**Adverse Event Reporting: When TMI is Risky**  
*By Bill Myers*

As sponsors and sites have expanded their global reach, they’ve run into myriad local and regional regulations requiring them to report adverse events in their clinical trials. Hoping to simplify, many sponsors or sites have tried to create a one-size-fits-all form that sends out nearly automated alerts for nearly every single glitch.

“A lot of pharma companies take the approach that they’ve got to be compliant with everyone, so they say, ‘We’ll just send out everything,’” says Steven Beales, WCG’s senior vice president for safety. That might sound OK. [But] you’re wasting site hours and you’re not improving safety because you’re diluting the message. 

A decade ago, for instance, Roche discovered that it was distributing more adverse event warnings from trials than any other drug developer, with nearly a million notices going out to patients, regulators and others at a cost of more than $75 million in one year. As the company expanded through mergers and acquisitions, it was looking at having to dispatch in excess of 25 million alerts every year, Beales says.

The root of the problem was the scattershot regulatory regimes across the globe — Beales and his colleagues analyzed worldwide clinical trial regulation and found at least 40 different variances. “Patient safety is obviously the most important thing we do and sometimes that responsibility is put out everything,” says Beales.  

**FDA Guidance Clarifies Agency Regulations v. Revised Common Rule**  
*By James Miessler*

The FDA released new guidance last week on how researchers can comply with both agency regulations and pending Common Rule revisions that protect human subjects in clinical trials.

The guidance focuses on requirements for informed consent, expedited review procedures and IRB continuing review. It says new requirements for informed consent documents in the revised Common Rule — the baseline body of regulations across federal departments and agencies for human subjects in clinical research — don’t conflict with any FDA regulations.

But the agency says IRBs still have to comply with its regulations for expedited and continuing reviews. IRBs must conduct continuing reviews of research at least once a year at “intervals appropriate to the degree of risk,” the guidance says. For expedited review procedures, IRBs must adhere to the 1998 list for FDA-regulated clinical investigations, including those subject to both HHS and FDA regulations.

David Borasky, vice president of quality management for the Copernicus Group Independent Review Board, says this is essentially business as usual, noting the guidance doesn’t reveal anything new about the FDA’s plans for harmonization between agency regulations and the Common Rule revisions.

**Order Today!**

The CRC’s Guide is the most comprehensive easy-to-read training guide for novice and experienced CRCs. Includes industry facts, insights on the role and responsibilities, key take-aways and case studies.

**Register Now**

**CLINICAL TRIAL RISK AND PERFORMANCE MANAGEMENT SUMMIT**  
**WEDNESDAY-THURSDAY**  
**NOVEMBER 14-15, 2018**  
**PRINCETON, NJ**

**Register Now**
FDA: Generic Skin Patch Trials
Generic drug developers that use patches, inhalers, eye drops or similar means to deliver meds should hold clinical trials to test for potential side effects of skin irritation and, in the case of patches, adhesion quality, the FDA says.

The agency says it’s worried that skin patches may lose potency if jarred and loosened by everyday movements or conditions (such as moisture).

So in new draft guidance, released last week, it recommends generic drug developers hold separate clinical trials to make sure patches continue to stick and provide promised doses for the duration of treatment.

The guidance urges them to hold single-dose, randomized, two-treatment, two-period crossover trials with participants most likely to use patches to show they can withstand ordinary pressures. The draft, set to replace 2016 adhesion guidance, says single-period two-treatment-per-subject designs may also work if developers can justify why they’re a better option.

Developers should test adhesion several times, and at regular intervals, and use a four-point scale, ranging from 0 (90 percent adhesion or better) to 4 (the patch completely peels off), the agency says.

In another new draft guidance, the FDA further advises developers to measure generics’ potential side effects — most notably skin and/or eye irritation depending on the delivery system employed — against those of their brand name competitors.

It recommends testing them in clinical trials involving a “relatively small population” (i.e. hundreds of patients) and conducted under “relatively provocative conditions” during which researchers repeatedly take off and put back skin patches to see if they retain their holding power.

The best bet, says the FDA: a two-phase trial — the first, a 21-day induction phase during which patches are worn, removed and replaced for the recommended course of treatment.

That phase should be followed by a 14-to-17-day rest period and, then, a “challenge phase” during which patches are put on a new part of the body for 48 hours and the skin is tested for reactions after 30 minutes, 24 hours, 48 hours and, again, 72 hours after the patch’s removal.

Developers are urged to use a seven-point rating scale for skin irritation — from 0 (clear skin) to 7 (“Strong reaction spreading beyond the application site”).

Read the adhesion draft guidance here: www.fdanews.com/10-09-18-ANDAs.pdf.
Read the irritation draft here: www.fdanews.com/10-09-18-ANDAs2.pdf.

China OKs Rabies Vaccine Trials
A Chinese drug company says national regulators have approved pivotal clinical trials for a new rabies vaccine.

YiSheng BioPharma believes its vaccine, called PIKA, can become a “best in class” immunization against this contagious and fatal virus that causes tens of thousands of deaths annually, according to the World Health Organization.

The company plans to begin recruiting participants for its Phase III trials, set to start early next year. The vaccine won orphan status from the FDA in 2016 and has already successfully finished Phase I and Phase II studies in Singapore.

Celgene Claims Win in MS Trial
Celgene Corp’s experimental multiple sclerosis drug helped stave off symptoms better than its rival in clinical trials.

The New Jersey-based pharma announced last week that ozanimod topped Biogen’s Avonex (interferon beta-1a or IFN) in a pair of Phase III trials. In the first trial, called SUNBEAM, researchers randomly gave two different oral doses of ozanimod or IFN to 1,346 relapsing MS patients over a year and then tested their cognitive function, which typically declines as the disease progresses. The ozanimod patients, on average, scored significantly higher than the IFN patients.

The second trial, dubbed RADIANCE, compared the annualized relapse rates for 1,392 patients in the early stages of MS and another 1,267 patients with more advanced cases of the neurological disease who took either ozanimod or IFN. Both sets of patients who took ozanimod suffered fewer relapses or exacerbations than those who took IFN, Celgene says.

MS affects an estimated one million adults in the U.S. and 2.3 million globally; women are up to three times more likely to develop the disease. There are several types of the condition; left untreated, those who suffer from relapsing MS will develop the more serious secondary progressive form.

Celgene says it plans to apply for FDA approval to market ozanimod.

Sickle Cell Trial, Positive Results
An experimental treatment helped prevent a painful, potentially fatal complication in a clinical trial of patients with sickle cell disease.

Novartis tested crizanlizumab in 132 patients in a Phase II clinical trial over three years to see if it could prevent vaso-occlusive crisis. More than half of the patients received crizanlizumab compared to the annualized relapse rates for 1,392 patients in the early stages of MS and another 1,267 patients with more advanced cases of the neurological disease who took either ozanimod or IFN. Both sets of patients who took ozanimod suffered fewer relapses or exacerbations than those who took IFN, Celgene says.

MS affects an estimated one million adults in the U.S. and 2.3 million globally; women are up to three times more likely to develop the disease. There are several types of the condition; left untreated, those who suffer from relapsing MS will develop the more serious secondary progressive form.

Celgene says it plans to apply for FDA approval to market ozanimod.

Sickle Cell Trial, Positive Results
An experimental treatment helped prevent a painful, potentially fatal complication in a clinical trial of patients with sickle cell disease.

Novartis tested crizanlizumab in 132 patients in a Phase II clinical trial over three years to see if it could prevent vaso-occlusive crisis. More than half of the patients received crizanlizumab compared to the annualized relapse rates for 1,392 patients in the early stages of MS and another 1,267 patients with more advanced cases of the neurological disease who took either ozanimod or IFN. Both sets of patients who took ozanimod suffered fewer relapses or exacerbations than those who took IFN, Celgene says.

MS affects an estimated one million adults in the U.S. and 2.3 million globally; women are up to three times more likely to develop the disease. There are several types of the condition; left untreated, those who suffer from relapsing MS will develop the more serious secondary progressive form.

Celgene says it plans to apply for FDA approval to market ozanimod.
“A lot of pharma companies take the approach that they’ve got to be compliant with everyone, so they say, ‘We’ll just send out everything.’”
—Steven Beales, senior vice president for safety, WCG

‘OK, you say you’ve notified so-and-so. How do you know the email arrived? How do you know they’ve read it?’ Beales says.

Given the sheer volume of alerts, it’s hard to know if patients are reading them all if any, Beales says, noting they may be so common that patients simply disregard or dismiss them as insignificant.

Despite efforts to bring international regulations into alignment, it’s unlikely that reporting requirements will get substantially easier. In January, for instance, The Oncologist carried an op-ed urging the FDA to include data about the duration of an adverse event in its reporting requirements.

Whether or not that idea catches hold — Steven Beales, senior vice president for safety, WCG

The good news, Beales says, is that technology has now made it possible for companies to hone their focus. Advanced algorithms, once in place, can help determine whether an event needs to be reported, and if so, by and to whom: Should an alert go to patients? Regulators? Sites?

Beefing up a company’s alert system isn’t easy and it’s not always cheap. It requires a soup-to-nuts approach, beginning with an audit. That can sometimes be a logistical nightmare, especially at the outset. The first year that he worked with Roche, Beales says, he and his colleagues discovered the company was actually under-reporting events by 2 million cases.

A warning sign might be that a company doesn’t actually know what it costs to send out alerts, Beales says.

“If they go through their contracts, they’re going to go, ‘We can’t work out what we’re spending on this. We don’t have a clear idea of whether we’re compliant,’” Beales says.

So, is it worth it to discard the one-size-fits-all approach and go through the arduous route to a tailored alert system? Last year, Roche saved a hefty $65 million by personalizing its alert system, Beales says.
FDA Guidance continued from page 1

“This is the consistent message from FDA since the Common Rule revisions were published almost two years ago,” he tells CenterWatch.

The bottom line is that FDA regulations for human subject protection and IRBs won’t change when the Common Rule revisions take effect in January, Borasky says.

That means clinical investigations regulated by both the FDA and the Common Rule will still have to comply with agency regs if they’re more stringent. “The FDA still has an expectation that institutions, IRBs, sponsors, etc., continue to follow the FDA regulations as written, even when their requirements go beyond what is required by the revised Common Rule.”

—David Borasky, VP of quality management, WIRB

“The FDA still has an expectation that institutions, IRBs, sponsors, etc., continue to follow the FDA regulations as written, even when their requirements go beyond what is required by the revised Common Rule,” Borasky says.

He adds that the real question is how soon the agency will release more “substantive” guidance on its harmonization plans and what it will allow IRBs to implement between the time the Common Rule revisions go live and it harmonizes its regulations (set to be completed in December 2019) as part of the 21st Century Cures Act.

Who is Insearch
AND WHAT CAN WE DO FOR YOU?

- **Insearch is a clinical business development company** that has an exclusive network of successful and experienced clinical research sites located throughout the United States.

- **Insearch is not a study broker** and all network sites are thoroughly vetted to ensure their quality prior to entry into the group.

- **We vet our sites via a thorough process of conversation**, site visit (if necessary) and survey.

- **We are not a SMO.** We do not mandatorily handle budgeting, contracting or site management.

- **We can provide consultation** in areas where you may need assistance.

- **We identify studies within your areas** of expertise as well as areas where you would like to grow.

- **We track the progress of CDAs and feasibilities** from identification to study award in our database.

- **We are staffed to remain in front of the feasibility process.**

- **We provide comprehensive communication.**

- **We offer a flat monthly fee** that may be paid by check or credit card.

**Insearch**
A Clinical Business Development Company

Founded in 2008

**TO PARTNER WITH INSEARCH**
or learn more about the services we provide,
please contact Vinny Napoli today!

(727) 544-4842
WWW.INSEARCHGROUP.NET
## Drug & Device Pipeline News

For news on trial results, FDA approvals and drugs in development, Join the LinkedIn Drug Research Updates group!

<table>
<thead>
<tr>
<th>Company</th>
<th>Drug/Device</th>
<th>Medical Condition</th>
<th>Status</th>
<th>Sponsor Contact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akcea Therapeutics</td>
<td>TEGSEDI™ (inotersen)</td>
<td>Polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults</td>
<td>Granted approval by the FDA</td>
<td>TEGSEDI.com</td>
</tr>
<tr>
<td>Akcea Therapeutics</td>
<td>Akcea-APO(a)-LRx</td>
<td>Cardiovascular disease (CVD) and elevated levels of lipoprotein(a), or Lp(a)</td>
<td>Positive topline results from a Phase II clinical trial</td>
<td>akceatx.com</td>
</tr>
<tr>
<td>Bausch Health Companies, Inc.</td>
<td>BRYHALI™ (halobetasol propionate) Lotion, 0.01%</td>
<td>Plaque psoriasis in adults</td>
<td>FDA tentatively approved New Drug Application; final OK pending expiration of exclusivity for related product</td>
<td>bauschhealth.com</td>
</tr>
<tr>
<td>Eximo Medical Ltd</td>
<td>B-Laser™ Atherectomy System</td>
<td>Peripheral artery disease (PAD)</td>
<td>Granted 510(k) clearance by the FDA</td>
<td>eximomedical.com</td>
</tr>
<tr>
<td>YiSheng BioPharma Co.</td>
<td>PIKA® rabies vaccine</td>
<td>Rabies</td>
<td>Granted clearance by the China FDA to proceed with a clinical trial</td>
<td>yishengbio.com</td>
</tr>
<tr>
<td>Genentech</td>
<td>Hemlibra</td>
<td>Hemophilia A patients without factor VIII inhibitors</td>
<td>Granted approval by the FDA</td>
<td>gene.com</td>
</tr>
<tr>
<td>Leadiant Biosciences, Inc.</td>
<td>Revcovi™ (elapegademase-lvlr) injection</td>
<td>Adenosine deaminase severe combined immune deficiency (ADA-SCID) in children and adults</td>
<td>Granted approval by the FDA</td>
<td>leadiantbiosciences.com</td>
</tr>
<tr>
<td>Breckenridge Pharmaceutical, Inc.</td>
<td>Roflumilast Tablets, 500mcg (generic for Daliresp® Tablets)</td>
<td>COPD</td>
<td>Abbreviated New Drug Application approved by the FDA</td>
<td>bpirx.com</td>
</tr>
<tr>
<td>Valneva USA</td>
<td>IXIARO® (Japanese Encephalitis Vaccine, Inactivated, Adsorbed)</td>
<td>Japanese encephalitis</td>
<td>Accelerated dosing regimen approved by the FDA</td>
<td>PreventJE.com</td>
</tr>
<tr>
<td>Eidos Therapeutics, Inc.</td>
<td>AG10</td>
<td>amyloidosis (ATTR)</td>
<td>Granted Orphan Drug designation by the FDA</td>
<td>eidostx.com</td>
</tr>
<tr>
<td>Paratek Pharmaceuticals, Inc.</td>
<td>NUZYRA™ (omadacycline)</td>
<td>Community-acquired bacterial pneumonia; acute skin infections (ABSSSI) in adults</td>
<td>Granted approval by the FDA</td>
<td>ParatekPharma.com</td>
</tr>
<tr>
<td>Poxel SA</td>
<td>Imeglimin, an investigational therapeutic agent</td>
<td>Type 2 diabetes</td>
<td>Patient enrollment completed in the TIMES 2 trial of the Phase III registration program</td>
<td>poxelpharma.com</td>
</tr>
<tr>
<td>Chugai Pharmaceutical Co., Ltd</td>
<td>HEMLIBRA® (US generic name: emicizumab-kxwh)</td>
<td>Hemophilia A without factor VIII inhibitors in newborns, children and adults</td>
<td>Granted approval by the FDA</td>
<td>chugai-pharm.co.jp/english</td>
</tr>
<tr>
<td>Genentech</td>
<td>baloxavir marboxil</td>
<td>Influenza type A/H3N2 and type B</td>
<td>Phase III CAPSTONE-2 trial showed symptoms improved significantly faster in patients at high risk of serious flu who took the drug v. a placebo</td>
<td>gene.com</td>
</tr>
<tr>
<td>Zealand Pharma A/S</td>
<td>Glepaglutide</td>
<td>Short bowel syndrome (SBS)</td>
<td>First patient enrolled in a global Phase III trial</td>
<td>zealandpharma.com</td>
</tr>
</tbody>
</table>
## Upcoming Event Highlights

### Conferences

- **OCTOBER 23-25, 2018**
  - FDA Inspections Summit – 13th Annual
    - Bethesda, MD

- **NOVEMBER 1-2, 2018**
  - SOPs and Policies for the 21st Century: Why Less is More
    - Washington, DC

- **NOVEMBER 14-15, 2018**
  - Conducting Advanced Root Cause Analysis & CAPA Investigations
    - Princeton, NJ

- **NOVEMBER 14-15, 2018**
  - Clinical Trial Risk and Performance Management Summit
    - Princeton, NJ

- **DECEMBER 10-12, 2018**
  - Design of Medical Devices Conference, China 2018
    - Beijing, China

### Training Programs

- **NOVEMBER 1-31, 2018**
  - Phlebotomy Training — Two Day Training
    - Various locations

### Webinars

- **OCTOBER 18, 2018**
  - Retooling Risk-Based Quality Management Approaches in the Era of ICH EG(R2)

- **OCTOBER 30, 2018**
  - Understanding ISO 19011:2018 The Path to Better Medical Device System Audits

---

## JobWatch

The Source for Clinical Research Jobs and Career Resources

Twice monthly, CWWeekly provides featured listings of clinical research job openings, upcoming industry conferences and educational programs from JobWatch, CenterWatch’s online recruitment website for both clinical research employers and professionals.

For conferences, webinars, training programs and job postings, Join the LinkedIn JobWatch group!

## Jobs via Kelly Services

<table>
<thead>
<tr>
<th>Position</th>
<th>Company</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Trial/Study Manager</td>
<td>Indianapolis, IN</td>
<td></td>
</tr>
<tr>
<td>Lab Supervisor</td>
<td>Indianapolis, IN</td>
<td></td>
</tr>
<tr>
<td>Laboratory Tech Assistant</td>
<td>San Marcos, TX</td>
<td></td>
</tr>
<tr>
<td>Health Program Representative</td>
<td>Denver, CO</td>
<td></td>
</tr>
<tr>
<td>Associate Principle Scientist</td>
<td>Gaithersburg, MD</td>
<td></td>
</tr>
<tr>
<td>Principle Clinical Research Scientist</td>
<td>Milpitas, CA</td>
<td></td>
</tr>
<tr>
<td>Clinical Program Manager</td>
<td>Cambridge, MA</td>
<td></td>
</tr>
<tr>
<td>SAS Programmer II</td>
<td>Warsaw, IN</td>
<td></td>
</tr>
<tr>
<td>Regulatory Affairs Specialist</td>
<td>Pittsburgh, PA</td>
<td></td>
</tr>
<tr>
<td>Triage Manager</td>
<td>Ridgefield, CT</td>
<td></td>
</tr>
<tr>
<td>Sr. Research Associate</td>
<td>San Francisco, CA</td>
<td></td>
</tr>
<tr>
<td>Associate Director</td>
<td>Cranbury Township, NJ</td>
<td></td>
</tr>
<tr>
<td>Medical Technologist</td>
<td>Beaumont, TX</td>
<td></td>
</tr>
<tr>
<td>Research Associate II</td>
<td>Seattle, WA</td>
<td></td>
</tr>
</tbody>
</table>

[ VIEW ALL KELLY SERVICES JOBS ]

## More Jobs

<table>
<thead>
<tr>
<th>Position</th>
<th>Company</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Research Coordinator</td>
<td>The Ohio State University</td>
<td>Columbus, Ohio</td>
</tr>
<tr>
<td>Clinical Research Coordinator II</td>
<td>Emory University</td>
<td>Atlanta, GA</td>
</tr>
<tr>
<td>Sr. Director, Quality Assurance</td>
<td>IQVIA</td>
<td>Research Triangle Park, NC</td>
</tr>
<tr>
<td>Pharmaceutical Teaching Positions (April 2019)</td>
<td>International Education Services</td>
<td>Tokyo, Japan</td>
</tr>
<tr>
<td>Study Concierge, Virtual Trials</td>
<td>IQVIA</td>
<td>Research Triangle Park, NC</td>
</tr>
</tbody>
</table>

[ VIEW ALL JOB LISTINGS ]

---

© 2018 CenterWatch. Duplication or sharing of this publication is strictly prohibited.
Designed to Make Every Second of your Enrollment Period Count.

Achieve enrollment timelines with a customized, end-to-end recruitment plan from WCG Patient Engagement services. Backed by proven methods, a knowledge base of industry site enrollment performance, and our on-the-ground site support, we partner with you to enable your sites to achieve recruitment milestones on or ahead of schedule. These efficiencies could amount to you saving two months in patient screening time, or 4,838,400 seconds.