Much controversy surrounds equivalence and switchability between brand name and generic antiepileptic drug products or among different generic products. Clinicians are faced with conflicting publications, editorials, position statements from professional organizations, and statements from the FDA about the safety of generic substitution (1–3). The FDA has funded several ongoing trials testing bioequivalence of antiepileptic drugs in people with epilepsy (4–7). In addition, the FDA has begun implementing modified bioequivalence standards for drugs that fulfill criteria for narrow therapeutic index (NTI), and the FDA is in the process of determining which medications fulfill its criteria for NTI status (8). Further, the FDA has enumerated the following general characteristics of NTI drugs: 1) little separation between therapeutic and toxic doses (or the associated drug concentrations), 2) subtherapeutic concentrations lead to serious therapeutic failure, 3) subject to therapeutic drug monitoring, 4) possess low-to-moderate (i.e., ≤30%) within-subject variability, and 5) in clinical practice, doses often adjusted in very small increments (<20%).

The FDA collected literature, new drug application, and amended new drug application (ANDA) data to assess whether lamotrigine when used as an antiepileptic drug qualifies as an NTI drug (9). Based on these sources, the FDA could not find any data indicating that lamotrigine would qualify as an NTI drug. Specifically, there was little data that blood levels were used other than during pregnancy, and the magnitude of dose changes was rarely reported in clinical trials—if dose changing was allowed at all. We speculated that many of the NTI characteristics—especially subtherapeutic concentrations and dose adjustments—were common in general clinical practice for lamotrigine but not reported in the medical literature. We therefore enlisted the help of the Q-PULSE panel with the goal of determining from the Q-PULSE survey participants how they use therapeutic drug monitoring and the magnitude of lamotrigine dose changes that are typically used in practice.

The Q-PULSE panel was organized by the American Epilepsy Society in 2012 (10). It is a panel of epilepsy specialist physicians chosen from epilepsy centers belonging to the National Association of Epilepsy Centers representing a broad cross-section of Epilepsy Centers across the United States. The aim of the Q-PULSE program is to capture expert opinion on issues for which quality evidence is lacking by having panel members complete online surveys on specific topics.

For the lamotrigine survey, the cases and questions were created by Michael Privitera and Michel Berg (principal investigators for Equivalence Among Antiepileptic Drug Generic and Brand Products in People With Epilepsy-EQUIGEN studies), with comments from the EQUIGEN steering committee. The EQUIGEN studies are FDA-funded antiepileptic drug generic bioequivalence studies. Cases and questions were provided to the FDA Office of Generic Drugs staff, who provided comments. The Q-PULSE Steering Committee approved the final version to adhere to general rules on survey length and question types.

Questions were of two types: case scenarios with questions on concentration testing and dosing, and more general questions, for example, “In which of these situations would you obtain lamotrigine blood levels?” The survey opened on December 29, 2013, and closed with data compiled February 4, 2014. There were a total of 113 responses from the 200-member panel, a 57% response rate.

Questions were of two types: case scenarios with questions on concentration testing and dosing, and more general questions, for example, “In which of these situations would you obtain lamotrigine blood levels?” The survey opened on December 29, 2013, and closed with data compiled February 4, 2014. There were a total of 113 responses from the 200-member panel, a 57% response rate.

Survey Results
The first two case scenarios and then two general questions explored when respondents would obtain blood level monitoring for loss of seizure control or adverse effects and the impact that a concentration result had on their clinical thinking.
**Case 1 (Figures 1 and 2)**
A 30-year-old woman has well-controlled seizures for 3 years on lamotrigine monotherapy at 300 mg daily (150 mg twice per day) with trough blood concentrations in the 4–6 mcg/ml range. She begins receiving an oral contraceptive with a combination of an estrogen and a progestin. One month later, she experiences a seizure. She assures you she has been compliant with both medications.

**FIGURE 1.** What is the likelihood that you would check a lamotrigine blood level to assess a possible drug-drug interaction?

**FIGURE 2.** A trough blood level is 2.5 mcg/ml. In your opinion, what is the likelihood that the seizure was related to this drop in blood level?

**Case 2 (Figures 3, 4, 5 and 6)**
A 42-year-old man with idiopathic generalized epilepsy has been receiving lamotrigine 300 mg twice daily with trough levels in the 8–10 mcg/ml range. In the past several months, he has had 3 tonic-clonic seizures and frequent myoclonus. For better seizure control, his physician added valproate 250 mg twice daily. The patient has no further seizures or myoclonus, but after 2 weeks, he is experiencing dizziness and diplopia, usually maximally about 2 hours after he takes his lamotrigine.

**FIGURE 3.** What is the likelihood that the adverse effects the patient is experiencing are related to lamotrigine?

**FIGURE 4.** What is the likelihood that you will check a lamotrigine blood level to assess for a possible drug-drug interaction?

**FIGURE 5.** For the same case scenario (#2) above, a trough blood level is checked and comes back at 16 mcg/ml. What is the likelihood that the adverse effects are related to this increase in blood level?
FIGURE 6. The next lamotrigine dose you would like to use is:

The next two questions were general questions unrelated to a specific case scenario.

FIGURE 7. Thinking about the patients you treat with lamotrigine (excluding patients who are pregnant), what percentage of these patients have received at least once yearly lamotrigine blood level monitoring?

FIGURE 8. For what percent of your patients on lamotrigine (excluding patients who are pregnant) do you obtain regular blood levels and use the blood level result to help guide lamotrigine dose adjustment? (The interval between levels can be short or long).
The next two case scenarios were designed to determine the specific dose increment size in the clinical situation where symptoms of toxicity or increased seizures developed in a previously well-controlled patient.

**FIGURE 9.** You are treating a patient who is taking lamotrigine 300 mg bid for medical refractory epilepsy who has had a >50% improvement in seizure frequency since adding lamotrigine. More than 6 months after being on unchanged therapy, the patient develops what you believe are peak level side effects of ~30 minutes of dizziness starting 1.5-2 hours after the morning dose ~2 times per week. You attribute side effects to the lamotrigine and you decide to decrease the lamotrigine dose. The next dose you would most likely use is:

![Responses Graph](image)

**FIGURE 10.** You are treating a patient who is taking a lamotrigine 300 mg twice daily and has been seizure free for almost a year. When this dose was first reached, the patient experienced dizziness, but this resolved after several weeks. The patient has experienced two seizures in the last 2 months without obvious triggers, denies missing medications, and blood levels are in the same range (8-10 mcg/ml) they have been for the past year. You decide to increase the dose. The next dose you would most likely use is:

![Responses Graph](image)
Q-PULSE Survey on adjusting lamotrigine doses

Discussion

This Q-PULSE survey provides a snapshot of how a group of neurologists who provide specialized care for people with epilepsy use lamotrigine in clinical practice. The survey response was strong at 57%. Data on use of lamotrigine blood levels and magnitude of lamotrigine dose adjustments were obtained, which can inform decisions about whether a drug qualifies for NTI categorization.

The combination of case-related and general questions indicate that this group of epileptologists uses lamotrigine blood levels frequently to guide the therapy with lamotrigine. More than 90% of respondents answered that they are highly or somewhat likely to use lamotrigine blood levels to check for a drug–drug interaction, whether the interacting drug was suspected of inhibiting (80% highly likely) or inducing (70% highly likely) lamotrigine metabolism.

Nineteen percent of respondents answered that they get yearly levels on less than 20% of their patients, whereas 24% of respondents get yearly levels on more than 80% of their patients. More than one-third (36%) of respondents answered that they obtain regular blood levels and use the results to guide dose adjustments for more than 40% of their patients. Fewer than 10% of respondents indicated that they do not use blood levels regularly. These findings show that there is incomplete consensus among epileptologists on the routine use of blood level monitoring to guide dose adjustments, but most of the survey respondents will use blood level monitoring in specific clinical situations.

In several common clinical situations where small dose changes might occur, many respondents indicated that they would make dose changes of <20% of the total daily dose. When a dose reduction was required because of a presumed drug–drug interaction (figure 6), almost 50% of respondents answered that they would have reduced the lamotrigine dose by less than 20% of the total daily dose. In the question in Figure 10, a patient who had previously experienced adverse effects on the current dose of lamotrigine required in increased dose because of loss of seizure control. For this patient, over 90% of the responders would increase the dose, and all of these responders stated that they would have increased it by <20% of the total daily dose. Of importance, the doses used for these questions were specifically selected to be within the range of doses used for lamotrigine in clinical practice.

This survey is not an exhaustive exploration of the clinical management approaches for lamotrigine use in epilepsy, but it does represent common clinical situations of people with epilepsy treated with lamotrigine at epilepsy centers. The survey is limited in its generalizability because the cases are hypothetical. However, the goal of the survey was neither to precisely define appropriate lamotrigine dose changes nor to establish guidelines for when to measure lamotrigine blood levels. The survey is valuable because it demonstrates that practicing epileptologists report a standard of care that commonly uses lamotrigine blood levels to guide therapy and often adjust the dose of lamotrigine in small increments (less than 20% of the daily dose) in several frequently encountered clinical situations. This type of data cannot be ascertained by a review of the published medical literature or medication prescribing information. We believe the data gathered in this survey should help inform the decision about the NTI status of lamotrigine; and similar data should be sought for other antiepileptic drugs.

The final general question used a multi-answer format to assess the circumstances where lamotrigine concentrations were useful in clinical care.

FIGURE 11. In which of the following circumstances do you use lamotrigine blood levels (the interval between levels can be short or long):
Acknowledgments
The authors appreciate the comments of Jacqueline French, MD, who initiated the Q-PULSE project, as well as the EQUIGEN investigators, Jerzy Szaflarski, MD, PhD, Barbara Dworetzky, MD and Lebron Paige, MD.

References
10. French JA. Taking the “Pulse” of our society with Q-PULSE. Epilepsy Curr 13: 304.
Instructions
The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. Each author should submit a separate form and is responsible for the accuracy and completeness of the submitted information. The form is in four parts.

1. Identifying information.
   Enter your full name. If you are NOT the main contributing author, please check the box “no” and enter the name of the main contributing author in the space that appears. Provide the requested manuscript information.

2. The work under consideration for publication.
   This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. Checking “No” means that you did the work without receiving any financial support from any third party – that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds with which to pay you. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation or commercial sponsor, check “Yes”. Then complete the appropriate boxes to indicate the type of support and whether the payment went to you, or to your institution, or both.

3. Relevant financial activities outside the submitted work.
   This section asks about your financial relationships with entities in the bio-medical arena that could be perceived to influence, or that give the appearance of potentially influencing, what you wrote in the submitted work. For example, if your article is about testing an epidermal growth factor receptor (DGFR) antagonist in lung cancer, you should report all associations with entities pursuing diagnostic or therapeutic strategies in cancer in general, not just in the area of EGFR or lung cancer.

   Report all sources of revenue paid (or promised to be paid) directly to you or your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. Please note that your interactions with the work’s sponsor that are outside the submitted work should also be listed here. If there is any question, it is usually better to disclose a relationship than not to do so.

   For grants you have received for work outside the submitted work, you should disclose support ONLY from entities that could be perceived to be affected financially by the published work, such as drug companies, or foundations supported by entities that could be perceived to have a financial stake in the outcome. Public funding sources, such as government agencies, charitable foundations or academic institutions, need not be disclosed. For example, if a government agency sponsored a study in which you have been involved and drugs were provided by a pharmaceutical company, you need only list the pharmaceutical company.

4. Other relationships
   Use this section to report other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work.
Section #1 Identifying Information

1. Today’s Date: 7/13/14

2. First Name  Michael   Last Name Privitera  Degree MD

3. Are you the Main Assigned Author?  ✔ Yes  ☐ No

   If no, enter your name as co-author:

4. Manuscript/Article Title: How Do Clinicians Adjust Lamotrigine Doses and Use Lamotrigine Blood Levels?—A Q-PULSE Survey

5. Journal Issue you are submitting for:

Section #2 The Work Under Consideration for Publication

Did you or your institution at any time receive payment or services from a third party for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Complete each row by checking “No” or providing the requested information. If you have more than one relationship just add rows to this table.

<table>
<thead>
<tr>
<th>Type</th>
<th>No</th>
<th>Money Paid to You</th>
<th>Money to Your Institution*</th>
<th>Name of Entity</th>
<th>Comments**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grant</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consulting fee or honorarium</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Support for travel to meetings for the study or other purposes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fees for participating in review activities such as data monitoring boards, statistical analysis, end point committees, and the like</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Payment for writing or reviewing the manuscript</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Provision of writing assistance, medicines, equipment, or administrative support.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* This means money that your institution received for your efforts on this study.
** Use this section to provide any needed explanation.
**Section #3 Relevant financial activities outside the submitted work.**

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the “Add” box. You should report relationships that were present during the 36 months prior to submission.

Complete each row by checking “No” or providing the requested information. If you have more than one relationship just add rows to this table.

<table>
<thead>
<tr>
<th>Type of relationship (in alphabetical order)</th>
<th>No</th>
<th>Money Paid to You</th>
<th>Money to Your Institution*</th>
<th>Name of Entity</th>
<th>Comments**</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Board membership</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Consultancy</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Employment</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Expert testimony</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Grants/grants pending</td>
<td></td>
<td>Yes</td>
<td>UCB; Neuren Pharma</td>
<td>Clinical trials</td>
<td></td>
</tr>
<tr>
<td>6. Payment for lectures including service on speakers bureaus</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Payment for manuscript preparation.</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Patents (planned, pending or issued)</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. Royalties</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10. Payment for development of educational presentations</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11. Stock/stock options</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12. Travel/accommodations/meeting expenses unrelated to activities listed.**</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13. Other (err on the side of full disclosure)</td>
<td></td>
<td>yes</td>
<td>Upsher Smith, Lilly, DSMB</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* This means money that your institution received for your efforts.

** For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

**Section #4 Other relationships**

Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

☒ No other relationships/conditions/circumstances that present a potential conflict of interest.

☐ Yes, the following relationships/conditions/circumstances are present:

Thank you for your assistance.

_Epilepsy Currents_ Editorial Board