Reporting Device-Related Effects

6th Annual Device Research and Regulatory Conference

Sarah Zanon, MS
Disclosure Statement of Financial Interest

Within the past 12 months, I have had a financial interest/arrangement or affiliation with the organization listed below:

<table>
<thead>
<tr>
<th>Affiliation/Financial Relationship</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full time employee</td>
<td>D-TARGET (a Premier Research Company)</td>
</tr>
</tbody>
</table>
MEDICAL DEVICE REPORTING: Agenda

- MD Reporting for Medical Devices marketed in U.S.
- MD Reporting for CE-marked Medical Devices (EU)
- MD Reporting in Investigational Clinical Trial in U.S.
- MD Reporting in Pre-market Clinical Investigation (EU)
- Q&A
MD REPORTING for
MEDICAL DEVICES MARKETED IN U.S.
What is **Medical Device Reporting (MDR)**?

Medical Device Reporting (MDR) is the mechanism for the Food and Drug Administration (FDA) to receive significant medical device reporting from:

- device user facilities
- manufacturers
- importers
Device user facility means

- hospital,
- ambulatory surgical facility,
- nursing home,
- outpatient diagnostic facility, or
- outpatient treatment facility that are not physicians’ offices
Manufacturer means any person who manufactures, prepares, compounds, assembles, or processes a device, including also:

- repackages or otherwise changes the container or the labeling of a device
- provide specifications for devices that are manufactured by a second party
- manufactures components or accessories ready to be used and intended to be commercially distributed
- is the U.S. agent of a foreign manufacturer
**Importer** means any person who:

- imports a device into the U.S.
- furthers the marketing of a device from the original place of manufacture to the person who makes final delivery or sale to the ultimate user,

**but who does not**

- repackage or otherwise change the container, wrapper, or labeling of the device or device package
Food and Drug Administration (FDA)

- Take corrective action on problem devices
- Prevent injury and death by alerting the public when potentially hazardous devices are discovered
- Detect unanticipated events and user errors
- Monitor and classify recalls
- Update medical device labels
- Develop educational outreach
MD REPORTING: the FDA Role

Center for Drug Evaluation and Research
Center for Devices and Radiological Health
Center for Veterinary Medicine
Center for Tobacco
Center for Biologics Evaluation and Research
Center for Food Safety and Applied Nutrition
SAE reporting is mandatory for manufacturer

1984

FDA sets forth regulations requiring manufacturers and importers to notify CDRH when they become aware of a death or serious injury that may be associated with one of their devices.
The Safe Medical Devices Act of 1990 extends reporting requirements to facilities that use medical devices (so-called user facilities).
SAE reporting is mandatory for manufacturer

1984

SAE reporting extended to user facilities

1990

Definition of a standard for SAE reporting

1992

The Medical Device Amendments of 1992 requires a single reporting standard and defines the serious injuries that must be reported.
1984
SAE reporting is mandatory for manufacturer

1990
SAE reporting extended to user facilities

1992
Definition of a standard for SAE reporting

1996
Final regulation for MDR requirements

The final regulations governing these reporting requirements took effect in 1996
MD REPORTING: Regulatory Definition of REPORTABLE EVENT

**MDR reportable event** means:

1. An event that **device user facilities** become aware of that reasonably suggests that a device has or may have caused or contributed to a **death** or **serious injury**; or

2. An event that **manufacturers** or **importers** become aware of that reasonably suggests that one of their marketed devices:
   i. May have caused or contributed to a **death** or **serious injury**, or
   ii. Has **malfunctioned** and that the device or a similar device marketed by the manufacturer or importer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

CFR Title 21 FOOD AND DRUGS – Part 803: MEDICAL DEVICE REPORTING
Sect. 803-3: How does FDA define the terms used in this part?
Serious injury means any injury or illness that:

- is life-threatening,
- results in permanent impairment of a body function or permanent damage to a body structure, or
- necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.

CFR Title 21 FOOD AND DRUGS – Part 803: MEDICAL DEVICE REPORTING
Sect. 803-3: How does FDA define the terms used in this part?
A **device malfunction** is a failure of the device to meet its performance specifications or otherwise perform as intended.

Performance specifications include all claims made in the labeling for the device.
A *malfunction* should be considered *reportable* if any one of the following is true:

- the chance of a death or serious injury is not remote;
- the consequences of the malfunction affect the device in a manner that may lead to a death or serious injury;
- the device fails to perform its essential function and compromises the device’s therapeutic, monitoring or diagnostic effectiveness which could cause or contribute to a death or serious injury.
A malfunction should be considered reportable if any one of the following is true:

- the malfunction involves a long-term device implant that would prevent the implant from performing its function;
- the device is considered life-supporting or life-sustaining, and thus essential to maintaining human life.
### Device User Facility

<table>
<thead>
<tr>
<th>Section of 21CRF</th>
<th>Type of Information</th>
<th>Report Form</th>
<th>To Whom</th>
<th>When</th>
</tr>
</thead>
<tbody>
<tr>
<td>803.30</td>
<td>Device may have caused or contributed to <strong>death</strong></td>
<td>Form FDA 3500A</td>
<td>to Manufacturer, and to FDA</td>
<td>Within <strong>10 work day</strong></td>
</tr>
<tr>
<td>803.30</td>
<td>Device may have caused or contributed to <strong>serious injury</strong></td>
<td>Form FDA 3500A</td>
<td>to Manufacturer or FDA if manufacturer is unknown (only)</td>
<td>Within <strong>10 work day</strong></td>
</tr>
<tr>
<td>803.33</td>
<td><strong>Annual report</strong>: summary of previously submitted reports (not required if no reports)</td>
<td>Form FDA 3419</td>
<td>to FDA</td>
<td><strong>Yearly</strong> (by January 1)</td>
</tr>
</tbody>
</table>

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**CFR Title 21 FOOD AND DRUGS – Part 803: MEDICAL DEVICE REPORTING**

**Sect. 803-10**: What are the reporting requirements that apply to me?
# MD REPORTING: Reporting Requirements

## Manufacturer

<table>
<thead>
<tr>
<th>Section of 21CFR</th>
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<th>Report Form</th>
<th>To Whom</th>
<th>When</th>
</tr>
</thead>
<tbody>
<tr>
<td>803.50</td>
<td>Device may have caused or contributed to death or serious injury; or device malfunctioned and would be likely to cause or contribute to death or serious injury if malfunction recurs</td>
<td>Form FDA 3500A</td>
<td>to FDA</td>
<td>Within 30 calendar day</td>
</tr>
<tr>
<td>803.53</td>
<td>MDR reportable event that requires remedial action to prevent unreasonable risk of substantial harm to public health, or 5-day report requested by FDA</td>
<td>Form FDA 3500A</td>
<td>to FDA</td>
<td>Within 5 work day</td>
</tr>
<tr>
<td>803.56</td>
<td>Supplemental (follow-up) reports to identify and provide basic data on each device that is subject of an MDR report</td>
<td>Form FDA 3417</td>
<td>to FDA</td>
<td>Within 30 calendar day</td>
</tr>
</tbody>
</table>

CFR Title 21 FOOD AND DRUGS – Part 803: MEDICAL DEVICE REPORTING
Sect. 803-10: What are the reporting requirements that apply to me?
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<th>Report Form</th>
<th>To Whom</th>
<th>When</th>
</tr>
</thead>
<tbody>
<tr>
<td>803.40</td>
<td>Device may have caused or contributed to <strong>death</strong> or <strong>serious injury</strong></td>
<td>Form FDA 3500A</td>
<td>to Manufacturer, and to FDA</td>
<td><strong>Within 30 calendar day</strong></td>
</tr>
<tr>
<td>803.40</td>
<td>Device has <strong>malfunctoned</strong> and would be likely to cause or contribute to death or serious injury if malfunction recurs</td>
<td>Form FDA 3500A</td>
<td>to Manufacturer</td>
<td><strong>Within 30 calendar day</strong></td>
</tr>
</tbody>
</table>
Voluntary Reporting of adverse events noted spontaneously in the course of clinical care, not events that occur during clinical trials under an Investigational Device Exemption (IDE) application. Those mandatory reports are to be submitted to FDA as specified in the IDE Form FDA 3500 for Consumers and Individual Healthcare Professionals.

It is not required by law or regulation to submit AE or product problem reports to the Agency or to the manufacturer.
MD REPORTING: Voluntary Reporting Requirements

U.S. Food and Drug Administration

MedWatch Online Voluntary Submission Form 3500

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. [ ] Adverse Event
   [ ] Product Use Error

2. Outcomes Attributed to Adverse Event (Check all that apply)
   [ ] Death (MM/DD/YYYY)
   [ ] Life-threatening
   [ ] Hospitalization - initial or prolonged
   [ ] Disability or Permanent Damage

3. Date of Event
   (MM/DD/YYYY)

4. Date of This Report
   (MM/DD/YYYY)

5. Describe Event, Problem or Product Use Error up to a total of 5400 characters allowed
   [ ]

6. Relevant Tests/Laboratory Data, Including Dates
   up to a total of 2000 characters allowed
   [ ]

7. Other Relevant History, Including Preexisting Medical Conditions (e.g. allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.) up to a total of 2000 characters allowed
   [ ]
FDA reporting programs:

- MedWatch Program
- Alternative Summary Reports (ASR)
- MedSun Program
- Manufacturer and User Facility Device Experience Database (MAUDE)
- eMDR – Electronic Medical Device Reporting
MedWatch Program

MedWatch is FDA’s program, founded in 1993, for collecting information about injuries and adverse events that occur when using medical devices and drugs.

MedWatch can be used for reporting serious adverse events; product quality problems; therapeutic inequivalence or failure; and product use errors with human medical products, such as drugs and medical devices.
SAFETY INFORMATION

- Safety Alerts for Human Medical Products
- Safety-Related Information
- Safety Data
  - Adverse Event Reporting System (AERS)
  - Vaccine Adverse Event Reporting System (VAERS)
  - Manufacturer and User Facility Device Experience Database (MAUDE)
On October 1, 1999, CDRH began the Alternative Summary Report (ASR) program. Manufacturers can submit abbreviated and aggregated adverse event reports. Manufacturers must apply for permission from FDA to submit quarterly ASRs for individual medical devices. CDRH may request a manufacturer to submit a full report if it needs additional information about a specific event.
MedSun Program

• In 2002, CDRH launched the Medical Product Safety Network (MedSun) pilot project, an adverse event reporting network aimed to increase user facility reporting rates and improve the quality of reports.

• MedSun participants submit additional information that help the identification, comprehension, and resolution of adverse events related to medical devices use.

• MedSun is based on a network of about 350 hospitals that participate voluntarily. User facilities receive additional training and feedback on reporting events.
MD REPORTING: MedSun Program

- Total Number of MedSun hospitals
- Number of MedSun hospitals that have submitted at least 3 reports in the previous 12 months
Manufacturer and User Facility Device Experience Database (MAUDE)

• The Manufacturer and User Facility Device Experience (MAUDE) database collects all voluntary and mandatory adverse event reports to CDRH, including reports submitted through MedSun.

• The data consists of
  – voluntary reports since 1993,
  – user facility reports since 1991,
  – distributor reports since 1993, and
  – manufacturer reports since 1996.
Information Accessibility

The Freedom of Information Act (FOIA) generally provides that any person has the right to request access to federal agency records or information except to the extent the records are protected from disclosure by

- trade secrets and confidential business information exemption
- personnel and medical files exemption

FOIA applies to the release of information in the reports found in MAUDE
eMDR – Electronic Medical Device Reporting

The electronic Medical Device Reporting (eMDR) project provides the capability for electronic data entry and processing of medical device adverse event reports.

eMDR utilizes the FDA Electronic Submissions Gateway, an agency-wide entry point for all electronic submissions, to receive electronic MDRs. The Gateway authenticates and validates electronic submissions and routes it to CDRH.
eMDR – Electronic Medical Device Reporting

FDA Electronic Submissions Gateway (ESG) provide the following services:

- Enables the FDA to process regulatory submissions automatically
- Functions as a single point of entry for the receipt and processing of all electronic submissions in a secure environment that complies with secure messaging standards
- Serves as a conduit, or “highway,” along which submissions travel to reach their final FDA destination
- Automatically routes submissions to the appropriate FDA Center or Office.
MD REPORTING for
CE-MARKED MEDICAL DEVICES (EU)
Reportable event - INCIDENT means:

(1) Any malfunction or deterioration in the characteristics and/or performance of a device,

(2) Any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a patient, or user or of other persons or to a serious deterioration in their state of health.

Article 10 of the MDD (COUNCIL DIRECTIVE 93/42/EEC)
**EU REGULATIONS: Reporting Requirements**

<table>
<thead>
<tr>
<th>Type of Information</th>
<th>To Whom</th>
<th>When</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious public health threat</td>
<td>to the National Competent Authority in the Country of occurrence</td>
<td>Immediately (without any delay that could not be justified) but not later than 2 calendar days after awareness</td>
</tr>
<tr>
<td>Death or UNANTICIPATED serious deterioration in state of health</td>
<td>to the National Competent Authority in the Country of occurrence</td>
<td>Immediately (without any delay that could not be justified) after the Manufacturer established a link between the device and the event but not later than 10 elapsed calendar days following the date of awareness</td>
</tr>
</tbody>
</table>

**MEDDEV 2.12-1 rev 7: Guidelines on a Medical Devices Vigilance System**

The revised guidance will be applicable as of **15 June 2012**
EU REGULATIONS: Reporting Requirements

Report Form
Manufacturer’s Incident Report
Medical Devices Vigilance System (MEDDEV 2.12/1 rev 7)

<table>
<thead>
<tr>
<th>1. Administrative information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recipient</td>
</tr>
<tr>
<td>Name of National Competent Authority (NCA)</td>
</tr>
<tr>
<td>Address of National Competent Authority</td>
</tr>
<tr>
<td>Date of this report</td>
</tr>
<tr>
<td>Reference number assigned by the manufacturer</td>
</tr>
<tr>
<td>Reference number assigned by NCA</td>
</tr>
<tr>
<td>Type of report</td>
</tr>
<tr>
<td>Initial report</td>
</tr>
<tr>
<td>Follow-up report</td>
</tr>
<tr>
<td>Combined Initial and final report</td>
</tr>
<tr>
<td>Final report</td>
</tr>
<tr>
<td>Does the incident represent a serious public health threat?</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>Classification of incident</td>
</tr>
<tr>
<td>Death</td>
</tr>
<tr>
<td>Unanticipated serious deterioration in state of health</td>
</tr>
<tr>
<td>All other reportable incidents</td>
</tr>
<tr>
<td>Identify to what other NCAs this report was also sent</td>
</tr>
</tbody>
</table>

2. Information on submitter of the report
National Competent Authorities (NCA)

The NCA should send an *acknowledgement of receipt of the report to the sender.*

NCA’s actions as a result of a report of the Manufacturer or Authorized Representative may include, for example:

- no further action
- gathering more information
- making recommendations to MANUFACTURERs
- keeping the Commission and other Competent Authorities informed
- consulting with the relevant Notified Body on matters relating to the conformity assessment
- consulting the Commission
MD REPORTING in INVESTIGATIONAL CLINICAL TRIALS in U.S.
For clinical investigations of medical devices conducted under an Investigational Device Exemption (IDE) application, information about adverse events must be communicated among:

- Investigators
- Sponsors
- IRB
- FDA
**Investigator** means an individual who actually conducts a clinical investigation, i.e., under whose immediate direction the investigational device is administered or dispensed or used to a subject.

In the event of an investigation conducted by a team of individuals, he is the responsible leader of that team.
Sponsor means a person who initiates, but who does not actually conduct, the investigation, that is, the investigational device is administered, dispensed, or used under the immediate direction of another individual.
**Institutional review board (IRB)** means any board, committee, or other group formally designated by an institution to review, to approve the initiation of, and to conduct periodic review of, biomedical research involving human subjects.

The primary purpose of such review is to assure the protection of the rights and welfare of the human subjects.
MD REPORTING: IDE Reporting requirements

MD CLINICAL STUDY

INVESTIGATOR reports to:
- Sponsor
- Pertinent IRB

SPONSOR reports to:
- FDA
- All Investigators
- All IRBs

UADEs
An **Investigator** shall prepare and submit the following complete, accurate, and timely reports **Unanticipated Adverse Device Effects (UADE)**.

Investigator is required to submit a UADE report to the **Sponsor** and the **reviewing IRB** as soon as possible, but in no event later than **10 working days** after the Investigator first learns of the event.

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**Title 21 FOOD AND DRUGS – Part 812 INVESTIGATIONAL DEVICE EXEMPTIONS**

**21 CFR Sect. 812.150** Reports
A Sponsor shall prepare and submit the following complete, accurate, and timely reports Unanticipated Adverse Device Effects (UADE).

Sponsor must immediately conduct an evaluation of a UADE and must report the results of the evaluation to FDA, all reviewing IRBs, and all participating investigators within 10 working days after the sponsor first receives notice of the effect.
**Unanticipated adverse device effect (UADE)** means any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application.

Title 21 FOOD AND DRUGS – Part 812 INVESTIGATIONAL DEVICE EXEMPTIONS
21 CFR Sect. 812.3 Definitions
CDRH review process includes due diligence inspecting GCP-regulated entities, to verify the integrity of the data submitted to the agency, as well as the ethical rights and safety of clinical trial.

Failure to inform investigators, FDA, or the IRB is one of the most frequently observed non compliance in CDRH inspections.

<table>
<thead>
<tr>
<th>Sponsor Observations</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failure to inform investigators, FDA or IRB</td>
<td>35%</td>
</tr>
<tr>
<td>Inadequate monitoring</td>
<td>30%</td>
</tr>
<tr>
<td>Inadequate device accountability</td>
<td>23%</td>
</tr>
<tr>
<td>Failure to secure investigator compliance</td>
<td>19%</td>
</tr>
<tr>
<td>Inadequate UADE analysis and reporting</td>
<td>16%</td>
</tr>
<tr>
<td>Failure to obtain signed investigator agreement</td>
<td>16%</td>
</tr>
<tr>
<td>Informed consent</td>
<td>9%</td>
</tr>
</tbody>
</table>

the most frequent Form 483 sponsor observations in FY 2008
If FDA uncovers condition violations of the regulatory requirements during an inspection, FDA may take enforcement action:

- **FDA-INITIATED OR VOLUNTARY RECALLS**
- **CIVIL MONEY PENALTIES**
- **WARNING LETTERS**
- **SEIZURE**
- **CITATION**
- **INJUNCTION**
- **PROSECUTION**
MD REPORTING in PRE-MARKET CLINICAL INVESTIGATION (EU)
Reportable events under Annex 7 and Annex X of Directives 90/385/EEC and 93/42/EEC respectively:

- any SAE
- any Investigational Medical Device Deficiency that might have led to a SAE if
  i. suitable action had not been taken or
  ii. intervention had not been made or
  iii. if circumstances had been less fortunate
- new findings/updates in relation to already reported events.
### EU REGULATIONS: Regulatory Definition of ADVERSE EVENTS

<table>
<thead>
<tr>
<th>ADVERSE EVENTS</th>
<th>Non-device-related</th>
<th>Device- or procedure-related</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non serious</td>
<td>Adverse Event (AE)</td>
<td>Adverse Device Effect (ADE)</td>
</tr>
<tr>
<td>Serious</td>
<td>Serious Adverse Event (SAE)</td>
<td>Serious Adverse Device Effect (SADE)</td>
</tr>
<tr>
<td>Tupled</td>
<td>Anticipated</td>
<td>Unanticipated</td>
</tr>
<tr>
<td></td>
<td>Anticipated Serious Adverse Device Effect (ASADE)</td>
<td>Unanticipated Serious Adverse Device Effect (USADE)</td>
</tr>
</tbody>
</table>

ISO 14155: 2011 – Clinical investigation of medical devices for human subjects – Good Clinical Practice
Annex F – Adverse Event Categorization
**EU REGULATIONS: SAE definition in European Regulations**

<table>
<thead>
<tr>
<th>MEDDEV 2.7/3 CLINICAL INVESTIGATIONS: SERIOUS ADVERSE EVENT REPORTING</th>
<th>ISO 14155: 2011 Clinical Investigation of Medical Devices for human subjects – Good Clinical Practice</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>An adverse event is serious if:</strong></td>
<td><strong>An adverse event is serious if:</strong></td>
</tr>
<tr>
<td>• led to a death,</td>
<td>• led to death,</td>
</tr>
<tr>
<td>• led to a serious deterioration in health that either:</td>
<td>• led to serious deterioration in the health of the subject, that either resulted in:</td>
</tr>
<tr>
<td>1) resulted in a life-threatening illness or injury, or</td>
<td>1) a life-threatening illness or injury,</td>
</tr>
<tr>
<td>2) resulted in a permanent impairment of a body structure or a body function, or</td>
<td>2) a permanent impairment of a body structure or a body function,</td>
</tr>
<tr>
<td>3) required in-patient hospitalization or prolongation of existing hospitalization, or</td>
<td>3) in-patient or prolonged hospitalization,</td>
</tr>
<tr>
<td>4) resulted in medical or surgical intervention to prevent 1) or 2)</td>
<td>4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,</td>
</tr>
<tr>
<td>• led to fetal distress, fetal death or a congenital abnormality or birth defect</td>
<td>• led to foetal distress, foetal death or a congenital abnormality or birth defect</td>
</tr>
</tbody>
</table>
EU REGULATIONS: Regulatory Definition of DEVICE DEFICIENCY

Device deficiency: inadequacy of a medical device with respect to its
• identity
• quality
• durability
• reliability
• safety
• performance

NOTE: Device deficiencies include malfunctions, use errors, and inadequate labeling.
## EU REGULATION: Reporting Requirements

<table>
<thead>
<tr>
<th>Regulation</th>
<th>Type of Information</th>
<th>To Whom</th>
<th>When</th>
</tr>
</thead>
<tbody>
<tr>
<td>European Directive 2007/47/EC, Annex X, section 2.3.5</td>
<td>All serious adverse events</td>
<td>to all competent authorities of the Member States in which the clinical investigation is being performed</td>
<td>Immediately</td>
</tr>
<tr>
<td>MEDDEV 2.7/3 Clinical Investigations: Serious Adverse Event reporting under Directives 90/385/EEC and 93/42/EEC</td>
<td>All serious adverse events and all device deficiency</td>
<td>at the same time to all NCAs where the clinical investigation has commenced</td>
<td>Immediately, but not later than 2 or 7 calendar days after awareness</td>
</tr>
</tbody>
</table>
**EU REGULATIONS: Reporting Requirements**

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<td>MEDDEV 2.7/3 Clinical Investigations: Serious Adverse Event reporting under Directives 90/385/EEC and 93/42/EEC</td>
<td>All serious adverse events and all device deficiency</td>
<td>to the Sponsor</td>
<td>in acceptable timely conditions, but not later than <strong>within 3 calendar days</strong> after the occurrence of the event.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>to the Ethics Committee</td>
<td>According to local regulation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>To the Competent Authority (Germany only)</td>
<td>Same rule as for the Sponsor</td>
</tr>
</tbody>
</table>