Urgent Field Safety Notice 001

Commercial name: TheraScreen: EGFR29 Mutation Kit
FSCA-identifier: AER-09-001
Type of action: Advice and Device Destruction (T790M Vials only)

Date: 15th June 2009

Details on Affected Devices:
Type of Device: IVD Device
Model Name: TheraScreen: EGFR29 Mutation Kit
Product Codes: EG-21/EG-22
Affected Batches: DE003-01, DE004-01, DE005-01, DE006-01, DE007-01

Description of the problem:

We have identified a problem with the T790M reaction mix in the TheraScreen EGFR29 Mutation Kit. This problem is specific to the T790M reaction and all other reactions in the kit are unaffected.

Two T790M ARMS Primers are normally included in the formulation of the T790M Reaction Mix (ARMS Primer 1 and ARMS Primer 2). Two ARMS primers are necessary because there is a naturally occurring single nucleotide polymorphism nine base pairs upstream of the T790M mutation. ARMS primer 1 is complementary to the G variant and ARMS primer 2 is complementary to the A variant.

It has been identified that a formulation problem has occurred. For the affected kit batches, twice the required volume of ARMS Primer 1 was added to the Reaction Mix vial. No ARMS Primer 2 was added to the Reaction Mix vial. ARMS primer 1 gives inefficient amplification of mutations on the A haplotype. This means that patients who carry the T790M mutations on the A haplotype may be incorrectly identified as normal – particularly if the mutation is present at low level.

Investigations have also highlighted that the ARMS primer 1 can form a primer-primer interaction in the T790M Reaction Mix with the Scorpion primer and generate low level signals in the absence of template. This problem manifests itself as intermittent and low level (Ct>34) No Template Control (NTC) amplification of the T790M reaction. As the problem is intermittent the possibility exists that the
amplification would be seen in a sample but not the NTC thereby potentially leading to false positive results.

The clinical implications of false positives and false negatives are indicated in the table below:

<table>
<thead>
<tr>
<th>Incorrect Result</th>
<th>Potential Clinical Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>False positive</td>
<td>It may incorrectly influence a doctor’s decision to deny a patient access to tyrosine kinase inhibitor therapies e.g. Iressa or Tarceva. The patient may benefit from the drug.</td>
</tr>
<tr>
<td>False negative</td>
<td>In the absence of other sensitising mutations it may incorrectly influence a doctor’s decision to treat a patient with a tyrosine kinase inhibitor therapy e.g. Iressa or Tarceva. The patient might be less likely to benefit from the drug.</td>
</tr>
</tbody>
</table>

**Action to be taken by the User:**
Please destroy any T790M Reaction Mix vials contained within TheraScreen: EGFR29 Mutation Kits from the affected batches. These tubes must be disposed of into general laboratory waste.

Please confirm disposal or that the vials have previously been used or discarded by completion of the fax back form included in Appendix 1.

Please review any T790M results obtained from TheraScreen: EGFR29 Mutation Kits from the affected batches (as indicated above). This review should include the clinical implications of any treatment decisions made regarding prescription of any tyrosine kinase inhibitor therapies e.g. Iressa or Tarceva.

Should you have any concerns or if you require further clarification, please contact DxS Technical Support as indicated below.

**Contact Details:**
DxS Limited, 48 Grafton Street, Manchester, M13 9XX, UK
Tel: +44 (0) 161 606 7201
Email: technical@therascreen.com

Please advise the appropriate personnel working in your Laboratory of the content of this Field Safety Notice.

We sincerely apologize for any inconvenience and thank you in advance for your co-operation.

The undersigned confirms that this notice has been provided to the appropriate Regulatory Agencies.

Signed …D. Clennell……………………………….. Date …15th June 2009………………………..

Dave Clennell
Director of Quality
## Confirmation of Disposal Form

### Details on Affected Devices:
Type of Device: IVD Device
Model Name: TheraScreen: EGFR29 Mutation Kit
Product Codes: EG-21/EG-22
Affected Batches: DE003-01, DE004-01, DE005-01, DE006-01, DE007-01

<table>
<thead>
<tr>
<th>Name</th>
<th>[DxS to insert Company/Organisation Name]</th>
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<tbody>
<tr>
<td>Company/Organisation</td>
<td>[DxS to insert specific batches and numbers of kits per batch shipped to the customer]</td>
</tr>
<tr>
<td>Position</td>
<td></td>
</tr>
<tr>
<td>Affected Batches</td>
<td></td>
</tr>
</tbody>
</table>

I confirm that all T790M Reaction Mix vials included in TheraScreen: EGFR29 Mutation Kits from the affected batches (as indicated above) have been:

- Used/Destroyed/Discarded*

*Please delete as appropriate

| Signed | |
| Date | |

Please Fax this form to and/or scan and e-mail the signed form to:

Vicki Wilson (Product Manager) on +44 161 6067313
Victoria.wilson@dxsdiagnostics.com