Department for Business Innovation & Skills

FOCUS ON ENFORCEMENT REGULATORY REVIEWS

Review of the pharmaceutical manufacturing and production sector

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EXECUTIVE SUMMARY

The need for regulation in the pharmaceutical sector is very clearly understood, accepted and valued by industry. We received considerable positive feedback on the operation of the regulatory regime and were consistently told that the MHRA is a highly respected regulator, not just in Europe, where it was frequently described as a leader and 'punching above its weight', but also worldwide. Many businesses also described the MHRA as a generally open organisation, which made considerable effort to be risk-based and was willing to engage with industry and tried to 'do the right thing'. We also received evidence that MHRA inspectors have very good knowledge of the sector and offer a professional service. Most businesses felt that MHRA inspectors understood their business (and had usually worked within the sector) and were able to speak the same business language as them. This was something which they really valued.

Businesses operating in this sector that also fell in scope of the Environment Agency's remit were generally complimentary about their engagement with them.

In addition to this positive feedback, the review team heard considerable evidence from businesses on areas where they believed the regime could operate more effectively. These findings are summarised below and explained in more detail in section 2 of the report;

Finding 1: MHRA Licence Applications and Variations

Businesses raised numerous concerns over the process for MHRA licence applications and variations, both for site licences and market authorisations (required for each pharmaceutical product before it can be made available to the UK market) resulting in delays in getting products to market, uncertainty and additional costs. Businesses raised a collection of issues including; lengthy timescales (we were told that it could take up to 120 days to process a licence variation), errors and inaccuracies (some businesses reported *never* having received certain licences with the correct information first time round) and duplication of information requests resulted in businesses experiencing unnecessary delays in getting products to market (particularly important for seasonal products, when there are limited windows for getting a product to market), uncertainty and additional costs.

Finding 2: Batch Specific Variations

Businesses told us that the MHRA process for allowing businesses to accommodate one off, low risk, changes to their usual procedures (via a 'Batch Specific Variation') is often unreasonably long, unpredictable and opaque, creating uncertainty and, in some cases, delays in their production processes. Businesses estimated that the type of variation generally submitted would take no more than half a day to deal with but reported periods of up to 3 months to gain approval from the MHRA. Comparisons between the MHRA's timescales and those of the Irish Medicines Board (IMB) were made as businesses told us that similar applications to the IMB would regularly be dealt with within 24 hours.

Finding 3: Unlicensed Medicines

Businesses reported that it can take a long time to process approved notifications to import unlicensed medicines[1] - they said that it can take up to 80 days between submitting notification of approval to import to gaining an approved 'importation from' date. This causes companies to lose out on securing business, with one telling us that these delays had resulted in them losing out on numerous contracts.

Finding 4: Controlled Drugs

We were told by businesses that the process for obtaining licences for controlled drugs is sometimes slow; that they would welcome clearer and more consistent advice and guidance; and that they had experienced inaccuracies and delays in finalising licence documentation which had on occasion caused financial losses. Some businesses felt that this was partly caused by a lack of knowledge and understanding of the sector within the Unit and difficulties in business and the Home Office understanding each other's terminology. We were told that this resulted in misunderstandings arising during inspections and, in some cases, inaccuracies in the licence documentation following the site visit.

Finding 5: Qualified Persons

Qualified Persons in pharmaceutical businesses reported significant irritation due to (what they described as) a lack of sufficient discretion when releasing products to market. They said that this leads to an increasingly bureaucratic workload – some referred to UK QPs as 'highly trained box tickers', increased cost (businesses reported wasting products which they deemed to be safe as a result) and delays in the release of products with knock on effects to the overall production process.

Finding 6: Inconsistency

Businesses complained about inconsistency in MHRA advice, meaning that they are uncertain as to their compliance obligations and, at times, resulting in significant costs to the business where changes have been made to accommodate different interpretations or particular 'bug bears' of different inspectors. We were given several examples of agreements made with one inspector, which were then deemed unacceptable or ignored by another inspector, meaning the business received a deficiency on their report and had to change equipment or processes to accommodate the new interpretation. In some cases, we were told that this was then reversed by the next inspector, requiring the business to revert back to the original position.

Finding 7: Global Recognition and Harmonisation

Businesses welcome work to increase global recognition and harmonisation but are keen to see further integration as quickly as possible on this, in order to save them time and money. Almost every business we spoke to reported high volumes of visits from medicine and healthcare regulators from countries that were importing their products. One company reported fifteen days of auditing activity in the UK within the last year and another reported an average of seven GMP inspections per year, each lasting between 3 and 5 days and costing the business £8000-£10,000 per day.

[1] See para. 7, Annex A

Finding 8: EU Co-ordination

Businesses told us that they are often left to resolve issues caused by inconsistent application of the rules by different EU regulators. Those who had experienced difficulties first hand said that they felt like they were left to act as the ‘go-between’ between the different regulators. This causes them delays when working across the EU, with one company reporting delays of at least a year in the production of their drug.

Finding 9: MHRA Guidance

Businesses told us that, in general, they appreciate and value MHRA guidance. However, they reported that there is a lot of redundant information on the MHRA website. Those who commented were generally aware that action was being taken to address this but all stressed the importance of this work and were keen to see progress as soon as possible.

Finding 10: MHRA Fees

Businesses told us that the calculation of MHRA fees is not always very transparent, both for maintaining licences and, in some case, also for inspection visits. This means that they are not always clear why the structure is applied in the way it is.

BACKGROUND

Purpose of FoE reviews

1. This paper summarises the findings of the tenth Focus on Enforcement review. The reviews examine the impact of regulatory delivery and enforcement in particular sectors of the economy. Each review is a short, sharp investigation of stakeholder experiences and evidence; they are carried out by a small review team and typically involve a six to eight week fieldwork phase.

2. The purpose of this paper is to present the findings and evidence that the review team heard. The aim of the report is not to make specific recommendations for reform but to identify the impact and consequences of current enforcement practice, and to invite the relevant regulators to respond.

3. The focus of each review is to identify areas of good practice, as well as those elements of the approach to regulatory enforcement that affected companies, and other stakeholders, feel could be improved.

Input to the evidence gathering

4. The review team gathered evidence through visits, face-to-face discussions and telephone interviews. The Focus on Enforcement website also provided the opportunity for industry to feed into the review anonymously online. Input was received from a range of trade bodies, from individual businesses and from the regulators. The review team also accompanied inspectors from the Medicines and Healthcare Products Regulatory Agency (MHRA) and the Environment Agency (EA) on inspections of various pharmaceutical manufacturing businesses. The review team are grateful to both organisations for the opportunity to do this.

Sector coverage of the review

5. Businesses engaged in the manufacture and production of pharmaceuticals in the UK vary greatly in size - from multinationals with multiple sites, turnover in the billions and tens of thousands of employees to individual facilities with less than 20 employees. Manufacturing and production processes include making active ingredients, manipulating ingredients, mixing and producing pharmaceutical products, packaging and labelling products. Pharmaceutical products may be produced for use in clinical trials, to be sold over the counter, as prescription only products and patient specific products. The review received evidence from businesses involved across this spectrum of manufacturing and production.

6. The MHRA's definition of medicinal products, based on Article 1 of Directive 2001/83/EC, defined the limits of the review's scope. This defines a 'medicinal product' as:

- Any substance or combination of substances presented as having properties for treating or preventing disease in human beings;
- Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.

Features of the domestic regulatory regime

Key domestic regulators

7. The **Medicines and Healthcare Products Regulatory Agency (MHRA)** (formed in 2003 following the merger of the Medicines Control Agency and the Medical Devices Agency) is the competent authority responsible for ensuring that all medicines in the UK work and are acceptably safe. It provides the market authorisation necessary in order to place medicinal products on the UK market unless authorised centrally by the European Commission (see page 15 section 2 for more detail). The MHRA licenses and inspects businesses and premises involved in the manufacture, production and distribution of medicines. It also licenses and constantly monitors the medicinal products that these businesses produce.

8. The MHRA inspects all pharmaceutical manufacturing and production businesses to confirm compliance with Good Manufacturing Practice (GMP) standards; this essentially means ensuring that production and testing practices are in place to help ensure a quality product which is safe for consumption. The MHRA also inspects distribution, clinical and laboratory practices. It issues various licences for a wide range of activities and products and carries out ongoing tracking and monitoring of products once they enter the market (which is known as pharmacovigilance). Please see Annex A for more information on these key functions, including;

- *Site licences*
- *Market authorisation*
- *Parallel import licences*
- *Variations to licences*
- *Batch Specific Variations (BSVs)*
- *Pharmacovigilance (Drug Safety)*
- *Unlicensed medicines*
- *Qualified persons*

9. The **Home Office Drugs Licensing and Compliance Unit (DLCU)** is responsible for regulating and licensing individuals and organisations to produce, supply, possess, import or export ‘controlled drugs’ (named in the Misuse of Drugs legislation, and grouped in schedules). Pharmaceutical producers and manufacturers who undertake any of this activity are therefore also regulated and licensed by this dedicated unit within the Home Office. Prior to applying for a domestic licence, all applicants named on the application form need to have undergone a Disclosure and Barring Service check and will be subject to an inspection from a Drugs Licensing and Compliance Unit (DLCU) compliance officer.

10. Any company that intends to import or export a controlled drugs and precursor chemicals will need the relevant domestic licence before they can apply for an import/export licence and will need to be registered with the National Drugs Control System (NDS), which is used to administer the import and export licensing regime of the United Kingdom for controlled drugs and precursor chemicals.

11. The **Environment Agency (EA)** is responsible for regulating waste and water discharges in England. It regulates pharmaceutical sites which manufacture active ingredients for a pharmaceutical product for commercial sale. There are approximately 20 such sites in England. Natural Resources Wales and the Scottish Environment Protection Agency are the equivalent competent authorities responsible for regulation in Wales and Scotland.

Features of the international regulatory regime

12. As mentioned above, across the EU the national competent authority responsible for the regulation of medicines in a country or the European Commission must grant a market authorisation before a product can be marketed. Since the mid 1990s EU agreements have harmonised market authorisation decisions. These are aimed at reducing the administrative costs and burdens faced by businesses trading in multiple nations. For example, the EU mutual recognition procedure[2] facilitates the coordination of market authorisation applications to multiple member states, by requiring one member state to take the lead and then inform the others of its assessment. The other member states then have 90 days to recognise the decision of the lead member state or refer to a co-ordination group to discuss any issues of contention before a common decision is made. This ensures that decisions on the granting of market authorisations are harmonised. In addition, the centralised EU procedure[3] allows market authorisation applications to be submitted directly to the community regulatory agency, the European Medicines Agency (EMA), whose decisions are valid in all member states.

13. Mutual recognition agreements within Europe cover certification for all key areas. As such EU members only receive inspections from their national regulator. Other countries will periodically inspect a UK manufacturing site which is exporting products to them, although EU states also have mutual reliance agreements to varying degrees with Australia, Canada, Switzerland, Japan and New Zealand which negates the need for some inspections from those countries.

Economic context

14. Pharmaceutical products are primarily demanded in the pursuit of curing illness and disease and the profitability of most individual companies is linked to their ability to discover research and create new drugs. It is a sector where large companies benefit from economies of scale in research, manufacturing, and marketing and small companies tend to compete by specialising in drugs that target specific ailments.

15. The pharmaceuticals manufacturing industry contributed over £13bn of Gross Value Added (GVA) to the UK Economy in 2012; approximately 1% of the total UK GVA. The contribution of the pharmaceutical sector has been growing steadily over recent years, having contributed only 0.5% of GVA in 2004.

16. The industry employs around 44,000 people in the UK, which is roughly 0.14% of the total UK workforce. This is a rise of 6,000 since 2008/9 but is still some way from the levels of employment seen in the early 2000s. The industry produced exports worth £24bn in 2012, up from £12.7bn in 2005.

Other recent programmes of activity

17. The life sciences sector is very important to the UK economy and there have been a number of Government initiatives in recent years to help the sector flourish and grow. This review seeks to build on the previous work in this area.

18. Annex B includes more information on these other programmes of activity.

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[2] Laid down in Directive 2001/83/EC

[3] Set out in Regulation (EC) No 726/2004

SECTION 2: WHAT WE HEARD

Focus on Enforcement reviews look at the impact on the regulated of how regulations are enforced by national regulators and local authorities. Areas are reviewed from the point of view of businesses operating within the sector. Reviews therefore cover the totality of the regime in order to reflect the various interfaces businesses may have with different regulators, or even different divisions or teams of the same regulator. Taking this approach allows us to highlight where distinctions are made within regulators' structures to reflect different regulatory functions or roles which, when looked at in the context of a wider regime, do not always make as much sense from a business perspective.

This section summarises the key evidence gathered through the review. It begins by highlighting areas which were identified as good practice and then deliberately focuses on areas that were identified as issues and therefore present the most fruitful opportunities for change and development.

Good Practice

The need for regulation in this area is very clearly understood, accepted and, valued by the sector. We received considerable positive feedback on the operation of the regulatory regime and heard several specific examples of good practice that were welcomed by the regulated community. These are outlined below:

- **Industry told us that the MHRA is a highly respected regulator**, not just in Europe, where it was frequently described as a leader and 'punching above its weight', but also worldwide. Business acknowledged and welcomed the fact that this gives the organisation an ability to influence the global agenda and was keen for the MHRA to use this influence to its full potential (see Finding 7). Many businesses also described the MHRA as a generally open organisation, which was willing to engage with industry and tried to 'do the right thing'.

- **We were told by several businesses that the organisation made considerable effort to be risk-based**; some even made specific reference to the sophisticated infrastructure which the MHRA has in place to support a risk-based approach, although others said they were not sure as to how decisions were arrived at but were, on the whole, content with the results.

- **There was evidence that MHRA inspectors have very good knowledge of the sector and offer a professional service.** Most businesses felt that MHRA inspectors understood their business (and had usually worked within the sector) and were able to speak the same business language as them. This was something which they really valued. In terms of the inspection visits themselves, business reported that they generally receive timely reports and feedback from MHRA inspections, which they also find extremely useful.

- **Businesses operating in this sector were generally complimentary about their engagement with the Environment Agency** – those businesses who also fell in scope of the Environment Agency's remit (ie where they produce, for commercial sale, an active ingredient in a pharmaceutical product) seldom reported problems in their interactions with them (either in relation to inspections or with regard to permits) and felt that inspectors made themselves available for conversations regarding regulatory compliance and gave helpful advice.

In addition to this positive feedback, the review team heard considerable evidence from businesses on areas where they believed the regime could operate more effectively:

Finding 1: MHRA Licence Applications and Variations

Businesses raised numerous concerns over the process for MHRA licence applications and variations, both for site licences[4] and market authorisations[5] (required for each pharmaceutical product before it can be made available to the UK market), **resulting in delays in getting products to market, uncertainty and additional costs.** In particular, they reported the following issues:

A. Lengthy, inconsistent and unpredictable timeframes - businesses told us that;

- the time it takes the MHRA to process licence applications and variations can be lengthy, causing them financial disadvantage and frustration, which also impacts on their ability to plan ahead. We were told that this was a particular problem for seasonal products as delays in processing variations to a manufacturing and import licence have meant that products have missed bi-annual windows to market, causing businesses financial losses. Another business told us that whilst they had seen improvements in the licence variation process, it can take up to 120 days for the MHRA to process a variation. This means that they frequently keep products in quarantine for long periods of time leading to increased financial pressures and delays in their supply chain.

- there is little transparency, consistency or predictability in how long it will take the MHRA to process licence applications and variations. Some businesses said they felt that the MHRA were reluctant to tie themselves to a timeframe (despite placing strict timeframes on industry to submit licence applications) and so avoided being transparent on progress of applications. For example, one company reported that the MHRA enforce rigid time limits on businesses which if not met, mean their application is automatically rejected, but had not adhered to the same time limits themselves. Another business told us that they had submitted applications which had been processed extremely quickly, but on other occasions they had taken so long a licence of a similar nature “hadn’t come out the other end”. This resulted in businesses spending time chasing up licence applications, taking them away from core business. Other businesses reported difficulties caused by not knowing who to speak to or how to find out where an application was in the process.

B. Errors and inaccuracies - nearly all of the businesses we spoke to reported errors and inaccuracies on a wide variety of licences, including manufacturers’ and importers licences (MIAs), market authorisations and wholesale dealers’ licences. The most consistent complaint was in relation to the MIA licence, with some businesses going as far as to say that they had never received an MIA with the correct information first time round. A number of businesses attributed these errors and inaccuracies to the fact that some processes are still “relatively out of date” and paper-based rather than electronic. These errors and inaccuracies mean that businesses have to spend time sorting out the issues and in some cases, resubmitting applications. We were told that this can cause delays in the supply chain and ultimately results in delay to products reaching the market.

[4] See para. 1, Annex A
[5] See para. 2, Annex A

C. Duplication of information requests - businesses told us that they were required to repeatedly duplicate the information they gave to the MHRA for different licences and did not understand why these licence applications couldn't be cross referenced, so that an update on one licence was automatically reflected on another licence containing the same information. Businesses were concerned that a slight error in the parallel administration of these licences could lead them to be judged as non- compliant.

Finding 2: Batch Specific Variations

Businesses told us that the MHRA process for allowing businesses to accommodate one off, low risk, changes to their usual procedures (via a 'Batch Specific Variation[6]') is often unreasonably long, unpredictable and opaque, creating uncertainty and, in some cases, delays in their production processes. Businesses reported the following issues:

A. Timeframes - industry reported that the vast majority of Batch Specific Variations (BSVs) they submit are in relation to very minor variations and deviations, which would clearly not have any effect on the end product. They believed that the type of variation generally submitted would take no more than half a day to fully understand and reach a conclusion on. As such, they expressed frustration with what they considered to be unreasonably long application processing times, citing periods of up to 3 months to gain approval. Several businesses compared the MHRA's timescales to those of the Irish Medicines Board (IMB), stating that whilst applications to the MHRA could take 3 months, similar applications to the IMB would regularly be dealt with within 24 hours. In this context, businesses did not understand why the MHRA could not deal with simple batch specific variation applications within a greatly reduced timeframe.

B. Commercial need - businesses told us that they sometimes submit BSV applications in instances where there is a critical patient or commercial need. They reported that whilst the MHRA expedites applications due to critical patient need; they often have a lack of concern for critical commercial need.

C. Unpredictability and Opaqueness - in addition to the lengthy timeframes, businesses also reported (as with other licence applications and variations) a lack of predictability and transparency regarding BSV processing timescales. Again, this leaves them unable to effectively plan their production requirements and has a knock on impact to the production process.

Finding 3: Unlicensed Medicines

Businesses reported that it can take a long time to process notifications to import unlicensed medicines[7]. This causes companies to lose out on securing business. We were told that it can take up to 80 days between submitting a notification to import and the approved 'importation from' date. Those we spoke to understood the legislative requirement for the MHRA to assess the notification in 28 days (including consideration of whether there was a licensed alternative available), however could not understand the length of time between the notification being approved and the date from which they can import. One business told us that the length of time taken to receive an approved 'importation from' date has meant that they have lost out on contracts on numerous occasions. In addition to this, several businesses

[6] See para. 5, Annex A
[7] See para. 7, Annex A

mentioned a review by the MHRA of unlicensed medicines. Some felt that the consultation around the proposed changes had not been effective or genuine and others were not clear of the status of the review and whether changes would be made as a result of it.

Findings 1-3: In relation to the above findings, a number of the businesses we spoke to made **comparisons between the inspectorate and the licensing teams**. Some said they found the inspectorate to be generally pragmatic, transparent and helpful; this was in stark contrast to the licensing process and the teams who handle the applications, where we received many more complaints.

Finding 4: Controlled Drugs

We were told by businesses that the process for obtaining licences for controlled drugs is sometimes slow; that they would welcome clearer and more consistent advice and guidance; and that they had experienced inaccuracies and delays in finalising licence documentation which had on occasion caused financial losses. Some businesses felt that this was partly caused by a lack of knowledge and understanding of the sector within the Unit and difficulties in business and the Home Office understanding each other's terminology. **We were told that this resulted in misunderstandings arising during inspections and**, **in some cases, inaccuracies in the licence documentation following the site visit.** Issues raised included:

A. Slow application processes - businesses complained about the application process and told us that it caused delays in the production of pharmaceutical products. We were given an example of a site that had waited nine months from the original application submission before an initial inspection took place, after which the rest of the process took a further three months. We were told that this prevented the business from fulfilling the market demand for their product, and as such missed out on a year's worth of potential sales.

B. Inconsistent advice and guidance - Businesses also told us that they had difficulty understanding exactly what was required when applying for site licences for controlled drugs, with one going as far as to describe it as "an absolute minefield". We were told that this was due to descriptions in the application process being unclear and a feeling that it was difficult to get clear and consistent advice on what to do. Businesses attributed this lack of clarity to two key areas; firstly, the fact that they could not always speak to the same person in the DLCU (either citing a belief that staff had moved on or that they did not consistently deal with the same person or have a single point of contact) and secondly, that there does not seem to be a common understanding of terminology between the Unit and pharmaceutical businesses. For example, one business told us that they believed a change in staff (who they had previously built up a relationship with) had led to a reinterpretation of guidance such that the company's client was required to be licensed for controlled drugs when, in fact, their client would never be handling the material because they had fully outsourced the production of it to the business we spoke to. This placed additional costs on the client (because they needed a licence despite having fully outsourced this area of work). The company believed that this was a misunderstanding of the work that they (the company) did. We were told that this placed the business at a competitive disadvantage because they felt that other firms were not subject to the same reinterpretation.

C. Inaccuracies in the licence documentation and inappropriate licence requirements were also cited as areas of concern for industry. We heard from numerous businesses who had lost contracts and who said that their products were kept out of the market place for up to a year whilst inaccuracies in licences were corrected. In some cases, they reported that they had to bear the burden of the cost of the original licence application, despite the fact that it had expired

before it could be used. Businesses also told us of cases where they and their customers were required to hold licences that they felt were inappropriate for the respective functions they performed (see example above for one illustration of this).

D. Perceived lack of understanding of the sector - we were told by several businesses that they felt that during site inspections, Home Office staff demonstrated a lack of understanding of the business; this made inspection processes disruptive to the operation of the site, caused significant irritation and, in some cases, we were told that this translated into inaccuracies in the licence documentation following the site visit, including incorrect descriptions of activities carried out on the site, incorrect categories and schedules listed and, we were told of one case where the licence was also issued to the wrong site.

Finding 5: Qualified Persons

Qualified Persons[8]in pharmaceutical businesses reported significant irritation due to (what they described as) a lack of sufficient discretion when releasing products to market. They said that this leads to an increasingly bureaucratic workload, increased cost (businesses reported wasting products which they deemed to be safe as a result) and delays in the release of products with knock on effects to the overall production process.

A. 'Discretion' - businesses complained that the approach to QP discretion in the UK since 2000 compared unfavourably to the approach they had experienced in other European countries. QPs told us that the MHRA takes a much stricter view on what discretion a QP can or can not have than other EU regulators. As such, they observed that QPs in other member states are afforded much greater discretion to judge batches of products to be suitable for release to the market, despite the regimes interpreting the same underlying regulation. Businesses perceive that the MHRA applies the rules in this area 'to the letter rather than to the spirit'. They told us that this had resulted in QPs now effectively being 'highly trained box tickers' and that the burden of paper based work generated by compiling evidence, risk assessments and justifications, completing and chasing variation applications capitalised a significant amount of their time. They were also concerned that this increased paper-based responsibility meant that they were drawn away from the factory floor, leading to QPs holding a less intimate knowledge of the manufacturing processes. Some companies also reported wasting products which they believed to be safe as a result of this lack of discretion.

B. Batch specific variations - in the context of QP discretion, we heard from some businesses that the MHRA's 'batch specific variation' process is, in principle, a welcome development. Some businesses felt that it provided an opportunity to receive a clearly defined decision from the MHRA on an issue which otherwise might require the QP to 'stick their neck out' and bear the risk themselves. Others felt that greater discretion would be the favoured option, but that this went some way in addressing this issue. However, in both cases, a primary complaint of businesses was the **lengthy timescale** that it took to process batch specific licence variations (see Finding 2).

C. Lack of clarity and consensus across the sector about whether a UK-based QP needs to release imported products previously signed off by a European QP – a number of businesses raised concerns about a perceived requirement for a UK-based QP to sign off products for release if they have been imported from outside of the EU (but via another EU member state), even if they have been signed off by a European QP. They do not believe that

[8] See para. 8, Annex A

this requirement is replicated in other EU countries and view this role largely as a 'tick-box' exercise, as the UK-based QP does not undertake any additional product testing. In the experience of businesses that we spoke to, other EU member states would accept the original QP release and would not require a second release by a QP in their respective countries. This creates an additional burden on the business by requiring them to employ another QP in the UK (on top of any other QPs that they employ). Businesses told us of instances when increased expense was incurred and planned orders and operations were disrupted due to a lack of prior knowledge or awareness of this requirement, which they believe is unique to the UK. Businesses told us that they had to adjust plans and arrangements for the distribution of products throughout the EU when they became aware of this requirement. In one instance a whole batch of product had to be relabelled and leaflets changed with the updated address of the UK based QP who had to release the product in the UK, replacing the address of the EU based QP. However, we were told by other businesses that they did not think this was a requirement at all, and that an EU based QP release was all that was required. This suggests that there is significant confusion in the industry as to what is actually required.

Finding 6: Inconsistency

Businesses complained about inconsistency in MHRA advice, meaning that they are uncertain as to their compliance obligations and, at times, resulting in significant costs to the business where changes have to be made to accommodate different interpretations or 'bug bears' of different inspectors. Specific reasons which business associated with this inconsistency included;

A. '**Unwritten rules'**, creating substantial angst and uncertainty for business. Several businesses gave the example of the MHRA 'unwritten rule' that businesses update certain documentation every two years, despite the fact that guidance states that documentation should be updated after "an appropriate" length of time. One business we spoke to had stopped dealing with a supplier who refused to provide an updated Transmissible Spongiform Encephalopathy **(**TSE**)** statement after two years. This decision was based on the advice of a previous inspector. The company said that despite their recent inspector advising them to use a "risk-based approach" and continue using the supplier they felt that they couldn't be sure that a future inspector wouldn't overturn this decision. Another business told us they had previously set their "appropriate time" for updating their TSE statements at three years, due to the nature of their business, but we were told that they had been fined by the MHRA for not updating them after two years. As a result the business was forced to change their processes.

Businesses also told us about the 'unwritten rule' that inspectors change sites after three inspections. They reported that this can make it feel as though inspectors change very regularly. Many commented that, whilst they appreciated a 'fresh pair of eyes' looking at the site and could appreciate the need to keep the relationship fresh, they also welcomed having a long-standing relationship with an inspector and, in particular, knowing who they could ask if they needed advice. We were told that each time a new inspector started, the business needed to invest time in bringing a new inspector up to speed on company processes and ensuring the new inspector was familiar with business operations.

B. Different interpretations by different inspectors - we heard from a number of companies that what one inspector accepts as compliance may not satisfy another inspector, who may have a different interpretation of requirements. Again, there seemed to be a number of different reasons for this;

- The MHRA takes a principles-based approach which businesses understand and appreciate in principle. However, they reported that the **ability for an inspector to interpret a requirement in a different way and then effectively overturn a decision agreed at a previous inspection**, with a different inspector made them feel that they could not be confident that the compliance arrangements agreed with one inspector would satisfy the next one. For example, a business told us that on a previous inspection they had agreed a lengthy and detailed change to one of their processes with the MHRA inspector. At their next inspection, a different inspector challenged the process and disregarded the agreement the business had in place. The business received a deficiency on their inspection report which they felt went against the decisions made at the previous inspection.

- **Individual inspector 'bug bears'** leading to inconsistent advice and different demands. For example, we spoke with a business which used a sterile product in bottles, certified as safe to use for three months. However their inspector had told them that, once opened, they must throw out bottles after 24 hours. The business told us that they pointed out the certificate and three month lifespan but they felt the inspector was uninterested and refused to read the material. Due to the cost of the sterile product and the compliance requirement for them to discard bottles every 24 hours they can no longer afford to use the product. Another company reported that their previous inspector had what they considered a 'bug bear' in relation to cross-contamination; this resulted in them receiving previously unheard of demands, which were very costly for the business to install.

- **Disproportionate interpretation** – we heard several examples of interpretations which seemed to have a disproportionate impact on the businesses affected. For example, one inspector giving a deficiency for not maintaining standards of the building due to one crack in one single light fitting, to another inspector deciding that the fabric of a building at a site was not adequate, despite no change to the building. We were told that the changes required by the inspector would need such huge investment that they were unsure whether they could afford to make them and, as such, were considering whether they can continue to operate or whether they would need to close down. The company added that they were confused by the decision as no previous inspectors had ever raised or mentioned an issue with the building.

C. Inconsistency between teams within the MHRA – we were told by some businesses that they felt that "if you were to ask the same question [to the MHRA] you won't necessarily get the same answer every time." A specific example given was in relation to changes to EU pharmacovigilance legislation, implemented in 2012. Businesses told us that they were expected to comply with the new rules but had no clarity or certainty as to what this means in practice. They were aware that this was a European level issue but told us that in the absence of guidance they sought help from the MHRA, but often received conflicting advice depending on who they spoke to.

Finding 7: Global Recognition and Harmonisation

Businesses welcome work to increase global recognition and harmonisation but are keen to see further integration as quickly as possible on this, in order to save them time and money.

Almost every business we spoke to reported high volumes of visits from medicine and healthcare regulators from countries that were importing their products. First and foremost, businesses commented on the amount of time these visits took up. One company reported fifteen days of auditing activity in the UK within the last year and another reported an average of seven GMP inspections per year, each lasting between 3 and 5 days and costing the business £8000-£10,000 per day. Businesses also complained about the resulting inconsistency of advice and requirements from different inspectors in different jurisdictions, which added to their operating costs. This said, nearly all those we spoke to positively acknowledged the progress the MHRA have already made with international harmonisation – for example, playing a leading role in Europe and the extension of mutual recognition with Japan (with European agreement). However, business was keen for the MHRA to use its influential position on the world stage to push for even more to increase global harmonisation in order to reduce the volume of inspections and increase consistency.

A number of businesses we spoke to welcomed the fact that the MHRA are beginning to conduct joint-inspections with the US Food and Drug Administration (FDA). Some told us that while these didn't always work out as well in practice as they do in theory – for example "different inspectors from different agencies are looking through their own individual lenses" – they were worth initial 'pain' for potential future benefits such as trust between the two agencies.

Some businesses also questioned why mutual reliance had not yet been established with the US FDA, given that the US is the largest pharmaceutical market, and the clear benefits that this would therefore bring.

Finding 8: EU Co-ordination

Businesses told us that they are often left to resolve issues caused by inconsistent application of the rules by different EU regulators. This causes them delays when working across the EU.

Businesses who engage with different European regulators told us that there is sometimes inconsistency in the way EU rules are applied and implemented in each member state. Whilst the high standards of manufacturing in the UK were unanimously welcomed, we were told that the lack of direct communication between the various European authorities made resolving the inconsistencies between regulators extremely difficult. Those who had experienced difficulties first hand said that they felt like they were left to act as the 'go-between' between the different regulators. For example, one company told us that they were inspected by another European inspection agency, who asked what the MHRA's point of view was on a particular issue but were not prepared to talk directly to the MHRA themselves. This lack of direct engagement resulted in significant delays in the process.

Finding 9: MHRA Guidance

Businesses told us that, in general, they appreciate and value MHRA guidance. However, they reported that there is a lot of redundant information on the MHRA website.

A. Principles-based guidance - in general, businesses told us that they appreciate this. We received several endorsements for the MHRA's 2007 Good Manufacturing Practice Guide (the 'Orange Bible'); although some commented that they would appreciate this being updated.

B. Redundant information and guidance on the MHRA website - businesses who commented on this were generally aware that action was being taken to streamline and improve the volume of guidance on the MHRA website (and in some cases recognised this as an outcome of the Red Tape Challenge exercise) but all stressed the importance of this work and were keen to see progress as soon as possible.

Finding 10: MHRA Fees

Businesses told us that the calculation of MHRA fees is not always very transparent, both for maintaining licences and, in some cases, also for inspection visits (which are not broken down but presented as a 'lump sum').

Some businesses commented that the fee system for maintaining licences is complicated and that it is not always clear why the structure is applied in the way it is. Businesses also reported that whilst MHRA were willing to engage in discussion over why a fee was at a particular level in a particular case, they felt there was not always a consistent rationale and that the MHRA rarely changed their mind.

ANNEX A: MHRA FUNCTIONS

This is a fuller version of the summary contained in Section 1 (p. 4) of the main report.

1. Site Licences

There are various different types of site licences which businesses involved in the manufacture, production and wholesale of pharmaceutical products might require[9]. Businesses involved in this review specifically mentioned the following MHRA site licences:

A. Manufacturers/importers licences (MIA)
These licences allow the holder to:

i. manufacture and/or assemble (package) medicinal products
ii. wholesale deal licensed medicinal products imported from countries outside the EEA

B. Manufacturers 'specials' licence (MS)

These licences allow the holder to:

i. manufacture unlicensed medicinal products (commonly referred to as 'specials')
ii. import unlicensed medicinal products from outside the EEA

2. Market authorisation (formerly product licences)

Market authorisation, previously know as a product licence, is required for each pharmaceutical product before it can be marketed in the UK. In order for medicines to be granted market authorisation they need to have been shown to have met required standards of safety, quality and efficacy. Market authorisation in the UK can be sought either by applying to the national competent authority the MHRA, or it can be sought centrally from the European Medicines Agency (EMA). However, in some specific instances market authorisation must be sought from the EMA.

Market authorisation fees are sorted into four main sections; major, abridged complex, abridged standard and abridged simple. Each of these groups is then split into five standard types of applications, with varying fee charges. The most expensive fee, for a national fee in a 'major' section, is set at £103,059. By contrast, all of the fees in the 'abridged simple' section are charged at £2,849 each.

3. Parallel Import Licences

The MHRA provide parallel import licences to allow medicinal products authorised in other EU Member States to be marketed in the UK, provided the imported products have no therapeutic

[9] For full list see http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/ManufacturersandWholesaleDealerslicences/index.htm#2

difference from the equivalent UK products. Parallel import licenses fall into three categories; (simple, standard and complex), dependent on the origin of the product.

4. Variations to Marketing Authorisation licences

Licence holders must notify the MHRA of any changes to the details included in their licence documentation by submitting a licence variation application. There are different categories of notifications depending on whether the change is major or minor. More minor changes can be implemented before notifying the competent authority - in some cases this notification needs to be immediately after the change has been made and in others notification just needs to be within 12 months of the change being implemented. The latter is known as a “Do and Tell” notification.

All major variations require notification and approval before they are implemented, so the product cannot be released prior to receiving approval from the competent authority.

Fees for variations to marketing authorisation licences range from being free for ‘Type IA’ variations, up to £39,829 for the most expensive ‘Extended Type II complex’ variations.

5. Batch Specific Variations

The ‘batch specific variation’ process is designed to allow businesses to accommodate ‘one off’, low risk, changes to their usual procedures (specified on their licence) without having to make a change to the core licence itself. Under this process, the business seeks approval from the MHRA to release the batch to market.

A successful batch specific variation application must prove that the quality safety and efficacy of the product has been unaffected by the deviation. The process should therefore mean that variations to a batch which do not have an impact on safety or quality are not wasted.

Batch specific variations are dealt with in a similar way to the standard variation applications as outlined above. Applications can be fast tracked if there is critical importance of the supply to the market and urgent patient need.

6. Pharmacovigilance (Drug Safety)

Medicines are tested before release to the market, in the form of clinical trials. However, because these only involve a relatively small number of people, some adverse effects may not be seen until the medicine has been received by a much larger group. Once a product is on the market its safety and efficacy continues to be monitored for previously un-experienced effects – this is known as pharmacovigilance. To help monitor any adverse effects the MHRA runs several regulatory schemes which require manufacturers to include information regarding how to report adverse effects, and identify products which effects need to be monitored more closely.

7. Unlicensed Medicines

The MHRA also regulate the import of medicines which are not licensed in the UK. As per regulation 46 of The Human Medicines Regulations 2012 (SI 2012/1916) the default position is that all medicines must have a UK market authorisation. However, there are specific circumstances when unlicensed medicines can be imported and placed on the UK market. Medicines that do not have a market authorisation can be imported into the UK in instances when there is a specific special patient need which is clinical in nature and licensed versions of the medicines are not available in the UK.

In these instances the prospective importers must still posses the relevant site licences (Wholesale Dealers Licence or Manufacturers 'Specials' Licence) and must notify the MHRA of their intention to import in accordance with part 2 and 4 of Schedule 4 of The Human Medicines Regulations 2012 (SI 2012/1916).

8. Qualified Persons

Before any batch of medicinal products can be released for clinical trials or to market, it must be certified by a Qualified Person (QP). QPs are responsible for ensuring that every batch of medicines meets legal and regulatory requirements (as well as efficacy, quality and safety standards) before it is released to market.

This certification includes ensuring that Good Manufacturing Practices have been adhered to, that the requirements of the market authorisation and the manufacturer's licenses have been met, that legal requirements for imported products have been met and that quality control, testing and manufacturing processes have been validated and conducted appropriately.

QPs are highly qualified, with extensive training and in-depth critical understanding of all aspects associated with pharmaceutical manufacturing. They must have completed 4 years theoretical and practical study in pharmacy and have completed at least an additional 2 years of practical experience at an authorised pharmaceutical manufacturer, engaged in qualitative analysis of medicinal products, quantitative analysis of active substances and testing and checking the quality of medicinal products.

In the UK, QP status eligibility is assessed and nominated by professional scientific bodies (the Society of Biology, the Royal Pharmaceutical Society and the Royal Society of Chemistry). Although it is the opinion of the professional body concerned whether a member meets the statutory requirements to become a QP, the MHRA is ultimately responsible for assessing the suitability of a QP to be named on a particular Manufacturer's Licence.

ANNEX B: OTHER RECENT PROGRAMMES OF ACTIVITY

1. The Strategy for UK Life Sciences was published by the Prime Minister in December 2011. It set out a range of measures to support growth in the UK health life science sector, based around 3 key areas; building a UK life sciences ecosystem, attracting, developing and rewarding talent and overcoming barriers and creating incentives for the promotion of healthcare innovation. It was launched alongside, and is being implemented in collaboration with, the NHS chief executive's review: 'Innovation, health and wealth: accelerating adoption and diffusion in the NHS.'

2. Since then, progress updates on both of these documents (including new commitments to the sector) have been published, reiterating the commitment of the UK Government to life sciences.

In addition, this review sits alongside three other recent initiatives which have sought to improve the regulatory environment for the life sciences sector in the UK;

A. The Red Tape Challenge Medicines theme. This ran from March to April 2012 and delivered a package of MHRA simplification proposals, including consolidating hundreds of pieces of legislation, a review of the MHRA's guidance and other MHRA processes which businesses had reported as burdensome.

B. Business Taskforce Report – Cut EU Red Tape. In summer 2013, the Prime Minister asked six business leaders to form a Taskforce and work with Government to identify European rules and regulations that needed abolition or reform to help British companies grow. The Taskforce identified 30 priority recommendations and key principles to sweep away barriers to growth and save billions of pounds; two of these related to the life sciences sector and called for a more competitive clinical trials framework and a quicker, more flexible licensing regime for medicines at European level.

C. Also during summer 2013, there was a joint initiative between Government and the pharmaceutical and biotechnology industry, to develop ideas to make the UK an even more attractive location to manufacture medicines. A strand of this work looked at the issues around the design and flexibilities in the regulation of medicines manufacture. The initiative reported into the Ministerial Industry Strategy Group (MISG) in November 2013 and had 3 key findings in relation to regulation;

- A high priority area should be vital ongoing work with global partners to reduce the overall inspection burden on UK sites. This could encompass formal Mutual Recognition of inspections with European agreement, as well as informal sharing of information between trusted authorities.

- MHRA will commit to joint work with industry to drive ongoing process improvement and to stimulate maximum use of innovative processes and existing regulatory flexibility through the Innovation Office or other mechanisms. That should include supporting the

centres and projects which are part of the technology roadmap e.g. Cell Therapy Catapult.

- Case studies of regulatory collaboration through the MHRA Innovation Office should be published. These would encourage further constructive engagement and foster innovation in what can be a complex regulatory framework.

ANNEX C: SCOPE OF THE REVIEW

Review of compliance and enforcement activity in the pharmaceuticals manufacturing and production sector.

The team may adjust the following scope statement as the review progresses, to ensure that the review covers a coherent and manageable range of issues.

This review will look at the regulatory activity of national regulators and local authorities that affects manufacturers and producers of pharmaceutical products.

It will consider, amongst other things, the interaction between different regulatory regimes affecting businesses operating in this sector, any aspects of regulatory activity that could be made more efficient and areas of good practice which could be replicated elsewhere.

In scope:

- Regulatory activity by national regulators and local authorities that affects / is perceived to affect the day-to-day operations of manufacturers and producers of pharmaceutical products.
- The impact of the overall regulatory regime on both large and small manufacturers.
- The whole of the manufacturing and production process, including applying for relevant licences.

It will look at the full range of issues faced by manufacturers and producers of pharmaceutical products in meeting their regulatory obligations, including but not limited to:

- how and where they access information about their legal obligations;
- what information is needed to support their compliance, and how they prefer to access advice and guidance;
- the cumulative impact of complying with different regimes, the interaction between them, and the impact of compliance activities and requirements carried out by different public authorities;
- any experience of how regulatory activity works in the UK, compared with other regimes;
- activity undertaken by the regulators to support business compliance;
- any ‘knock-on effects’ arising from compliance with legislation - for example, where action to meet one set of regulations leads to conflict with, or additional requirements to meet, another set of regulations;
- the interactions producers and manufacturers have with the regulatory authorities, including on the business premises;
- the consistency of compliance and enforcement decisions and the ease of appealing them;

- any issues encountered where third parties are encouraging companies to undertake unnecessary compliance activity e.g., where regulation does not actually require something to be done, but companies are led to believe it does;

Out of scope:

- Regulations themselves.
- Issues related to the distribution and sale of pharmaceutical products (but not issues relating to contracts to manufacture pharmaceutical goods which are in scope).
- Issues related to the manufacturing process for dietary supplements will not be included in this review, except where they become subject to the regime which applies for pharmaceutical production and / or manufacturing.
- Other regulatory activity with an impact that is not particular to businesses operating in the pharmaceutical manufacturing / production industry, e.g.; employment law, company law, planning applications etc.
- The review will seek to avoid duplicating the work of other reviews on related subjects, in particular, the Focus on Enforcement chemicals review (Control of Major Accident Hazards (COMAH)).

Regulatory Activity

“Regulatory Activity” in this context includes;

- provision of advice on compliance with the law;
- inspections visits and assessments of premises and equipment;
- any requirements to make formal applications, or provide specific information, for example, to obtain necessary permits and licenses ;
- any requirements on businesses and their staff to attend courses or obtain particular qualifications;
- Formal enforcement proceedings taken against individuals or organisations in the event of failure to comply with regulations (we cannot consider comments on specific cases unless all proceedings have finished - but we can consider general evidence in relation to enforcement proceedings).

We are interested in examples of good practice that is helpful to business in meeting their obligations, and suggestions for improving the way things work.

This publication available from www.gov.uk/bis

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