCES

[www.fda.gov](http://www.fda.gov)  Search “Investigator-Initiated IND”

**Investigator-Initiated Investigational New Drug (IND) Applications**

This table provides links to information for investigators about submitting Investigational New Drug (IND) applications to FDA. The resources for application reporting and applications procedures apply to IND applications for both clinical research and clinical treatment.

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RESOURCES

http://www.fda.gov/RegulatoryInformation/Guidances/default.htm

Search for FDA Guidance Documents

The table below lists all official FDA Guidance Documents and other regulatory guidance. You can search for documents using key words, and you can narrow or filter your results by product, date issued, FDA organizational unit, type of document, subject, draft or final status, and comment period.

This feature is provided to give a convenient way to search for all FDA guidance documents from a single location.

If you cannot find the document you're looking for here, you can browse separate collections of guidance documents by topic.

Search All Guidance Documents:

More Information

- About FDA guidance documents
- Browse guidance document collections by topic
- Commenting on guidance documents
- Report on good guidance practices
- FDA acronyms and abbreviations
CAMPUS RESOURCES

www.nationwidechildrens.org/ddd

https://ccts.osu.edu/content/indide-support
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