BETTER REGULATION OF MEDICINES INITIATIVE (BROMI):

FIFTH REPORT ON PROGRESS

March 2012
In January 2011, when the Better Regulation of Medicines Initiative (BROMI) group met to take stock of progress, the group considered a challenging question – is BROMI still the a key approach to delivering proportionate, risk-based, targeted and cost effective medicines regulation? The answer from the participants – from across industry and Government - was an emphatic “yes”: a conclusion based on evidence of the changes that BROMI has been able to deliver in the six years since the launch of the initiative.

Since the fourth report on the BROMI was published in Summer 2009, BROMI has continued to use the now time tested methodology of pilot, evaluate and mainstream to deliver real benefits that both industry and the regulator can feel, freeing up the industry to focus on the development of new products and regulators to better focus on important public health gains.

This fifth report charts the progress on the original BROMI work streams – patient information, authorisation and pharmacovigilance – but importantly, also highlights new priority areas of work in the reclassification of medicines and in regulatory communications. The report also highlights an example of the way the BROMI approach has been used proactively to address potential burdens in delivery of communications by companies to deliver a high quality outcome for healthcare delivery with significant savings in the process.

It is also reassuring to know that the BROMI approach will be informing how changes to the European Pharmacovigilance legislation are implemented, in the UK and across Europe.

So in moving forward in 2012, BROMI remains as relevant, and as productive a methodology for change, as it was when the initiative was launched. In a changing regulatory landscape, BROMI has continued to show that it can deliver real regulatory change in the UK and act as a model for Europe.

Kent Woods
Chief Executive, MHRA
BETTER REGULATION OF MEDICINES INITIATIVE (BROMI): FIFTH REPORT ON PROGRESS

1 Executive Summary

1.1 This fifth report reviews progress since the last report was published in the summer of 2009, firstly in the three original work streams – patient information, authorisation and pharmacovigilance – and in two new work streams – reclassification of medicines and communications. Key milestones include

- work to further expand the patient information self certification scheme
- a reduction in the volume of Anonymised Single Patient Reports (ASPRs) generated and sent out to industry
- a new approach to coordinated communications to healthcare professionals, and
- new work streams on reclassification of medicines and communications.

2 Introduction

2.1 The Better Regulation of Medicines Initiative (BROMI) is a ground-breaking program of work designed to strip away unnecessary regulatory burdens in relation to medicines. These burdens have been added incrementally over four decades. The opportunity has been grasped to introduce new, proportionate measures while ensuring safeguards to protect public health are maintained.

2.2 BROMI is led by the Medicines and Healthcare products Regulatory Agency (MHRA) and is a collaboration of industry, health professionals and government - MHRA, Department of Health (DH) and the Department for Business, Innovation and Skills (BIS). BROMI was first launched in 2005 and this is the fifth report on progress to be published.

2.3 At the heart of the initiative is the concept of matching regulation to risk and using different regulatory tools to deliver proportionate safeguards. This enables the MHRA to better focus its expertise on important public health issues rather than routine administrative work. BROMI is working to a three tier regulatory model: applications that can be self certified, changes requiring prior approval by a third party, and applications that would continue to require MHRA assessment. BROMI has also explored work sharing models to minimise duplication of work, as well as procedural simplification with IT solutions where appropriate. The outcome has been to deliver new and updated medicines to patients faster, minimise the burden on industry and free up both industry and regulator to focus on innovation and safety.
3 Summary of progress and further work since last report

3.1 A timetable of work is provided in Annex A. Importantly the future work programme includes new work streams in the area of Reclassification and Communications. An updated summary of the new ways of working introduced through BROMI and key highlights since the last report in 2009 are set out below and are grouped according to the BROMI model they exemplify.

Self certification
- Work to expand the self certification scheme of changes to patient information so as self certification becomes the default position for the vast majority of changes.
- Invalidation rates for Type IA notification scheme at an all time low following efforts to improve the scheme.
- A self certification scheme for Periodic Safety Update Reports (PSURs) mainstreamed after successful pilot.

Procedural simplification and IT solutions
- An improved processing scheme for national renewal applications mainstreamed following a successful pilot.
- Reduction in the number of ASPRs being sent to industry following key IT changes.
- Best practice guide on the ‘Reporting of Individual Case Safety Reports (ICSRs).
- Work on streamlining the reclassification procedure.
- Work on improving MHRA-industry communications for safety variations.
4 Progress in the Patient Information work Stream

Self certification scheme
4.1 The self-certification scheme for changes to patient information, which has been in operation since May 2006, continues to be a success. The graph below shows figures of notifications submitted through the scheme from its inception six years ago. The large numbers submitted in 2010 were as a result of the new legal provisions concerning Braille on the pack. Overall, numbers of notifications submitted annually have been around 1600. This accounts for around 40% of all changes to packaging submitted to the MHRA in a 12 month period.

Figure 2 showing numbers of BROMI notifications submitted over time

4.2 Audits of the scheme have not highlighted any issues relating to patient safety, few processing issues have been identified and the scheme appears to be working well. In light of this success a fundamental change to expand the self certification scheme is being introduced with a move from a positive list of changes accepted as notification to a negative list of changes that must be subject to full assessment. It is envisaged that the expanded scheme will be in place by July 2012 resulting in self certification/notification becoming the default position for the vast majority of changes to patient information. The expectation is that unless the changes being proposed fall into one or more of the four categories which will require professional assessment, all other changes will have to be self-certified by the marketing authorisation holder and notified to the agency. The expectation is that application numbers over a 12 month period will fall by around a further third. This will enable resource to be focussed on a smaller number of applications thereby speeding up throughput.

4.3 Guidance has been prepared to give industry time to prepare for the radical change in approach. Baseline metrics are being collected by the MHRA and industry to enable the impact of the change to be measured.
Code of practice on pack re-design

4.4 A Code of Practice on pack re-design which is focused on encouraging best practice has been operating since January 2007 and outlines a third party pre-approval model for non-statutory packaging information. Proposed changes are pre-approved by the Proprietary Association of Great Britain (PAGB) before coming to the MHRA for final approval. The Scheme has been extended to own label suppliers and was agreed as a mainstream process from 1 June 2009. Numbers submitted under this scheme have remained small and account for only around 4% of applications submitted to the MHRA through the Patient Information Quality Unit and 2% of all changes to labelling and PILs submitted to the MHRA in a 12 month period. Under the expanded notification scheme, changes to pack design will remain subject to full professional assessment by the MHRA. The Best Practice Guidance document being prepared will include the full details of the code of practice going forward.

5 Progress in the Pharmacovigilance work stream

ASPRs
5.1 The Pharmacovigilance work stream has been focussing on reducing the burden of Anonymised single Patient Reports (ASPRs) and Periodic Safety Update reports (PSURs) and good progress has been made. Key technical changes have been introduced on 2 August 2011 in relation to the MHRA’s obligation to send companies ASPRs so there is a reduction in the burden of processing these reports until electronic reporting (E2B) is fully implemented and all ASPRs can be handled electronically as Individual Case Safety Reports (ICSRs). Data was collected from 27 companies both before and after the ASPR change was implemented and this demonstrated an approximate saving of £1.2M to industry each year overall.

5.2 The volume of ASPRs based on literature articles the MHRA send to industry was identified as an area where efficiencies could be made. A proposal was made to prevent ASPRs being generated for Adverse Drug Reaction (ADR) reports based on literature articles. Industry was requested to collect numbers of ASPRs received per day for 4-6 weeks before after the change was applied on 24 October 2011. MHRA numbers of ASPRs/ICSRs sent to industry in Nov and December showed a 50% reduction compared with that sent in August and September. A 44% reduction in the number of ADR reports based in literature articles received by the MHRA was also seen in November/December compared to August/September.

5.3 A limited set of results was received from industry, showing range of reductions between 16% and 65% in overall ASPRs/ICSRs received after the change was introduced. This gave an average of a 37% overall reduction. A calculation using the annual reduction in ASPRs sent by the MHRA, resources estimated to process each ASPR and a full-time equivalent salary of £30,000 estimates a total saving of resource for industry of approximately £588,000 to £785,000 per year. Early feedback received from industry is that these...
estimates are conservative. Taking into account higher staff costs the actual savings are likely to be significantly higher.

**Periodic Safety Update Reports (PSURs)**
5.4 Following a successful BROMI pilot a self-certification scheme for PSURs has now been mainstreamed in April 2011 and will applies to purely national authorisations of well established medicines. This enables marketing authorisation holders to self certify PSURs for substances with an established safety profile, for which there is no risk management plan and where there is no new safety data since the last PSUR. Uptake of this scheme is being encouraged.

**Best practice guide for Adverse Drug Reaction (ADR) reporting**
5.5 In February 2011 the MHRA published a best practice guide - 'Reporting of Individual Case Safety Reports (ICSRs)'. This sets out the MHRA’s position on how to code ADRs to a high-quality standard for entry into the database. Data quality of ICSRs is an important issue that affects all stakeholders, particularly to support accurate detection and analysis of drug safety signals. Furthermore, errors in reports give rise to a large volume of enquiries, resulting in a significant administrative burden for both industry and the MHRA in updating cases. It is hoped the guide will contribute to delivering high standards in classification by highlighting common findings from audits of ICSRs and providing specific examples of good practice. The guide is seen as a useful way to improve quality without the need for face to face meetings with companies.

**European pharmacovigilance legislation**
5.6 New European Pharmacovigilance legislation will come into force in July 2012 and the BROMI Pharmacovigilance subgroup is looking at transitional measures which will help to reduce the burden on industry at a national level. There is opportunity to influence Europe, and the UK’s proposals on managing the transition are being fed back through the European system. In particular MHRA aims to facilitate early transition for companies from the Detailed Description of Pharmacovigilance Systems (DDPS) to the Pharmacovigilance System Master File.

**6 Progress with the Authorisation work stream**
6.1 The BROMI variations scheme was launched as a mainstream MHRA procedure from 1 April 2008. All companies are now able to self-certify the simplest changes to their medicines licences through a ‘do-and-tell’ procedure, and an expedited process is in place for other changes, allowing MHRA to devote more time to scrutinising the more significant changes. The invalidation rate for BROMI Type IA applications has remained under close review. A Type IA Variations subgroup has been created to consider how the IA notification scheme could be improved and the current rejection rates reduced. The subgroup met twice in 2011 and it is encouraging to see that the rejection rates are now at an all time low and have been reduced from a peak of 33% to 13%.
6.2 During the 2010-2011 financial year a total of 16,378 Type IA BROMI variation applications were submitted. From April 2009 no fee has been charged by the Agency for these variations.

6.3 A BROMI pilot for improved processing of national renewal applications started on 1 November 2008. Following a successful pilot this scheme was mainstreamed in August 2009. The new procedure involves a reduced submission whereby information that is currently held on the Sentinel database may be omitted from the consolidated renewal file. Thirty percent of renewals are now coming in to the Agency through the BROMI scheme. This is estimated to make a saving of around 15% of assessment time spent on renewals at the MHRA.

7 New BROMI work areas

7.1 In January 2011 the group met to discuss the future of BROMI and to develop new ideas. It was agreed that the BROMI principles should be applied to the reclassification of medicines process and that a regulatory communications work stream was also needed. This would examine how improved communications between the MHRA and industry throughout different regulatory procedures could help to reduce burden and streamline processes.

Reclassification of Medicines work stream

7.2 A BROMI Reclassification of Medicines subgroup has been established to develop proposals for streamlining the reclassification process. Proposals should ensure more predictable timelines for industry, with clear guidance on work up-front to support high quality “Right First Time” applications. The proposals would also provide a planned approach to moves from P to GSL (for products which would be appropriate for GSL supply) once sufficient experience has been gained in the Pharmacy setting. An updated reclassification guideline for applicants is being finalised (due Q1 2012), and this will be published following consultation with key healthcare professional groups to support the introduction of the new process.

Communications work stream

7.3 A Communications subgroup has been set up to look at how communications between companies and MHRA can be improved at different milestones in regulatory procedures. The subgroup has initially focussed on safety variations and improvement of communications to streamline the procedure. Innovative ideas are under discussion with the aim of driving the “Right First time” principle and minimising iterative interactions.

7.4 A good example of BROMI in action is the collaborative approach taken by the MHRA and the British Generic Manufacturers Association (BGMA) in relation to industry safety communications to health professionals. This is aimed at reducing cost and improving efficiency in communicating important
drug safety information to healthcare professionals when a number of companies are simultaneously involved.

7.5 When important new safety information on a medicine needs to be communicated, all individual drug manufacturers are required by law to send printed literature to all healthcare professionals - including GPs, nurses and pharmacists. Using a BROMI approach in a specific case, safety information was centrally co-ordinated by the BGMA on behalf of 12 companies, then approved by the MHRA and sent to healthcare professionals via a single communication. This meant the regulator was not required to approve 12 separate applications and healthcare professionals received one set of consistent, clear information.

7.6 The costs associated with a Direct Healthcare Professional Communication for distribution alone amount to around £30,000 for each communication. In this one example, the savings in distribution costs amount to around £350,000. Taking into account the time saved in the development and approval of a dozen sets of information about the same drug substance, and the savings could amount to £500,000 or more. Perhaps more importantly, healthcare professionals get a single set of information, making it more likely to be read, understood and acted upon – benefitting public health.

7.7 Communications resulting from Europe wide safety reviews are likely to increase as the changes to European Pharmacovigilance legislation come into force, so this new BROMI approach potentially has wide benefits – to the industry, regulator and healthcare professionals.

8 Forward look

8.1 Much progress has been made since the publication of the fourth BROMI report in the summer of 2009. Two new work streams are being explored and the self certification scheme for changes to product information is being expanded so that the BROMI scheme is the default position for the vast majority of changes to patient information.

8.2 In relation to Pharmacovigilance the BROMI subgroup is working to ensure a smooth transition to the new provisions of the European legislation to ease the burden on industry and regulators.

8.3 In order to continue to improve in the area of communications, it will be important to move away from paper mailing lists and towards electronic communication of drug safety information. The Agency will work with the interested stakeholders to progress this going forward.

8.3 The BROMI Working Group is constantly exploring where administrative burdens can be reduced. All ideas are welcome and can be sent directly to the dedicated BROMI email address BROMI@mhra.gsi.gov.uk.
9 Conclusion

9.1 Since its inception in 2005, it has become clear that the critical success factors for BROMI were to have clear goals, buy-in from both industry and regulators, investment in up-front work to pilot and evaluate projects, explicit allocation of responsibility, and moving new ways of working into Europe. As we move the work of BROMI forward in a changing regulatory landscape we continue to keep these critical success factors and the BROMI principles at the forefront of planning and action.

BROMI Working Group
March 2012
## Annex A - Better Regulation of Medicines Initiative (BROMI) Timetable of work

<table>
<thead>
<tr>
<th>Work item</th>
<th>Project start date</th>
<th>Delivery date</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction of self certification/notification procedures</td>
<td>Immediate</td>
<td>May 2006</td>
<td>Achieved</td>
</tr>
<tr>
<td>Self-certification of minor changes to patient information to be rolled out to POM sector</td>
<td>Nov 2006</td>
<td>Nov 2006</td>
<td>Achieved</td>
</tr>
<tr>
<td>Code of practice on pack re-design</td>
<td>Jul 2006</td>
<td>Summer 2008</td>
<td>Achieved</td>
</tr>
<tr>
<td>Self certification of simple variations</td>
<td>Mar 2006</td>
<td>1 Apr 2008</td>
<td>Achieved</td>
</tr>
<tr>
<td>Streamlined process for Copy licences</td>
<td>Mar 2006</td>
<td>Feb 2007</td>
<td>Achieved</td>
</tr>
<tr>
<td>Change of Ownership – timeframe and variations roll over</td>
<td>Summer 2006</td>
<td>Jul 2007</td>
<td>Achieved</td>
</tr>
<tr>
<td>Streamlining the renewals process</td>
<td>Jan 2008</td>
<td>Autumn 2009</td>
<td>Achieved</td>
</tr>
<tr>
<td>ASPR Simplification</td>
<td>2007</td>
<td></td>
<td>Changes have been implemented</td>
</tr>
<tr>
<td>Work sharing of PSUR for same active</td>
<td>Jul 2007</td>
<td>Review of pilot and applicability for roll out Jun 2008</td>
<td>Pilot completed and industry advised cost/time savings not sufficient to benefit full implementation</td>
</tr>
<tr>
<td>Self certification of PSURs</td>
<td>Dec 2008</td>
<td>Apr 2011</td>
<td>Implemented as mainstream process</td>
</tr>
<tr>
<td>Third party pharmacovigilance literature reviews</td>
<td>Nov 2006</td>
<td>Pilot Sep 2009</td>
<td>Under review in light of new PV legislation changes</td>
</tr>
<tr>
<td>Revision of the Code of practice on pack re-design</td>
<td>Summer 2009</td>
<td>Dec 2009</td>
<td>Completed. Guidance will be added to BPGLPM from expansion of notification scheme.</td>
</tr>
<tr>
<td>Expansion of the self certification scheme for minor changes to patient information</td>
<td>Dec 2010</td>
<td>Jul 2011</td>
<td>Guidance prepared and circulated for comment Dec 2011 for launch spring 2012</td>
</tr>
<tr>
<td>Reclassification of Medicines work stream</td>
<td>Jul 2011</td>
<td>Spring 2012</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Communications work stream</td>
<td>Oct 2011</td>
<td>Work-plan to be in place by end Mar 2012</td>
<td>Commenced Oct 2011</td>
</tr>
<tr>
<td>Healthcare professional communications</td>
<td>Dec 2012</td>
<td>Feb 2012</td>
<td>Achieved with a one off saving of £500,000</td>
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