A spirit of progress

Dr June Raine, Director of Vigilance Risk Management of Medicines at the UK's Medicines and Healthcare products Regulatory Agency (MHRA), talks about the BROMI initiative, the pharmaceutical package and the new key information section of the SPC and PIL, in an interview conducted by Zubair Hussain (Pfizer UK & Ireland), Peter Blakeney (Spectrum Regulatory Solutions), Quentin Clarke (Fulcrum Pharma) and Owen Lewellen (Charisbert Consultancy/EU Vigilance)

BROMI initiative

Q **ZH:** BROMI has been really well received by industry, starting with the consumer business and now with the ethical business. I understand that the MHRA has recently received an award from the 'Better Regulation Executive' – this was obviously tremendous news for the agency. This is a fantastic start in reducing regulation where patient safety is not compromised. But moving forward and considering the fact that the overall net complexity of regulation for the pharmaceutical businesses is increasing, despite the relatively small amounts being taken away by the BROMI-like initiatives, do you think that a step-wise change is needed to try and help reduce the administrative burden both for pharmaceutical companies but also for MHRA?

A **Dr Raine:** I'm delighted that BROMI won the Better Regulation award out of all the National Business Awards in a highly competitive field, including organisations right outside government. The concept of regulation proportionate to risk has therefore been validated in a very broad context. We think the initiative has the potential to go much further, and there is now a renewed programme of work that we are going to be taking forward on the springboard of winning the award. Watch out for the fourth BROMI report, which will be coming out in the first quarter of next year.

What we are particularly pleased about is that the European Commission has embraced the concept – 'BROMI' has been translated into every language in the Community and as you know the new Variations Regulations are built around the BROMI principle. The challenge now is identifying how much further we can go, and indeed the recently published pharmaceutical package picks up some of the themes of regulation proportionate to risk. For that reason I think we should be focusing particularly on the pharmacovigilance work stream out of the three BROMI pillars: patient information, licensing changes and pharmacovigilance.

Information for patients has been the spearheading initiative for BROMI, and we've seen important gains in terms of control passing to industry. For the BROMI licensing change we are looking at potentially vast gains in terms of savings. But now in the area of pharmacovigilance, where we've really got the test of targeting regulation to risk, we're going to be looking at a range of possibilities. We know that even in the run-up to any new legislation we want to make some early gains before implementation of changes. There are ideas around literature reporting, which is an area of considerable duplication of effort, around PSURs, and the detailed description of the pharmacovigilance system where we are aware of a pilot in Germany to support work-sharing. Those are the three areas under development, but in summary there is enormous potential for BROMI here and we are absolutely determined to realise that potential.

Q **ZH:** Have these areas been identified in conjunction with industry folk as well as colleagues from other regulatory agencies?

A **Dr Raine:** Yes, what we have done is continually introduce new thinking into BROMI via our steering group of stakeholders. The hands-on work is done in subgroups, which develop ideas and pilot and audit them. The steering group has been broadened to include all industry sectors; we started with the over-the-counter industry and then incorporated generics and ABPI companies, and in that way the ideas have come from right across the industry.

We're always keen to have fresh input into the BROMI process, and the call for ideas will be reiterated in our fourth report – we're open to good ideas whenever they arise, at any time.

Pharmaceutical Package

Q **ZH:** Firstly, do you have any general comments about the pharma package?

A **Dr Raine:** Let me say first of all how excited we all are to see this pharma package come forward from the European Commission, comprising a Communication and three sets of legislative proposals (on the provision of information about medicines to patients, anti-counterfeiting measures and proposals to improve pharmacovigilance). On pharmacovigilance, the Commission has truly delivered a comprehensive set of proposals as we had all expected following the Fraunhofer review, the very first time pharmacovigilance practices in the member states had been thoroughly reviewed. So I think we ought to pause and congratulate the Commission for having the vision and intention to deliver a very comprehensive package.

It would be wrong for me not to highlight that the Commission have truly set themselves some challenges in terms of clarifying roles and responsibilities, rationalising decision-making processes, focusing on transparency and communication, reducing the burden on industry and, what is key to us in the agency, emphasising proactivity as well as stakeholder involvement. So this is really something that overall we welcome wholeheartedly.

The big question is – is this package capable of taking pharmacovigilance into a new era? I think the answer is yes, but it is up to us as regulators and industry, together with other stakeholders, healthcare professionals and patients, to shape it so we get the best possible result for all.

Q ZH: There is a proposal for a new scientific committee, the Pharmacovigilance Risk Assessment Advisory Committee, to be created within the EMEA, and it will play a key role in pharmacovigilance assessments in the EU. Is this a replacement for the EU Pharmacovigilance Working Party or will it still exist, and how will it work in the future?

A Dr Raine: There is a lot of interest in the proposed creation of a Pharmacovigilance Risk Assessment Advisory Committee within the EMEA and its role. A lot of thought has clearly been given to how it will support not just the CHMP but the CMDh. What this is telling us is that the Commission is recognising the role played by member states, and the need to see the European system as a networked system of agencies. Our strength is in that network and in operating together. The role of this new committee, one can assume, will replace that of the existing working party, and will have a status in legislation which will be extraordinarily valuable. The context of the other more recent committees created under the paediatric and advanced therapy legislation will be relevant.

Since 2006, the Pharmacovigilance Working Party has incorporated co-opted experts in pharmacoepidemiology, risk management, and risk communication and in the specialist areas of paediatrics and biotechnology. What this experience has told us is that member states welcome this international scientific expertise in taking standards of decision-making to a new level. There's a lot in the new pharma package about quality, so what will be needed in the new committee is that blend of international expertise and regulatory know-how, in order to deliver high-quality outcomes for patients and healthcare professionals and the industry.

Q ZH: Do you envisage the chair of this new committee to rotate in a similar fashion to other committees?

A Dr Raine: I think it would be premature to make any prediction at this stage. This will be one of many topics we expect to be on the table for future discussion, and I expect the best possible outcome for not only Europe but also citizens of the UK.

Q ZH: What about this assessment of serious safety issues for nationally authorised products through this binding process with initiation criteria for member states? Is this something that is building on existing processes?

A Dr Raine: As you've highlighted, these proposals represent an important step towards improving efficiency, and we very much welcome the extent of focus on decision-making. While there is a substantial proportion of medicines still authorised through national routes, we have to ensure there are efficient mechanisms for acting as soon as new risk–benefit information emerges in relation to nationally authorised products. Clearly the detail needs to be worked through, but you'll be aware that we now see the legislation recognising drug class issues –the scenario where you may have a safety issue affecting a particular class of medicines which may have been authorised through different routes. So in general terms it's a very welcome step and builds on existing informal procedures.

Q ZH: Now to the new key information section of the SPC and PIL – is there any further information on that, or can you elaborate further on any discussions you have had on this with the Commission?

A Dr Raine: We are particularly pleased to see a step towards practically supporting communications with patients. You will have seen that the strategy outlined in our 'Always Read the Leaflet' report in the UK is to make it easy to distinguish the important information in what we all know is a very comprehensive and detailed document. Again the details need to be thought through, but the principle here is definitely something we can work with. We would hope by working with industry and other experts in communications to get a good outcome that will enhance the safe use of medicines for everyone.

Q ZH: I know at one point there was consideration given to having a lay version of a risk management plan that would replace the patient information leaflet. Is this something that is linked to this new key information or is it completely separate?

A Dr Raine: The idea of a lay summary risk management plan emanated from important work by the Ministerial Industry Strategy Group in the UK, and the thinking behind it is well set out in the publication on the Long-Term Leadership Strategy from the UK Department of Health and ABPI. Pilot lay risk management plans have received excellent feedback from the Commission on Human Medicines Patient Information Advisory Group. I think the idea of including more about the risk management plans will come up when the proposals in the new legislation on risk management plans are debated so, again, too early to be definitive about where we are going.

Q ZH: The proposals simplify the existing requirements by introducing the 'pharmacovigilance system master file'. In MA applications currently, only key elements of the pharmacovigilance system should be submitted, but this is balanced with a requirement for companies to maintain a detailed file on site. What will be the key elements of the new pharmacovigilance system?

A Dr Raine: We very much welcome the opportunity to simplify current practice and particularly to look at this as a key area for work-sharing. Traditionally, the requirement for multiple variations has resulted in duplication of effort with no public health benefit. We can now see a way through this to optimise the system and place responsibility where it needs to be, which is with the MA holder. However, it is too early to give specifics on the likely key elements.

Q ZH: The proposal is to amend the scope of periodic safety update reports to become an analysis of the risk–benefit balance of a medicinal product, rather than a detailed presentation of individual case reports as a result of the submission of all ADR data directly to the EudraVigilance database. There was a perception that such an analysis should have been done in the submission of every PSUR, but I guess this is more formalisation of the fact that the risk–benefit will be calculated on each occasion of a PSUR submission. Also there is a suggestion that the contents of a PSUR might change – is that right?

A Dr Raine: The background here is the longstanding debate on whether the effort and resource in producing PSURs has been reflected in demonstrable public health benefit. The direction of travel from data presentation to critical analysis is one that will be better able to deliver that benefit. The general context of reviewing what we really intend to achieve from PSURs will be in the ICH review of ICH-E2C. The key message in the Commission proposals is regulation in proportion to risk, and in the PSUR work-sharing group with other member states, we're already exploring the idea of waiving or reducing requirements where we believe that the risk–benefit of the product is well established and has not changed. So there are two aspects to this question – one is what the Commission is driving towards, which is analysis rather than data, and the second, at an international level, is re-looking at the scope of ICH-E2C. These two aspects could proceed in parallel and, if managed appropriately, drive forward exactly what we want to see – maximum public health benefit from resources appropriately used.

Q ZH: Do you think there is scope here for BROMI-type initiatives? It sounds like there potentially may be, as long as the focus is on risk–benefit balance calculations as 'data dumps' become less necessary?

A Dr Raine: In the UK we want in parallel to be further exploring BROMI-type approaches and at this stage there is everything to play for – anything from self-certification to reduced-format PSURs in the absence of new safety data, and the idea of waivers. I think we are in an excellent position in the UK, having had that 'Better Regulation Executive' endorsement of these BROMI principles, to carry out work that will support our negotiations in Europe.

Q PB: Could I just ask on the waiver possibility, thinking of a product with a very safe or high benefit–risk ratio, are you considering the possibility that the PSUR may become a very small document?

A Dr Raine: Yes, it might either be a reduced-format or even a self-certified declaration. Ideas are already on the table so it's an exciting area and one in which BROMI can play its part.

Bear in mind too that we have the safety net now of excellent signal detection systems, and the capability to ask for a PSUR at any time. So taking those two together, we know we have a robust safety net and that the PSUR isn't the prime vehicle for monitoring safety that it once was.

Q ZH: What do you foresee will be the major challenges affecting agencies arising from the new proposals? How will the MHRA be addressing these, and what will be the effect on the smaller agencies?

A Dr Raine: Any change is challenging, and we're seeing here a fundamental re-think of how we conduct pharmacovigilance, to take us to proactive risk management and a proportionate approach. So for the agencies there will substantial challenges, which could be considered as four R's:

- Reporting – for example for those agencies that don't currently accept patient reporting, there will be challenges
- Resources – the right skills, and the right quantity of resources
- Representation – we've already mentioned the new Pharmacovigilance Risk Assessment Advisory Committee and by implication, knock-on effects on CHMP and CMDh representation
- Review – of our own systems. We've already had the benchmarking initiative but we, like industry, have a duty to operate effective systems and also to review outcomes of actions.

So reporting, resources, representation and reviewing could be seen as a suite of challenges Finally I could add a fifth that doesn't begin with an 'R' – transparency. As we know here in the UK, increased communication and opening up pharmacovigilance to outside scrutiny means that our standards need to be as high as possible. We want to embrace the opportunity for European transparency and to really use this chance to be as open as possible with healthcare professionals and patients.

Q ZH: What do you consider will be the major challenges for industry?

A Dr Raine: For some parts of industry the move to electronic data and signal management will be a challenge. All of industry will need to embrace the opportunities and challenges of pharmacovigilance in the electronic era. Then there's the delivery challenge – we've already seen risk management plans come centre stage as a pharmacovigilance methodology, but you now see in the legislation the capability to set deadlines and the expectation is not just creating them, it's actually delivering them, and this challenge is a very important one. Finally, industry could clearly benefit from streamlining and simplification of its procedures. I'm sure there are more – but these three are a start.

Also, you might recall at a UK level during the 2001 Review we had a very productive engagement with industry, with close liaison throughout quite lengthy negotiations, and I know my policy colleagues are intent on not just reproducing that collaborative approach but also improving it.

Q OL: Seeing that we're at the beginning of a new year, what are your challenges and priorities personally, for your department and for the MHRA for 2009?

A Dr Raine: I would like to focus on the pharmacovigilance challenges, and top of the list remains getting the maximum value from risk management planning. This was the major new tool from the last legislative round to deliver proactive pharmacovigilance. We're working closely with Sweden and other member states to evaluate the value we have gained from risk management plans and to be clear that the investment in this area, both for us and for industry, has truly delivered. So that has to be top of my list.

The second priority area leads on from the BROMI heritage and involves work-sharing. We've seen this take off for PSURs and we've got to capture that benefit, but

also roll it out to, for example, DDPS, the 'Detailed Description of Pharmacovigilance System', as well as other areas. Maybe aspects of risk management plans for certain classes of medicines, maybe in terms of best practice communication: the work-sharing principle – the building of the European network – and best use of resource has got to be a key priority in the coming year.

And finally, I would highlight better risk communication, which has got to be at the heart of everything we do if we want to optimally support safe use of medicines. We've watched as the US FDA set up a risk communication committee and we're very interested in how signals are now published in the USA and how the early-stage communications are managed there. How can the UK and its work in this area help the developing European agenda? And of course underpinning all this is starting to build a platform for transition to the new legislation; it may seem long term but, as they say, the future depends on what we do today. I'd like to see the best possible transition to new pharmacovigilance legislative provisions.

Q OL: One interesting fact about yourself that some of our readers might not know?

A Dr Raine: I look back to my days in pharmacology research for that. You might not know that my research interest was cannabis, and because I was carrying out this research in a department of pharmacology in a university town and with the cooperation of the local constabulary, I believe we had the biggest repository of research material in the United Kingdom! I learnt a great deal both in terms of safety and also potential therapeutic uses.

Q OL: How would you like to be remembered, what legacy would you like to leave?

A Dr Raine: I hope this question is not a signal of things to come! It's an interesting challenge to focus on what has mattered to me personally. I am proud of contributing to the drive to proactive pharmacovigilance. I am coming up to ten years in pharmacovigilance next year, so this matters a lot to me. In the early days when only reactive pharmacovigilance was possible, we didn't have the systems and the capability to do anything else. Over a period of time we have seen a massive switch to proactivity which I hope I've helped to champion.

Coupled with that has been putting the patient at the centre of everything we do. I know industry has embraced this fully, for example with the achievement of user testing of all patient information leaflets. This will help take patient information to a new level, where people will not just check the leaflet but will value it and retain it, and all the resources that are put in to effective communication will have a real meaning for individuals.

And I guess in the last ten years there have been some difficult decisions along the way, and maybe people will recall that I wasn't afraid to take those difficult decisions?

I very much hope that your readers will be fired up with enthusiasm to follow the issues as the new pharmacovigilance legislation progresses. There will be focused debates on elements of it, but I really hope we can all see this as a comprehensive step forward and that your readers will feel inspired to engage!