FDA CBER Gene Therapy Data Base: Preliminary Analysis of a Work in Progress

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Food and Drug Administration

Structure of U.S. Government

- Legislative Branch- House of Representatives and Senate- *writes law*
- Executive Branch- includes Departments and Agencies- *interprets and enforces law*
- Supreme Court- 9 justices- one Chief and 8 Associates- *determines validity of law*

Fundamentals of Government

- Law (=Act, Statute)- developed and passed by Legislative Branch (Congress), signed by President. Published in the United States Code (USC). Effective until changed or expired.
- Regulation (=Rule)- developed and published by Executive Branch. Published in the Code of Federal Regulations (CFR). Binding until revised or withdrawn.
- Guidance: Issued by individual agencies to reflect current thinking. Published in the Federal Register (FR). Not binding.

Components of the U.S. Department of Health and Human Services

(partial listing)

- Office of the Secretary
- Bureau of Prisons
- Indian Health Service
- Office for Human Research Protection
- National Institutes of Health (NIH)
- Centers for Disease Control and Prevention (CDC)
- Food and Drug Administration (FDA)
- Health Resources Services Administration
- Center for Medicare and Medicaid Services

Structure of the U.S. Food and Drug Administration

- Office of the Commissioner
- Center for Food Safety and Nutrition
- Center for Veterinary Medicine
- Center for Drugs
- Center for Biologics
- Center for Devices and Radiologic Health

FDA Authority

- Derived from multiple laws and regulations

  For example

  - Food, Drug & Cosmetic Act
  - Public Health Service Act
- Focus is on product and product use

Evolution of Drug Regulation

- Three fundamental principles
  - Adequate and accurate label
  - Safety
  - Efficacy
- Evolved over 20th century with legislation partially in response to health crises in children

Safety as a founding principle

- Biologics-1903
  - Tetanus toxoid
- Drugs-1938
  - Sulfanilamide

Monitoring programs

- MedWatch- General Reporting Portal
- AERS-Adverse Event Reporting System for marketed drugs
- VAERS-Vaccine….
- MDAERS-Medical Device…
- Food Safety

MedWatch

FDA U.S. Food and Drug Administration

FDA Home Page | About Medwatch | Contact MedWatch | MedWatch Partners

MEDWATCH The FDA Safety Information and Adverse Event Reporting Program

Search MedWatch

MedWatch Home | Safety Information | Submit Report | How To Report | Download Forms | Join the E-list

Join the E-list
Get safety alerts by e-mail

What's New

Domperidone - Healthcare professionals and breastfeeding women warned not to use an unapproved drug, domperidone, to increase milk production (lactation). The agency is concerned with the potential public health risks associated with domperidone.
(Posted 6/10/2004)

Roche Diagnostics Tecan Clinical Workstation - Class I Recall due to a software error in the workstation software that may cause a mismatch among patient samples and test results, resulting in false positive and false negative results. This could lead to mistreatment and unneeded exposure to antibiotics.
(Posted 6/9/2004)

Crestor (rosuvastatin) - Public Health Advisory notified healthcare professionals of a revised package insert for use in the European Union, in response to adverse event reports in patients receiving Crestor. The labeling highlighted certain patient populations who may be at an increased risk for serious muscle toxicity (myopathy).
(Posted 6/9/2004)

Arlo MINSTREL Patient Lifts - Class I recall due to two mechanical

Welcome to MedWatch, your Internet gateway for timely safety information on the drugs and other medical products regulated by the U.S. Food and Drug Administration.

Safety Information

Medical Product Reporting

A Message About HIPAA Compliance for Reporters to FDA MedWatch

MedWatch

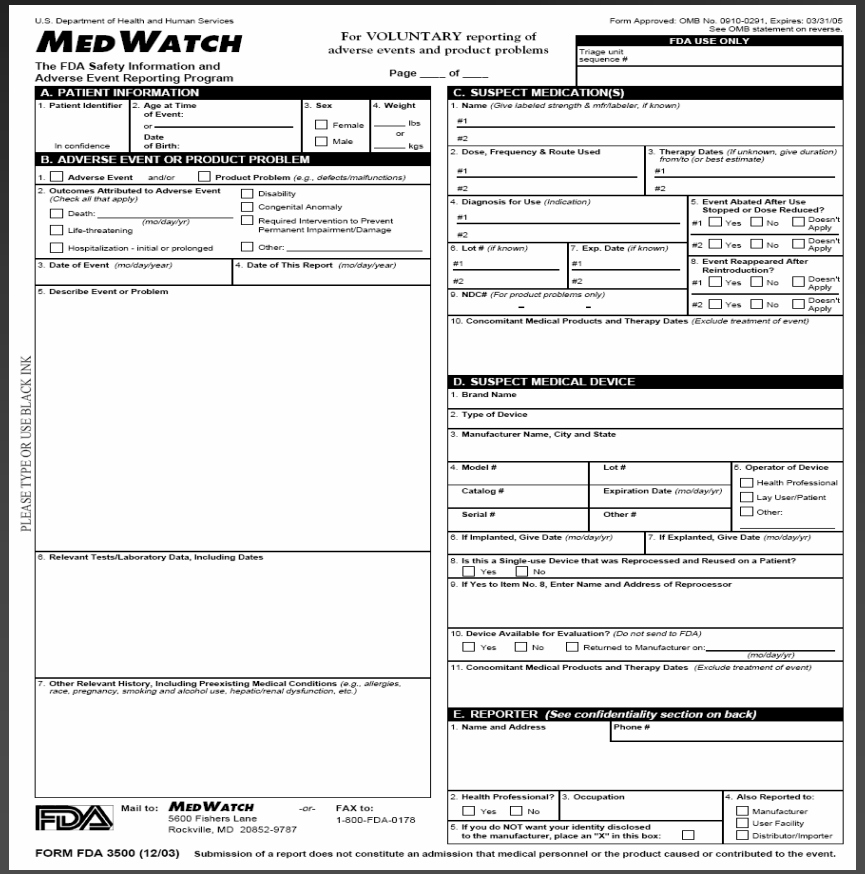
- Spontaneous events
- Multiple input sources
- Multiple reporters

What to report

Report SERIOUS adverse events. An event is serious when the patient outcome is:

- Death
- Life-threatening *(real risk of dying)*
- Hospitalization *(initial or prolonged)*
- Disability *(significant, persistent or permanent)*
- Congenital anomaly
- Required intervention to prevent permanent impairment or damage

3500-voluntary 3500A-mandatory



U.S. Department of Health and Human Services

MEDWATCH

The FDA Safety Information and Adverse Event Reporting Program

For VOLUNTARY reporting of adverse events and product problems

Form Approved: OMB No. 0910-0291, Expires: 03/31/05
See OMB statement on reverse.

Page ____ of ____

FDA USE ONLY

Triage unit
sequence #

PLEASE TYPE OR USE BLACK INK

A. PATIENT INFORMATION

1. Patient Identifier — In confidence
2. Age at Time of Event: or Date of Birth:
3. Sex — ☐ Female ☐ Male
4. Weight — ____ lbs or ____ kgs

B. ADVERSE EVENT OR PRODUCT PROBLEM

1. ☐ Adverse Event and/or ☐ Product Problem *(e.g., defects/malfunctions)*
2. Outcomes Attributed to Adverse Event *(Check all that apply)*
   ☐ Death: _____ *(mo/day/yr)*
   ☐ Life-threatening
   ☐ Hospitalization - initial or prolonged
   ☐ Disability
   ☐ Congenital Anomaly
   ☐ Required Intervention to Prevent Permanent Impairment/Damage
   ☐ Other: _____
3. Date of Event *(mo/day/year)*
4. Date of This Report *(mo/day/year)*
5. Describe Event or Problem
6. Relevant Tests/Laboratory Data, Including Dates
7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)*

C. SUSPECT MEDICATION(S)

1. Name *(Give labeled strength & mfr/labeler, if known)*
   #1
   #2
2. Dose, Frequency & Route Used
   #1
   #2
3. Therapy Dates *(If unknown, give duration)* from/to (or best estimate)
   #1
   #2
4. Diagnosis for Use *(Indication)*
   #1
   #2
5. Event Abated After Use Stopped or Dose Reduced?
   #1 ☐ Yes ☐ No ☐ Doesn't Apply
   #2 ☐ Yes ☐ No ☐ Doesn't Apply
6. Lot # *(if known)*
   #1
   #2
7. Exp. Date *(if known)*
   #1
   #2
8. Event Reappeared After Reintroduction?
   #1 ☐ Yes ☐ No ☐ Doesn't Apply
   #2 ☐ Yes ☐ No ☐ Doesn't Apply
9. NDC# *(For product problems only)*
   –
   –
10. Concomitant Medical Products and Therapy Dates *(Exclude treatment of event)*

D. SUSPECT MEDICAL DEVICE

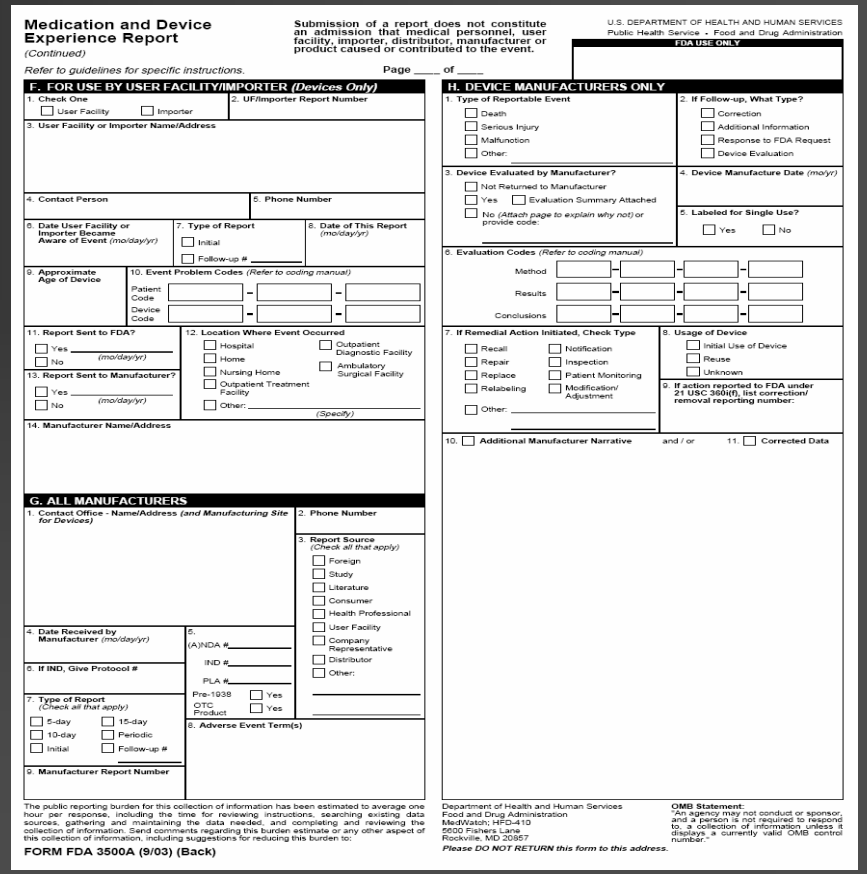
1. Brand Name
2. Type of Device
3. Manufacturer Name, City and State
4. Model # / Catalog # / Serial # / Lot # / Expiration Date *(mo/day/yr)* / Other #
5. Operator of Device
   ☐ Health Professional
   ☐ Lay User/Patient
   ☐ Other: _____
6. If Implanted, Give Date *(mo/day/yr)*
7. If Explanted, Give Date *(mo/day/yr)*
8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
   ☐ Yes ☐ No
9. If Yes to Item No. 8, Enter Name and Address of Reprocessor
10. Device Available for Evaluation? *(Do not send to FDA)*
    ☐ Yes ☐ No ☐ Returned to Manufacturer on: _____ *(mo/day/yr)*
11. Concomitant Medical Products and Therapy Dates *(Exclude treatment of event)*

E. REPORTER *(See confidentiality section on back)*

1. Name and Address
   Phone #
2. Health Professional? ☐ Yes ☐ No
3. Occupation
4. Also Reported to:
   ☐ Manufacturer
   ☐ User Facility
   ☐ Distributor/Importer
5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☐

Mail to: MEDWATCH 5600 Fishers Lane Rockville, MD 20852-9787 -or- FAX to: 1-800-FDA-0178

FORM FDA 3500 (12/03) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.



Medication and Device Experience Report

(Continued)

Refer to guidelines for specific instructions.

Submission of a report does not constitute an admission that medical personnel, user facility, importer, distributor, manufacturer or product caused or contributed to the event.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service - Food and Drug Administration

FDA USE ONLY

Page ____ of ____

F. FOR USE BY USER FACILITY/IMPORTER *(Devices Only)*

1. Check One ☐ User Facility ☐ Importer
2. UF/Importer Report Number
3. User Facility or Importer Name/Address
4. Contact Person
5. Phone Number
6. Date User Facility or Importer Became Aware of Event *(mo/day/yr)*
7. Type of Report ☐ Initial ☐ Follow-up # _____
8. Date of This Report *(mo/day/yr)*
9. Approximate Age of Device
10. Event Problem Codes *(Refer to coding manual)*
    Patient Code
    Device Code
11. Report Sent to FDA? ☐ Yes _____ *(mo/day/yr)* ☐ No
12. Location Where Event Occurred
    ☐ Hospital ☐ Outpatient Diagnostic Facility
    ☐ Home ☐ Nursing Home ☐ Ambulatory Surgical Facility
    ☐ Outpatient Treatment Facility
    ☐ Other: _____ *(Specify)*
13. Report Sent to Manufacturer? ☐ Yes _____ *(mo/day/yr)* ☐ No
14. Manufacturer Name/Address

G. ALL MANUFACTURERS

1. Contact Office - Name/Address *(and Manufacturing Site for Devices)*
2. Phone Number
3. Report Source *(Check all that apply)*
   ☐ Foreign ☐ Study ☐ Literature ☐ Consumer ☐ Health Professional ☐ User Facility ☐ Company Representative ☐ Distributor ☐ Other: _____
4. Date Received by Manufacturer *(mo/day/yr)*
5. (A)NDA #_____ IND #_____ PLA #_____ Pre-1938 ☐ Yes OTC Product ☐ Yes
6. If IND, Give Protocol #
7. Type of Report *(Check all that apply)*
   ☐ 5-day ☐ 15-day ☐ 10-day ☐ Periodic ☐ Initial ☐ Follow-up # _____
8. Adverse Event Term(s)
9. Manufacturer Report Number

H. DEVICE MANUFACTURERS ONLY

1. Type of Reportable Event
   ☐ Death ☐ Serious Injury ☐ Malfunction ☐ Other: _____
2. If Follow-up, What Type?
   ☐ Correction ☐ Additional Information ☐ Response to FDA Request ☐ Device Evaluation
3. Device Evaluated by Manufacturer?
   ☐ Not Returned to Manufacturer ☐ Yes ☐ Evaluation Summary Attached ☐ No *(Attach page to explain why not)* or provide code: _____
4. Device Manufacture Date *(mo/yr)*
5. Labeled for Single Use? ☐ Yes ☐ No
6. Evaluation Codes *(Refer to coding manual)*
   Method
   Results
   Conclusions
7. If Remedial Action Initiated, Check Type
   ☐ Recall ☐ Notification ☐ Repair ☐ Inspection ☐ Replace ☐ Patient Monitoring ☐ Relabeling ☐ Modification/Adjustment ☐ Other: _____
8. Usage of Device
   ☐ Initial Use of Device ☐ Reuse ☐ Unknown
9. If action reported to FDA under 21 USC 360i(f), list correction/removal reporting number:
10. ☐ Additional Manufacturer Narrative and / or 11. ☐ Corrected Data

The public reporting burden for this collection of information has been estimated to average one hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
MedWatch; HFD-410
5600 Fishers Lane
Rockville, MD 20857

Please DO NOT RETURN this form to this address.

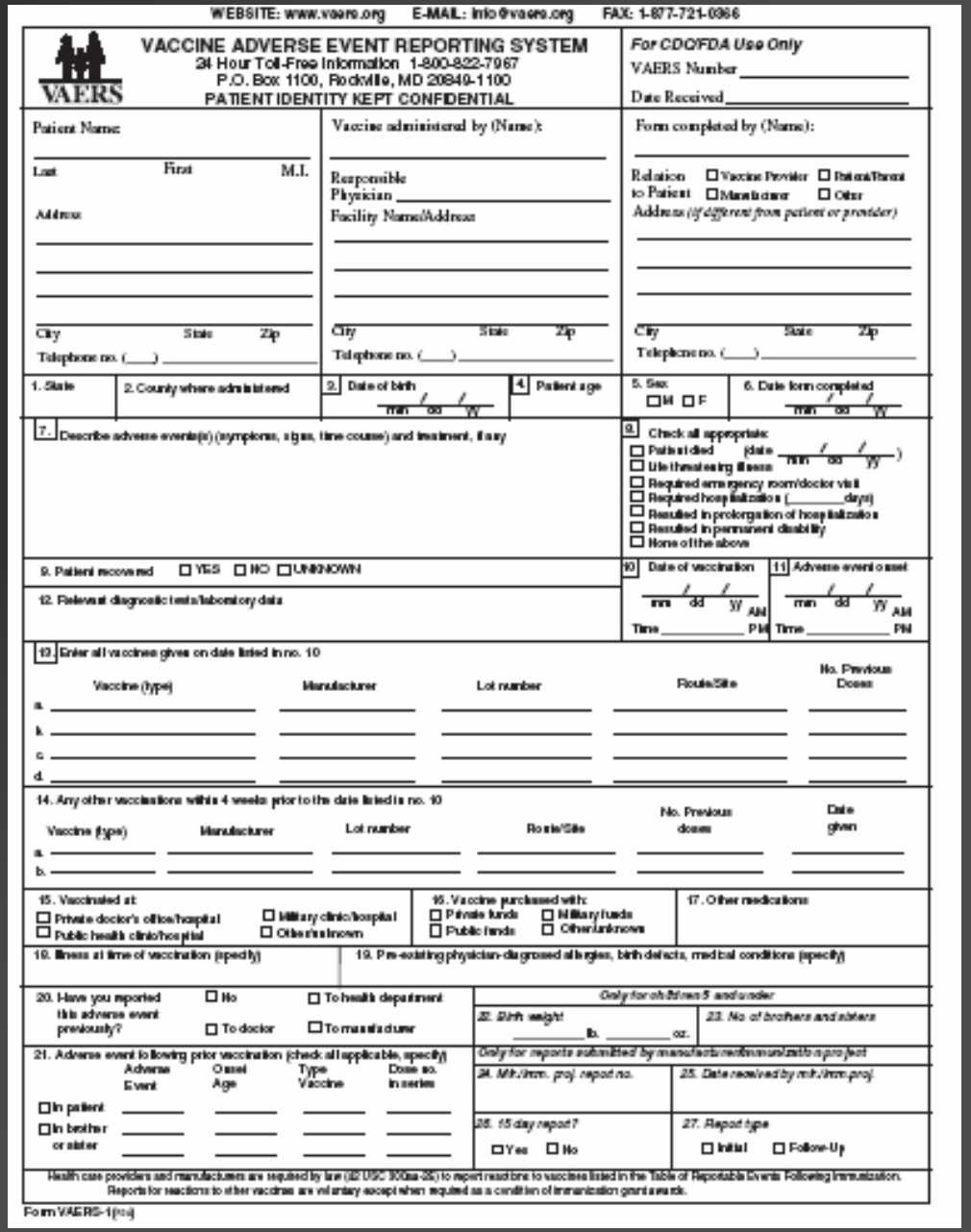
OMB Statement:
"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number."

FORM FDA 3500A (9/03) (Back)

Vaccine Adverse Event Reporting System (VAERS)

- The Vaccine Adverse Event Reporting System (VAERS) is a cooperative program for vaccine safety of the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA). VAERS is a post-marketing safety surveillance program, collecting information about adverse events (possible side effects) that occur after the administration of US licensed vaccines.
- VAERS provides a nationwide mechanism by which adverse events following immunization (AEFI) may be reported, analyzed and made available to the public. The VAERS Web site also provides a vehicle for disseminating vaccine safety-related information to parents/guardians, healthcare providers, vaccine manufacturers, state vaccine programs, and other constituencies.

VAERS Reporting Form



WEBSITE: www.vaers.org E-MAIL: info@vaers.org FAX: 1-877-721-0366

VACCINE ADVERSE EVENT REPORTING SYSTEM
24 Hour Toll-Free Information 1-800-822-7967
P.O. Box 1100, Rockville, MD 20849-1100
PATIENT IDENTITY KEPT CONFIDENTIAL

VAERS

For CDC/FDA Use Only
VAERS Number
Date Received

Patient Name: Last First M.I.
Address:
City State Zip
Telephone no. (___)

Vaccine administered by (Name):
Responsible Physician
Facility Name/Address:
City State Zip
Telephone no. (___)

Form completed by (Name):
Relation to Patient ☐ Vaccine Provider ☐ Patient/Parent ☐ Manufacturer ☐ Other
Address (if different from patient or provider)
City State Zip
Telephone no. (___)

1. State | 2. County where administered | 3. Date of birth mm dd yy | 4. Patient age | 5. Sex ☐ M ☐ F | 6. Date form completed mm dd yy

7. Describe adverse event(s) (symptoms, signs, time course) and treatment, if any

8. Check all appropriate:
☐ Patient died (date mm dd yy)
☐ Life-threatening illness
☐ Required emergency room/doctor visit
☐ Required hospitalization (_____ days)
☐ Resulted in prolongation of hospitalization
☐ Resulted in permanent disability
☐ None of the above

9. Patient recovered ☐ YES ☐ NO ☐ UNKNOWN

10. Date of vaccination mm dd yy AM PM Time

11. Adverse event onset mm dd yy AM PM Time

12. Relevant diagnostic tests/laboratory data

13. Enter all vaccines given on date listed in no. 10

	Vaccine (type)	Manufacturer	Lot number	Route/Site	No. Previous Doses
a.					
b.					
c.					
d.					

14. Any other vaccinations within 4 weeks prior to the date listed in no. 10

	Vaccine (type)	Manufacturer	Lot number	Route/Site	No. Previous doses	Date given
a.						
b.						

15. Vaccinated at:
☐ Private doctor's office/hospital ☐ Military clinic/hospital
☐ Public health clinic/hospital ☐ Other/unknown

16. Vaccine purchased with:
☐ Private funds ☐ Military funds
☐ Public funds ☐ Other/unknown

17. Other medications:

18. Illness at time of vaccination (specify)

19. Pre-existing physician-diagnosed allergies, birth defects, medical conditions (specify)

20. Have you reported this adverse event previously? ☐ No ☐ To health department ☐ To doctor ☐ To manufacturer

Only for children 5 and under
22. Birth weight _____ lb. _____ oz.
23. No. of brothers and sisters

21. Adverse event following prior vaccination (check all applicable, specify)

	Adverse Event	Onset Age	Type Vaccine	Dose no. in series
☐ In patient				
☐ In brother or sister				

Only for reports submitted by manufacturer/immunization project
24. Mfr./imm. proj. report no.
25. Date received by mfr./imm. proj.
26. 15 day report? ☐ Yes ☐ No
27. Report type ☐ Initial ☐ Follow-Up

Health care providers and manufacturers are required by law (42 USC 300aa-25) to report reactions to vaccines listed in the Table of Reportable Events Following Immunization. Reports for reactions to other vaccines are voluntary except when required as a condition of immunization grant awards.

Form VAERS-1 (rev)

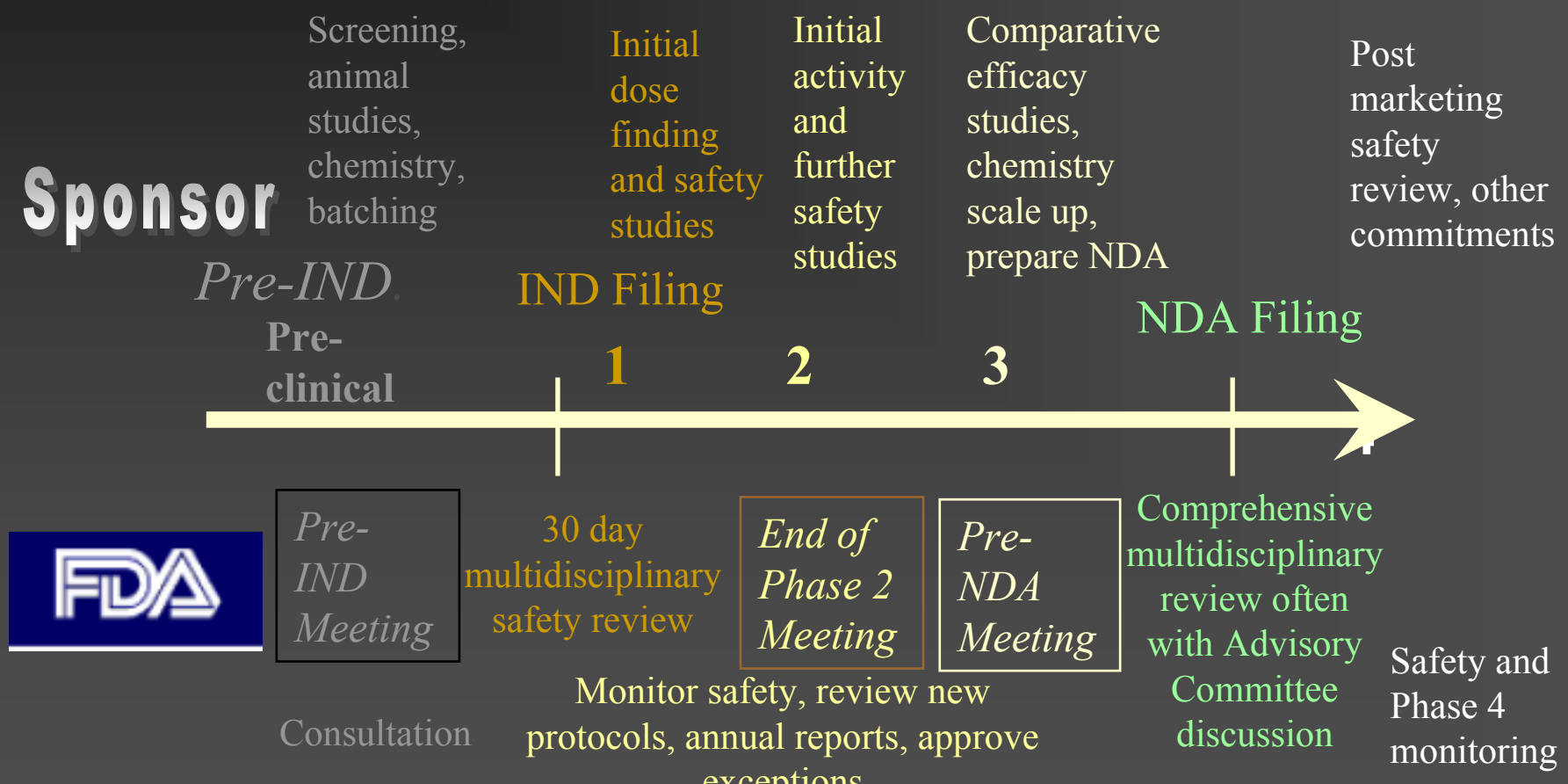
Standards for reporting

- MeDDRA- Medical Dictionary for Regulatory Activities
- Others?

Outcomes of Post Marketing Adverse Event Reports

- Epidemiological analysis and publication
- Label changes
- Warning letters
- Withdrawal from marketing

Overview of Therapeutic Development



Investigational New Drug (IND) Application

- To use an investigational agent in humans an IND must be filed and the FDA grants permission for studies to proceed
- IND filing is also required for the use of approved products that are being studied in new populations or in regimens where the risks are unknown.

IND Regulations

- The Code of Federal Regulations has a section devoted to INDs (21 CFR 312)
- The IND process is fundamentally designed to protect the vulnerable (healthy volunteers or patients)
- The IND process provides Federal oversight of clinical investigations

IND Clinical Hold

- Complete Hold= No studies may proceed
- Partial Hold= A subset of the studies may proceed

Clinical Hold Regulations
21 CFR 312.42 (b)

- For phase 1 studies
  - (i) Human subjects are or would be exposed to an unreasonable and significant risk of illness or injury;
  - (ii) The clinical investigators named in the IND are not qualified by reason of their scientific training and experience to conduct the investigation described in the IND;
  - (iii) The investigator brochure is misleading, erroneous, or materially incomplete; or
  - (iv) The IND does not contain sufficient information required under Sec. 312.23 to assess the risks to subjects of the proposed studies.
  - (v) Exclusion based on gender

Clinical Hold Regulations
21 CFR 312.42 b

- For phase 2 and 3 studies
  - Any of the criteria that apply to Phase 1 studies or
  - The plan or protocol for the investigation is clearly deficient in design to meet its stated objectives.

Clinical Hold Regulations
21 CFR 312.42 b

For a proposed or ongoing investigation that is not designed to be adequate and well-controlled

- Any of the previous conditions for Phase 1, 2 or 3 studies
- If the study is impeding enrollment in, or otherwise interfering with the conduct or completion of, a study that is designed to be an adequate and well-controlled investigation of the same or another investigational drug; or
- If insufficient quantities of the investigational drug exist to adequately conduct both the investigation that is not designed to be adequate and well-controlled and the investigations that are designed to be adequate and well-controlled

Clinical Hold Regulations
21 CFR 312.42 b

For a proposed or ongoing investigation that is not designed to be adequate and well-controlled

- Previous studies in adequate and well controlled studies strongly suggest lack of effectiveness
- Another drug under investigation or approved for the same indication and available to the same patient population has demonstrated a better potential benefit/risk balance
- Drug has already received marketing approval for the same indication in the same patient population

Clinical Hold Regulations
21 CFR 312.42 b

For a proposed or ongoing investigation that is not designed to be adequate and well-controlled

- The sponsor of the study that is designed to be adequate and well controlled investigation is not actively pursuing marketing approval with due diligence
- The Commissioner determines that it would not be in the public interest for the study to be conducted or continued

Clinical Hold

- The most common reasons for not allowing a protocol to proceed (clinical hold) are
  - Insufficient detail to evaluate the proposed study
  - Starting Dose: Insufficient data to support the intended starting dose
  - Dose escalation: Proposed dose increases too aggressive
  - Safety monitoring: Anticipated toxicities inadequately monitored
  - Patient population: Eligibility criteria include patients that have other therapeutic options that are documented to prolong life

Pre marketing Adverse Event Reporting

- Regulated for drugs and biologics by 21 CFR 312.32 -- IND Safety Reports
- No FDA comprehensive adverse event analytic system in place
- In addition reporting requirements to Institutional Review Boards

Recombinant DNA Advisory Committee

- Established in 1974 to review Federally funded research
- Technical advice committee with 15 members, one third non-scientists
- Expansion of Institutional Biosafety Committees ensures compliance with NIH guidelines at local level
- Review commercial as well as academic protocols

Gene Therapy Definition

- Manipulation of genetic material for therapeutic use in humans through recombinant techniques
- First guidelines published in 1976

Criteria to appear before RAC

- New vectors and new gene delivery systems
- New diseases
- Unique applications of gene transfer
- Other matters requiring public discussion

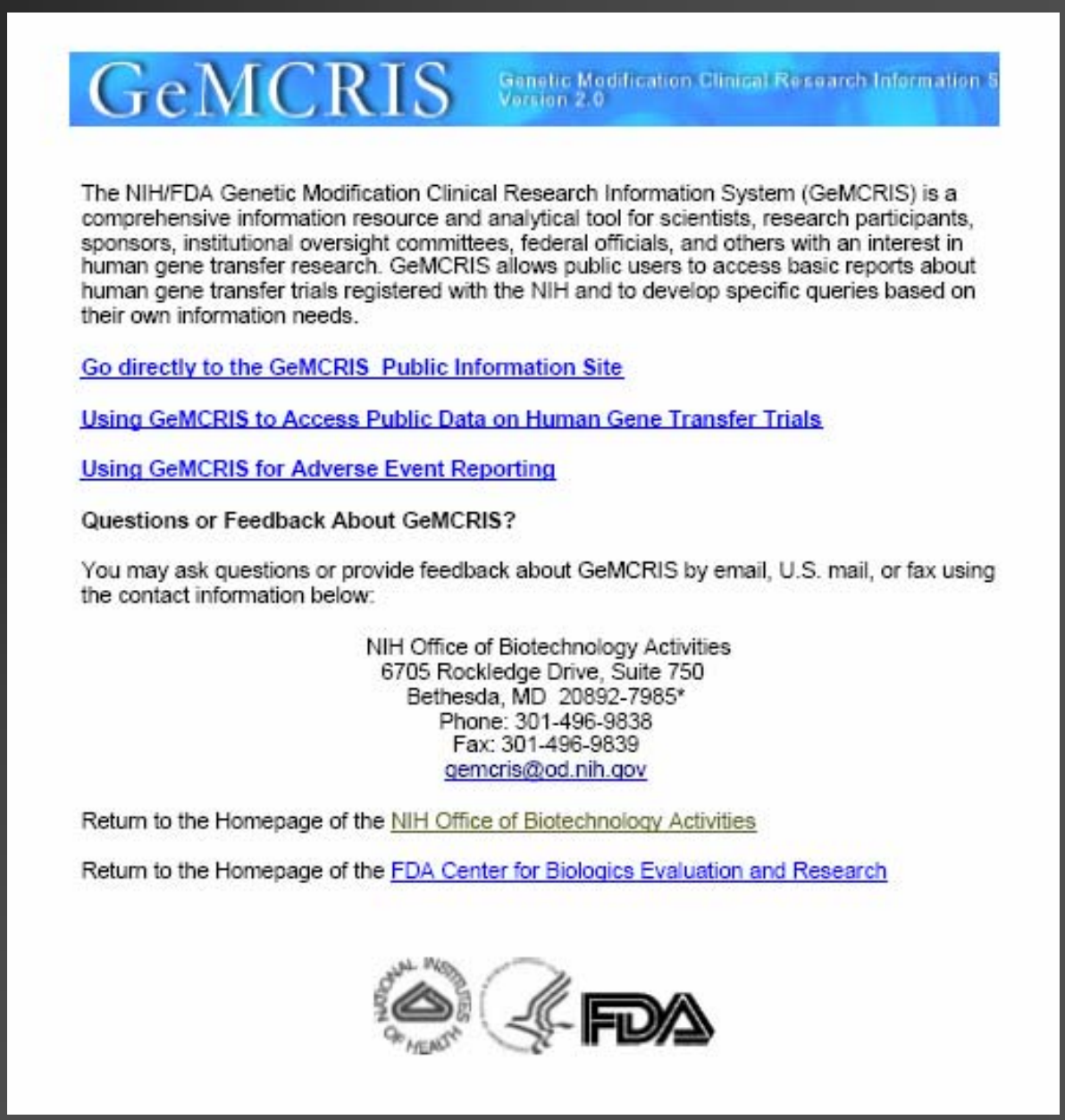
NIH Office of Biotechnology Activities

- Recombinant DNA and Gene Transfer
  - Monitors scientific progress in basic and clinical research
  - Recombinant DNA Advisory Committee
  - GeMCRIS- Genetic Modification Clinical Research Information System
- National Science Advisory Board for Biosecurity
- Secretary's Advisory Committee on Genetics
- Secretary's Advisory Committee on Xenotransplantation

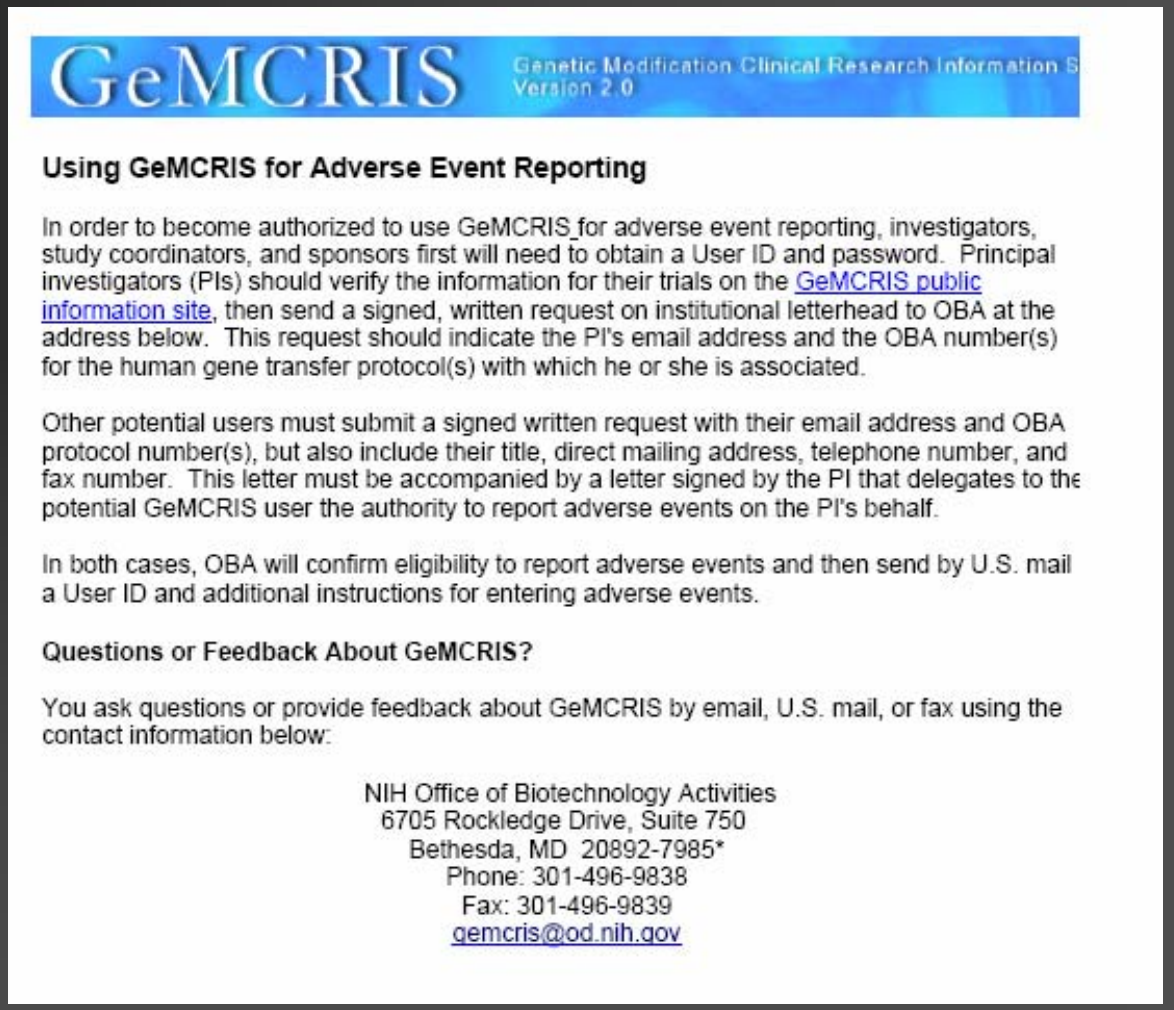
GeMCRIS

- Information about protocols registered with NIH
  - Medical conditions
  - Institutions
  - Investigators
  - Products
  - Route of delivery
  - Protocol summaries
- In collaboration with FDA

GeMCRIS Website



GeMCRIS Adverse Event Reporting



GeMCRIS Genetic Modification Clinical Research Information S
Version 2.0

Using GeMCRIS for Adverse Event Reporting

In order to become authorized to use GeMCRIS for adverse event reporting, investigators, study coordinators, and sponsors first will need to obtain a User ID and password. Principal investigators (PIs) should verify the information for their trials on the GeMCRIS public information site, then send a signed, written request on institutional letterhead to OBA at the address below. This request should indicate the PI's email address and the OBA number(s) for the human gene transfer protocol(s) with which he or she is associated.

Other potential users must submit a signed written request with their email address and OBA protocol number(s), but also include their title, direct mailing address, telephone number, and fax number. This letter must be accompanied by a letter signed by the PI that delegates to the potential GeMCRIS user the authority to report adverse events on the PI's behalf.

In both cases, OBA will confirm eligibility to report adverse events and then send by U.S. mail a User ID and additional instructions for entering adverse events.

Questions or Feedback About GeMCRIS?

You ask questions or provide feedback about GeMCRIS by email, U.S. mail, or fax using the contact information below:

NIH Office of Biotechnology Activities
6705 Rockledge Drive, Suite 750
Bethesda, MD 20892-7985*
Phone: 301-496-9838
Fax: 301-496-9839
gemcris@od.nih.gov

National Cancer Institute

- AdEERS- Adverse Event Expedited Reporting System
- Internet based remote data entry
- Uses Common Terminology Criteria for Adverse Events version 3.0, not MEDDRA

Origins of Gene Therapy Adverse Event Database

- In response to Congressional mandate, FDA was charged with collecting and analyzing safety data for gene therapy beginning in 2001

Resource and Methodology

- All INDs that were identified in the CBER corporate database as a gene therapy product (for example-viral or plasmid vector based or genetically modified cells) were flagged and the IND number entered into an MS Access Database.
- Detailed product information was added to each IND record
- All adverse events from both individual reports and annual reports were abstracted and entered

Results

- 482 INDs were identified of which 215 have adverse event data that is entered into the database

Total	*Cancer*	Other
215 INDs	*145 (67%)*	70 (33%)
340 protocols	*222 (65%)*	118 (35%)

Adverse Events

Total	*Cancer*	Other
11017 AEs	*7774 (71%)*	3243 (29%)
2456 SAEs	*1855 (76%)*	601 (24%)

Patients

- About 3850- Male/Female ratio 1.5/1
- About 160 children (< 18 years)- Male/Female ratio 1/1
  - About 26 patients with hemophilia- none children
  - Most children had a malignancy as primary diagnosis

Diagnoses

Primary Diagnosis	# of patients
Malignant melanoma stage IV	447
Glioblastoma multiforme	361
Squamous cell carcinoma	306
Peripheral Vascular Disorder	287
HIV infection	209
Prostate cancer	122
Cystic fibrosis	121
Renal cell carcinoma	111
Neuroblastoma	104
Breast cancer metastatic	87
Coronary artery disease	73
Ovarian Cancer	70
Cystic fibrosis	69
Non-small cell lung cancer	62
Head and Neck	57
Colorectal cancer	53
Chronic lymphocytic leukaemia	50

Patients

Total	*Cancer*	Other
3837 patients	*2743 (71%)*	1094 (29%)
1533 (40%) AE only	*966 (63%)*	567 (37%)
529 (14%) SAE only	*400 (76%)*	129 (24%)
1775 (46%) AE & SAE	*1377 (78%)*	398 (22%)
2304 (60%) SAE	*1777 (77%)*	527 (23%)

Some patients had multiple adverse events

Products

Total	*Cancer*	Other
325 products	*208 (64%)*	117 (36%)
232 products that had SAEs	*148 (64%)*	84 (36%)

Some INDs and Protocols had multiple products

Adverse Events All Patients

Per Cent	Event Description
31.6%	Disease progression NOS
12.5%	injection site pain
9.2%	Pyrexia
5.3%	N/A
4.5%	Vomiting NOS
4.4%	Headache NOS
3.9%	fatigue
3.8%	Pain NOS
3.3%	Nausea
3.1%	Anaemia NOS
3.0%	Injection site reaction NOS

NOS = Not Otherwise Specified

Serious Adverse Events All Patients

All SAEs	All AEs	Event Description
37.5%	22.6%	Disease progression NOS
2.4%	1.4%	Lung disorder NOS
2.3%	1.4%	death NOS
1.9%	1.1%	febrile neutropenia
1.6%	1.0%	pyrexia
1.3%	0.8%	cardio-respiratory arrest
1.1%	0.7%	dyspnoea NOS

Adverse Events Cancer Patients

Per Cent	Event Description
40.3%	Disease progression NOS
16.7%	injection site pain
9.2%	Pyrexia
4.8%	Pain NOS
4.7%	Vomiting NOS
4.4%	N/A
4.1%	Injection site reaction NOS
3.9%	Nausea
3.6%	headache NOS
3.3%	lymphopenia

Serious Adverse Events Cancer Patients

Cancer SAE	All Cancer	Event Description
46.4%	30.1%	Disease progression NOS
2.5%	1.6%	Death NOS
2.3%	1.5%	febrile neutropenia
1.7%	1.1%	cardio-respiratory arrest
1.6%	1.1%	Pyrexia
1.2%	0.8%	dyspnoea NOS
1.1%	0.7%	respiratory arrest
1.1%	0.7%	respiratory failure
1.0%	0.7%	Vomiting NOS

Adverse Events Non Cancer Patients

Patients	Per Cent
101	9.2%
86	7.9%
81	7.4%
80	7.3%
72	6.6%
71	6.5%

Serious Adverse Events
Non Cancer Patients

SAE NonCancer	All NonCancer	Event Description
10.4%	5.0%	Lung disorder NOS
7.6%	3.7%	Disease Progression NOS
2.3%	1.1%	Cellulitis
2.3%	1.1%	Condition aggravated
2.1%	1.0%	chest pain

Serious Adverse Events by Diagnosis- Cancer Patients

# of Pts.	Event Description	Outcome	PrimaryDiagnosis
187	Disease Progression NOS	Death	glioblastoma multiforme
182	Disease Progression NOS	Death	Squamous Cell Carcinoma
83	disease progression NOS	Death	malignant melanoma stage IV
41	Disease Progression NOS	Death	Neuroblastoma NOS
31	Disease progression NOS	Death	Breast cancer metastatic
21	cardio-respiratory arrest	Death	glioblastoma multiforme
20	Febrile neutropenia	Hospitalization	Neuroblastoma NOS

Serious Adverse Events by Diagnosis- Non Cancer Patients

# of Pts	Event Description	Outcome	PrimaryDiagnosis
55	Lung disorder NOS	Hospitalization - Initial or Prolonged	Cystic fibrosis lung
13	Disease Progression NOS	Hospitalization - Initial or Prolonged	Peripheral Vascular Disorder NOS
12	Condition aggravated	Hospitalization - Initial or Prolonged	Cystic fibrosis NOS
10	Cardiac failure congestive	Hospitalization - Initial or Prolonged	Peripheral vascular disorder NOS
10	disease progression NOS	Death	HIV infection NOS
8	Angina pectoris	Hospitalization - Initial or Prolonged	Coronary artery restenosis
8	Haemoptysis	Hospitalization - Initial or Prolonged	Cystic fibrosis lung
8	osteomyelitis NOS	Hospitalization - Initial or Prolonged	peripheral vascular disorder NOS
7	Cellulitis	Hospitalization - Initial or Prolonged	Peripheral Vascular Disorder NOS
7	Disease Progression NOS	Hospitalization - Initial or Prolonged	Coronary Artery Disease NOS

Conclusions

- The majority of INDs and studies using gene based therapy are for cancer patients
- Based on a total of over 11 000 adverse events in almost 4000 patients, the major risks appear to be related to progression of the underlying disease
- Analyses of product specific associations are ongoing

Future Plans

- The initial phase of the project is nearing conclusion
- The database will be migrated into an Oracle environment and become integrated into the overall CBER corporate database structure
- Compatibility with electronic submission of adverse event reports is designed into the system

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