

**BETTER REGULATION OF MEDICINES
INITIATIVE (BROMI):
THIRD REPORT AND RECOMMENDATIONS**



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BETTER REGULATION OF MEDICINES INITIATIVE (BROMI)

THIRD REPORT AND RECOMMENDATIONS

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BETTER REGULATION OF MEDICINES INITIATIVE (BROMI)

THIRD REPORT AND RECOMMENDATIONS

Chief Executive's foreword

Since the first meeting of the Better Regulation of Medicines Initiative (BROMI) Working Group, in 2005, real progress has been made. BROMI has achieved the first breakthroughs in simplifying the complex and time consuming systems of medicines regulation built up since thalidomide, and in doing so upheld the fundamental need to always put patient safety first.

The Medicines and Healthcare products Regulatory Agency (MHRA) continuously welcomes ideas on how administrative burdens can be reduced and intends to make the most of all the regulatory opportunities. I am pleased to say that the scope of BROMI has been widened to the innovative sector of the industry as well as the non-prescription sector, and that a third work stream in relation to Pharmacovigilance is underway and already making an impact.

I wish to thank the BROMI stakeholders for all the work they have done. We should all be proud of what BROMI has achieved and it is encouraging to know that the progress made has been recognised - firstly by winning an EU better regulation award in October 2007, the Red Tape Reduction award, hosted and presented by the Standard Cost Model Network, in competition against 21 other initiatives from across the EU - and secondly as one of 10 finalists in the better regulation category, at the 2007 National Business Awards.

Although a great deal has already been achieved, the work does not stop here and the future work plan demonstrates that there is still a great deal more progress to be made.

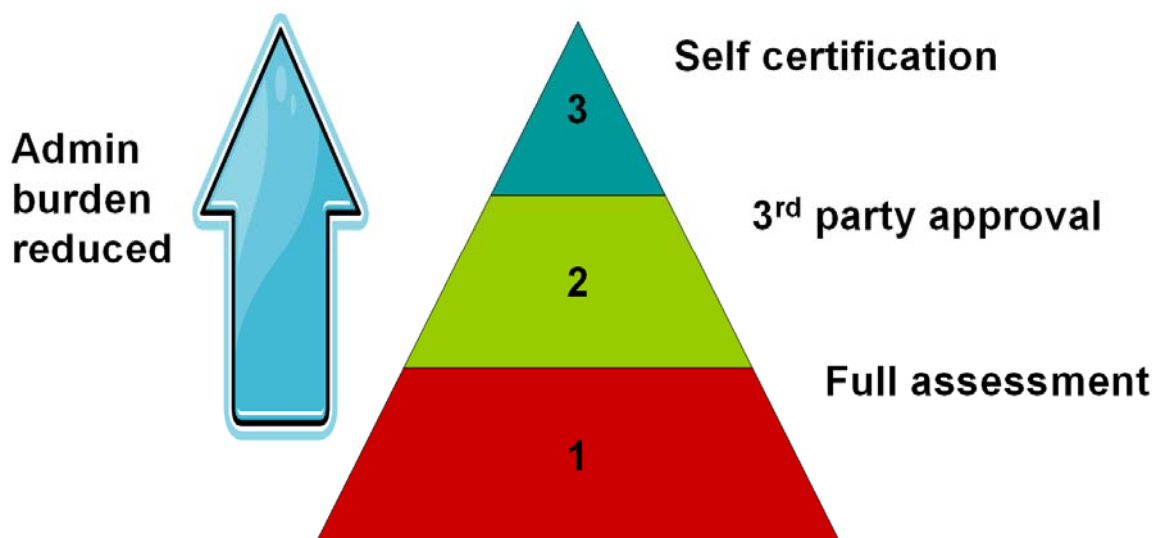
Kent Woods
Chief Executive, MHRA

Introduction

1. The Better Regulation of Medicines Initiative (BROMI) is a collaboration of industry, government, and health professionals led by the Medicines and Healthcare products Regulatory Agency (MHRA). BROMI is a ground-breaking initiative which is changing medicines regulation from within to deliver updated medicines to patients faster, thereby also benefiting patients.

2. The BROMI concept is that different regulatory models are appropriate in different circumstances. The key principle is that the regulatory framework should be proportionate to the risk. This enables the MHRA to better focus their expertise on important public health issues rather than routine administrative work. BROMI is working to a three tier regulatory model (**figure 1**): applications that can be self certified, changes requiring prior approval by a third party, and applications that would continue to require MHRA assessment. BROMI is also exploring work sharing models to minimise duplication of work, as well as procedural simplification with IT solutions where appropriate. In all situations BROMI works within the relevant legislative framework.

Figure 1



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Background

3. The MHRA is committed to developing regulation which is accountable, proportionate, targeted, consistent and transparent. In order to meet these five principles, since 2005 the Agency has been considering how medicines regulation could be adapted.

4. To take this important initiative forward, BROMI has brought together a broad ranging strategy group, which includes representatives from the Proprietary Association of Great Britain (PAGB), the non-proprietary sector, the National Pharmacy Association (NPA), the Department of Health, the Better Regulation Executive of the Department for Business, Enterprise & Regulatory Reform (BERR) and more recently the prescription sector of the pharmaceutical industry – the Association of the British Pharmaceutical Industry (ABPI), and is led by the MHRA.

5. BROMI was originally set up to look at how unnecessary regulatory burdens, primarily in relation to over the counter (OTC) medicines, could be eased, whilst maintaining safeguards to protect public health; however, the scope of BROMI has now been extended to the entire pharmaceutical industry.

6. Three main work streams are in place; a focussed piece of work on patient information (Patient Information work stream), wider consideration of MHRA processes (Authorisation work stream) and more recently a third work stream in relation to Pharmacovigilance (Vigilance work stream). The first and second reports and recommendations of BROMI were published in May 2006 and December 2006 and are available on the MHRA's website (www.mhra.gov.uk).

Summary or progress and future work

7. BROMI has made steady progress since publication of the first and second reports in May and December 2006 and is committed to making an impact on medicines regulation to the advantage of all stakeholders. BROMI has shown that medicines regulation can be targeted, risk based and proportionate and still deliver high levels of patient safety.

8. Where possible, administrative procedures have been simplified and barriers removed in specific areas such as changes to the details of Marketing Authorisations (MAs) (variations), changes to labels and leaflets, non-statutory changes to pack design, change of ownership from one company to another and duplicate MAs. As well as licensing approval procedures, the BROMI rolling programme of work is also tackling pharmacovigilance requirements at the very heart of safety monitoring. The opportunities for using IT systems to implement BROMI ideas are a key feature and the steering group is constantly considering how the BROMI initiative can be applied to other areas of medicines regulation.

9. BROMI made some initial recommendations in its first and second reports, many of which have already been implemented or progressed. Updated recommendations are outlined and grouped according to the BROMI model they exemplify.

Self certification

- Self-certification scheme for certain minor changes to labelling and patient information leaflets rolled out to the prescription only (POM) sector from 1 November 2006 and the quality audit system has moved from 100% to 10%.
- A self-certification scheme for certain Type IA national variations and an expedited process for certain Type IB and Type II variations went live on 1 April 2008.

Third party pre-approval

- A pilot for third party pre-approval of pack design changes to non-statutory information started in January 2007 and closed in January 2008. The Industry Trade Association, the PAGB is exploring the scope for enabling those other than existing PAGB members to use the scheme in order to gather more experience before it is signed off as a mainstream process.
- A third party model for literature searching is under investigation.

Work sharing

- A pilot is underway to assess the feasibility of MA holders working together to produce a common PSUR for the same active substance through a work sharing scheme.

Procedural simplification and IT solutions

- A streamlined process for processing applications for copy licences under Article 10c of Directive 2001/83/EC (as amended) went live on 1 February 2007 and is being monitored.
- A mechanism has been implemented to allow roll over of pending variations from the old to the new licence following a change of ownership application. This also includes the roll over of Periodic Safety Update Reports (PSURs) and renewals.
- Key changes have been introduced in relation to Anonymised Single Patient Reports (ASPRs). ASPRs are now only provided based solely on the Volume 9A Pharmacovigilance Guideline definition of seriousness, and the MHRA no longer provides ASPRs to the MA holder who expedited the report.
- A programme of work for streamlining renewals is under way.

Progress on the patient information work stream

Self certification scheme

10. The self-certification scheme for minor changes to patient information has been running since May 2006 and was extended to the whole of industry in November 2006. Over 800 notifications have been received and the audits undertaken have indicated that no serious risks to public health have been incurred. A summary of the audit findings has been published on the MHRA website (www.mhra.gov.uk) and these have provided the assurance to move from a 100% to a 10% audit.

11. This scheme is also supported by MHRA guidance to MA holders and training for companies has been provided on the submission of notifications. The scheme is also supported by an industry Code of Practice which sets out the principles which apply to MA holders in respect of their responsibilities and the need for specific standard operating procedures and quality systems to be in place in the company.

12. Underpinning these safeguards, the MHRA will not hesitate to remove company privilege where breaches of the conditions have occurred. These new processes will

enable MHRA to maximise opportunities for monitoring the impact this new scheme has on public health and will ensure that no new risks are being introduced.

Industry case study:

“There was no flexibility within the old system. We have to submit all requests for change of any kind to the MHRA, but the approval process, even for a minor change like a slightly longer or shorter label for a new type of bottle, was far too long. It was completely administrative. It didn’t affect safety. But it could take up to five months just to get that simple change through the system. Now, thanks to BROMI we are able to take advantage of a much faster approval system. We still submit to the MHRA but basically, we make the assessment of the change ourselves – we self certify.

For example, we had a Sudafed bottle label that needed to be changed in its shape. In the past, it would have taken 3-5 months to get this change approved. But because we now self certify, we could change it immediately.

For us, last year, speeding up that one label change saved us 8,000 Euros in line efficiency. So now we have a lot more control over our timings – and when we can get out to market.”

Gill Peckham, Head of Regulatory Affairs, Johnson & Johnson UK

Industry case study:

“Pharmaceutical regulatory processes are very complicated. Until recently, even something like changing a pack size was very time consuming. Under the old system, if you wanted to change your labelling in any way you would submit an application to the MHRA and the approval process would take up to 90 days. Now such administrative processes are much faster. The same application to change the pack size is now acknowledged in 14 days. So we can get products out to market much faster.

During last year’s hay fever season, the faster process helped the company get a time-specific product to market nearly three months earlier than before. It meant we were able to supply the product in the middle of the hay fever season in June. Having just one product on the shelves for an extra ten weeks earns an extra £20,000 a week in sales terms. So we gained sales last year that we would not have had. The valuable time now being saved by the reduction in red tape is also a tremendous advantage. It frees us up for new product development – the lifeblood of any pharmaceutical company.”

Nicholas Smalley, Regulatory Affairs Manager, Perrigo

Code of Practice on pack design

Figure 2



13. A Code of Practice on pack re-design (**figure 2**) has been developed and outlines a third party pre-approval model for non-statutory packaging information which is focused on encouraging best practice. Changes are pre-approved by the PAGB before coming to the MHRA for final approval. The code of Practice sets out requirements for participation in the scheme, such as the need for company standard operating procedures and quality systems.

14. A pilot of this new way of working with PAGB member companies ran from January 2007 to January 2008. The approach is already proving a great success, with final approvals being issued by the MHRA within 30 days instead of the usual 90 days. An evaluation of the pilot highlighted that although just over 50

applications have been made to MHRA, this reflects around half that number screened by the PAGB. Wider extension of the scheme would allow it to be properly evaluated and agreed as a mainstream process. The PAGB are now exploring the scope for enabling wider participation in the scheme for non PAGB members. Submissions made under this pilot are currently subject to 100% audit and there is close liaison between MHRA and those involved in the pre-approval process to ensure consistency in approach.

Statutory warnings

15. The BROMI group has also identified a need to review, update and improve the statutory label warnings encompassed within Schedule 5 of the Medicines (Marketing Authorisations etc.) Regulations 1994 number 3144 (as amended) [SI 1994/3144]. These warnings have been required since the late 1970s and there is an increasing body of evidence that some revisions to the warnings may be beneficial for patient understanding. In conjunction with key professional stakeholders, the Group is beginning work on developing proposals which will better alert patients to important safety messages within the labelling of certain medicines available for sale through pharmacies and general sales list outlets, and for inclusion in dispensing labels applied by the pharmacist. A scoping exercise is currently underway to review options for taking this forward.

Progress on the Authorisation work stream

16. The second broader work stream concerns opportunities, to reduce the burden on both industry and regulators in the licensing of medicines. The subgroup is focussing on the following work areas:

- variations – updates to licences in the light of new information
- change of ownership applications
- copy licences

- renewals

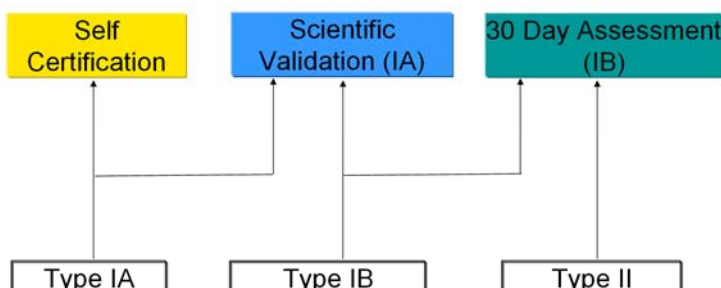
17. These areas were considered to have the greatest potential impact on work volume and costs for both industry and regulators.

Variation Applications

18. A pilot was initiated in February 2007 with a small group of MA holders to test the feasibility of developing a self-certification model for certain Type IA variations and to follow an expedited process for certain Type IB and Type II variations (**figure 3**).

Figure 3

19. The MHRA developed criteria and conditions for national variation procedures and the pilot came to an end on 31 January 2008. The results of the pilot have been evaluated and showed that any issues in relation to company submissions could be addressed by MHRA procedures and training. The scheme was extended to the entire pharmaceutical industry on 1 April 2008 for national variations received via the MHRA web portal. New fees were introduced on 1 April



2008 to reflect the new way of working. The fee for the self certified application has been reduced from a Type IA notification to the lowest application fee charged, which equates to a 7% reduction on a Type IA notification fee. The BROMI Type IA and BROMI Type IB fees now reflect the current Type IA and IB variation fees.

20. It is envisaged that approximately 80% of Type I notifications will be processed through self-certification, which will be a huge benefit to both industry and the Agency. Guidance and training for MA holders on how to use the scheme, together with support through the Regulatory Information Service has been organised to support applicants.

21. Initially a 100% audit is being conducted and it is envisaged that this will reduce to a 10% audit over time, reflecting delegation of the responsibility to the MA holder. The MHRA will not hesitate to remove company privilege where breaches of the conditions have been noted.

Change of Ownership Applications

22. From September 2006 the window during a Change of Ownership process when both old and new licences are current was extended from three to six months. Industry reported that the original shorter time frame caused problems with stock control leading to write-offs for some product in old livery that could not be released to the market within 3 months. An IT solution for rolling over outstanding variations onto the new licence in Change of Ownership applications went live in July 2007 and outstanding renewal applications and PSURs can also now be transferred to the new licence.

Copy Licences

23. The assessment process for applications for new (copy) licences under Article 10c of Directive 2001/83/EC (as amended) has been reviewed to see how approval times can be reduced. The MHRA and industry worked together to improve the quality of applications and reduce or eliminate the need for “deficiency” letters, so that these applications can be approved within predictable timelines. The streamlined process for these applications went live on 1 February 2007. A checklist is available on the MHRA’s website and progress is being continually monitored. Industry is encouraged to use this BROMI scheme to ensure the full potential is realised.

Renewals

24. Extensive work is underway in relation to streamlining the renewal process and a MHRA/industry subgroup is being established.

New BROMI Fees

25. To reflect the reduction in MHRA input as a result of the new ways of working, new fees were introduced on 1 April 2008 for self certified changes to labels and leaflets and self certified Type IA notifications. The fee for a self certified change to patient information has been reduced to the cost of a Type IA notification, which is a 64% reduction in the fee. New guidance has also been published on the MHRA’s website to reflect an updated fee structure for this BROMI process. The new self-certification fee for certain Type IA notifications has been reduced from a Type IA notification to the lowest application fee charged, which equates to a 7% reduction on a Type IA notification fee. New lower fees have been introduced for BROMI Type IA and IB applications to correspond with equivalent Type IA and IB application fees. The new fees are commensurate with the work involved in processing the BROMI work types.

Progress with the Vigilance work stream

26. In February 2007 BROMI began to identify where administrative burdens could be reduced in the area of pharmacovigilance and a subgroup is taking this work forward. There is a focus on models that encourage work sharing and avoid duplication of effort. The initial areas that are being focussed on are:

- published literature screening
- PSURs
- ASPRs

27. Key technical changes have been introduced 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. ASPRs are now only produced according to the Volume 9A Pharmacovigilance Guideline definition of seriousness, and no longer provided to the MA holder who expedited the report to the MHRA.

28. The Agency has continued to increase numbers of companies receiving ASPRs via either the MHRA Portal or electronically via E2B. In March 2008, 61% of ASPRs were sent electronically, up from 48% in April 2007. This 13% increase in electronic ASPRs means that around an extra 3000 ASPRs each month are sent electronically rather than via the post representing a cost saving of over £10,000 per year.

29. A pilot is underway to assess the feasibility of MA holders working together to produce a common PSUR for the same active substance through a work sharing scheme. A third party model for literature searching is also being investigated.

International impact of BROMI

30. Every opportunity is taken to share the principles and benefits of BROMI work with European colleagues and at an International level. BROMI principles feature in the amendments to the European Variations Regulations and the new EU Pharmacovigilance legislative proposals aim to reduce administrative burden in the same way as BROMI. The BROMI model has also been explored in recent US/EU co-operation discussions. The Organisation for Economic Co-operation and Development (OECD), in partnership with the European Commission, is currently under taking a review of better regulation in Member States. The progress of BROMI has been presented to the OECD review team and a report is expected to be published towards the end of the year.

Conclusion

31. BROMI has achieved the first breakthroughs in simplifying the complex and time consuming systems of medicines regulation built up since the thalidomide disaster and has shown that:

- Medicines regulation can be targeted, risk based and proportionate and still deliver high levels of patient safety
- Industry is benefiting not only in lifting resource burdens but in gaining market opportunities and empowerment
- BROMI principles have been grasped at a European and International level.

32. The stakeholders of BROMI consider the initiative to be of high priority and to have great potential to significantly impact on medicines regulation and reduce burden for both regulators and industry that will ultimately also benefit patients and the public. A number of short, medium and long term recommendations were made by the group in the previous reports and many of these have already been completed. Updated recommendations have now been identified and BROMI is committed to developing these. A timetable of work is at annex A. The third work stream on pharmacovigilance, consistent with EU strengthened pharmacovigilance proposals, offers further opportunity to streamline and focus regulation, enabling resources to be better targeted to public health protection.

Tell us your ideas....

33. 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.

BROMI Working Group, May 2008

Better Regulation of Medicines Initiative (BROMI)

Timetable of work

Strand of work	Project start date	Delivery date	Status
Introduction of self certification/notification procedures	Immediate	May 2006	Achieved
Self-certification of minor changes to patient information to be rolled out to POM sector	November 2006	November 2006	Achieved
Code of practice on pack re-design	July 2006	Summer 2008	Pilot for a self-certification scheme for pack design changes to non-statutory information closed in January 2008 and PAGB is exploring scope for widening use to increase experience.
Self certification of simple variations	March 2006	1 April 2008	Achieved
Streamlined process for Copy licences	March 2006	February 2007	Achieved
Change of Ownership – timeframe and variations roll over	Summer 2006	July 2007	Achieved
Streamlining the renewals process	January 2008	February 2009	Ongoing
ASPR Simplification	2007	Initial changes introduced January 2008	Part achieved. Some changes have already been introduced and further changes are being explored.
Work sharing of PSUR for same active	July 2007	Review of pilot scheme and applicability for roll out June 2008	Ongoing
Third party pharmacovigilance literature reviews	November 2006	2008	Ongoing
Streamlining of statutory label and leaflet warnings - Identification - Review - Public consultation - Revised Statutory Instruments issued	Summer 2006	September 2009	Ongoing