INDEPENDENT REVIEW ON ANTI-MICROBIAL RESISTANCE (AMR)

REGULATION-INNOVATION INTERACTIONS IN THE DEVELOPMENT OF ANTIMICROBIAL DRUGS:

AN EVALUATION OF DRUG AND IVD REGULATION

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1. Background

1.1 Concept

The issues around anti-microbial resistance (AMR) need to be considered holistically. In doing so, one can identify a number of diverse, interested parties. At the highest level, there are the political and societal interests, with the politicians setting the mission to address the problem of increasing levels of Anti-Microbial Resistance (AMR) and the lack in the development of new antimicrobials (AMs). Policy statements need to be implemented. This will involve many different interested parties covering topics such as health, research, industry, funding and regulation. Within each of these topics there is another level of granularity covering a wide range of activities requiring action and integration.

On that basis, regulation is one of several factors. Even within the definition and scope of regulation, many of the topics cited above are subject to regulation, which might influence the development of new anti-microbial products. The topic for consideration here is the regulation of medicinal products. The review will present:

- a brief summary of its basis;
- a more detailed look at adaptation in regulatory provisions, from 2000 – 2009, and more recently from 2009 – 2014;
- the evolution of the review procedures, including interaction between regulators of medicinal products and those involved with Medical Devices (MDs) / In-Vitro Diagnostics (IVDs); and
- general observations on the evolution in the systems for the regulation of medicinal products over the last 14 year with reference to antimicrobials and briefly how things may change in future years.

This approach will exemplify the modifications which have occurred in each of these areas and those which will continue, reflecting regulation as a 'living entity' which responds to, and also anticipates, the need for change.

1.2 Basis of the regulation of medicinal products – regional and global

Legislation was put in place in the mid-sixties following the thalidomide disaster. Since then the legislation, science and review and control of medicinal products throughout the life-cycle of such products have evolved.

Broadly speaking, the basis of the legislation in Europe lies in the Regulations, Directives and Guidelines which are issued by the European Commission. It is important to note that such tools are generated by the Commission's services. However, they are subject to extensive consultation amongst the Member States and their experts and discussion at Council level. For Guidelines, which supplement the legislation, there is additional consultation with a wider group of interested parties, including the pharmaceutical industry, trade associations etc. The Commission undertakes Impact Assessments for new legislation (EC Impact Assessment Guideline, 2014)to establish the need for the legislation, costs and benefits. Taken together such consultation is designed to strengthen the transparency and value of the Commission's proposals. Thus, the regulation of medicinal products is designed to cover all classes of product, including chemicals (small molecules), fermentation products, synthetic biologicals and classic biologicals within which are antibiotics.

In addition to the European Regulations other regional jurisdictions globally have their own legislation and administrative procedures to deal with the review of dossiers for Marketing Authorisations. In the 1980s, recognising the difficulty faced by the pharmaceutical industry in satisfying regulatory requirements from so many different regions, where varying data

requirements could cause problems in the licensing and manufacture of medicinal products, Japan, the United States and Europe collaborated with the pharmaceutical industry to harmonise regulatory requirements for quality, safety and efficacy through the International Conference on Harmonisation (ICH), set up in 1990. As time has passed, other global regions including Brazil, Russia, India and China - the BRIC countries - have now expressed interest in becoming involved in such harmonisation because of the global market in pharmaceuticals.

All global regions have addressed the requirements for Good Manufacturing Practices (GMP). Initially, in the mid-1970s the UK drug agency of the time prepared a GMP guideline entitled the "Orange Guide", which provided guidance on the manufacture and control of medicinal products. The 2014 version of the guideline is available (MHRA - Orange Guide, 2014). Other countries in Europe, Japan and the United States did the same and came together to produce the ICH guidance (ICH - GMP Guidleines, 2000). Now the BRIC countries are following the principles set out in these guidelines.

During the last 24 years there have been other drivers for harmonisation. The two major agencies, the Food and Drug Administration (FDA) and the European Medicines Agency (EMA), are often faced with similar tasks at the same time, e.g. reviewing dossiers, inspection of global manufacturing sites or dealing with pharmacovigilance and public health issues. To deal with this effectively, agreements were put in place between the European Commission and the United States administrations (2003) to share and exchange information to facilitate the work in all of these areas and others as they arise. Although this work has been successful, both the EMA and the FDA recognised that "despite recent successful innovative approvals, there has been a decline in innovative medicines that are being developed and potentially able to enter the market in the next 5 years" (Ehmann, F., 2013). The thrust behind this paper is captured within its title "Gatekeepers and Enablers: How drug regulators respond to a challenging and changing environment by moving toward a proactive attitude".

2. Regulatory Initiatives, 2000 – 2009

2.1 Background

In general, companies can utilise a range of regulatory tools in the development of their products. Any one or several tools may be used.

The value in using these tools may be financial and / or based on reduced time in the development of a product.

For Small and Medium-sized Enterprises and Orphan Drugs, there are certain incentives which will be described under the relevant heading.

2.2 Small and Medium-sized Enterprises (SMEs)

The EMA set up its SME offices in December 2005 with the aim of promoting innovation and the development of new medicines for human and veterinary use (Commission Regulation (EC) No 2049/2005 (EMA Human Incentives for SMEs, 2005) (EMA Veterinary Incentives for SMEs, 2005)). Applicants can apply for SME status and, should they comply with the requirements, they can then benefit from incentives laid down in the SME Regulation. These incentives include administrative and procedural assistance in a number of areas including for example fee reductions for pre- and post-authorisation phases, including scientific advice, site inspections, line extensions and variations, fee exemptions for certain administrative services etc. In addition workshops have been organised addressing the areas of regulatory and data requirements on quality, safety and efficacy (EMA Workshops for SMEs, 2007 - 2014). Each of these workshops allowed attendees to gain a more detailed

understanding of data requirements and procedural matters relating to scientific and regulatory advice, pharmacovigilance etc.

Such incentives reduce costs incurred by SMEs and should reduce the time taken to develop their product, thus promoting innovation and development. However, it is difficult to estimate the reduction in development time due to the many variables involved.

Nevertheless, these facilities could be useful for small companies developing anti-microbial products.

2.3 Innovative Task Force (ITF)

The Innovative Task Force was set up in 2003 with the objective of providing a forum for early dialogue with applicants for Marketing Authorisations – both human (EMA - Human - SME Workshops, 2007-2014) (EMA - Human - SME Workshops, 2007-2014) and veterinary (EMA - VeterinarySME Workshops, 2007 - 2014) (EMA-Veterinary, n.d.) - covering the range of products handled by the Agency. The team is a multidisciplinary group including expertise in scientific, regulatory and legal matters.

Early contact with the Agency is encouraged. It allows wide ranging discussions, for SMEs and all other companies, on any new emerging therapies and / or technologies. Such contact allows the identification by the company of topics they need to progress, and by the Agency of new expertise required or the updating or creation of guidelines in advance of an application being submitted for a Marketing Authorisation. This approach stimulates each party to address the 'hot spots' sufficiently early.

For new AM agents and any new technology addressing the identification of organisms to better target the use of antibiotics such as In Vitro Diagnostic tests (IVDs), contact with ITF will allow companies at an early stage to further develop their strategy and timelines for the development of their product(s).

2.4 Orphan Drugs

The Orphan Drug Regulation was adopted in 2000. It provides a basis for the rules on how to deal with medicines for rare diseases in the European Union. Sponsors who obtain orphan designation (OD) - e.g. where the incidence of condition is NMT 5 / 10,000 - benefit from certain incentives which include free protocol assistance, scientific advice, free application for Marketing Authorisation and market exclusivity - 10 years - once a Marketing Authorisation has been granted. (EMA Orphan Drug Regulation, 2000)).

Some treatments for tuberculosis (TB) have been difficult to implement due to multi-drug resistance (MDR); however, recently a product with the active ingredient Sirturo (EMA European Assessment Report - Situro, 2014), was granted OD status and a 'Conditional Marketing Authorisation'. This means that the product belongs to at least one of the following categories:

- Seriously debilitating or life-threatening disease
- Medical products to be used in emergency situations
- Orphan medicinal products

In addition certain requirements need to be fulfilled for these authorisations, namely

- The risk-benefit balance of the product is positive
- It is likely that the applicant will be able to provide comprehensive data. By way of specific obligations, the holder of the authorisation shall be required to complete ongoing studies, or conduct new studies with a view to confirming the risk-benefit balance being positive.
- Fulfilment of unmet medical need

- The benefits to Public Health of the immediate availability outweigh the risks inherent in the fact that additional data are still required.

This has shown that although at least two of the tools have been used in reality more of the tools cited in this section have also been used.

2.5 Development of Scientific and Clinical Guidelines (1965 – 2009)

As indicated in 1.2, guidelines support the Regulations and Directives and are put in place to act as a bridge of understanding between the legislation and the data requirements for the support of applications for Marketing Authorisations. Many guidelines - quality, non-clinical and clinical - have been prepared over the period 1965 – 2009, to support the scientific and technical requirements for Marketing Authorisation approval. These are needed because of new legislation and the evolution of science over the same period of time. They cover a wide range of topics in the manufacture and control of anti-microbials, non-clinical and clinical aspects.

Amongst these guidelines, specific guidance has been prepared in relationship to antimicrobial products e.g. a Guidelines on setting specifications for related impurities in antibiotics (EMA/CHMP/CVMP/QWP/199250/**2009**) and on the requirements for clinical trials (CPMP/EWP/558/**95** re.1). The former guideline provides guidance on how specifications for related impurities in antibiotics that are fermentation products or semi-synthetic substances derived from fermentation products, to augment the ICH guideline which does not address such products. The latter guideline initially prepared in 1995 provided recommendations on the design of clinical trials intended to support the approval of specific indications for use. After the original guidelines were updated, put out for consultation and discussed at a workshop (2011), it was decided to include in the guidelines: details of patient selection criteria; primary end points; indications for study designs for superiority or non-inferiority; and suggestions for non-inferiority margins. In addition, ideas were sought on the inclusion of possible clinical programmes for new antibacterial agents with very narrow spectra of AM activity and / or with activity against multi-drug resistant pathogens for which there are very limited treatment options. This resulted in revision 2 of the clinical guideline which came into effect in 2012 and will be addressed under point 3.3.

These guidelines have been instrumental in allowing the recent development and grant of Conditional Marketing Authorisations for Sirturo (Orphan Drug - Janssen) and Deltyba (Otsuka Novel Products GmbH), for the treatment of MDR-TB. These Conditional Approvals mean that more evidence will become available on the medicines within their respective licence conditions (see 2.4. and 2.10 for details).

2.6. Medical Devices (MDs) and In Vitro Diagnostic Devices (IVDs)

Current Position

The EMA deals with the regulation of medicinal products. However, in the review of dossiers for these products when devices are associated with them, it collaborates with those responsible for MDs and IVDs in Europe, through the appropriate Notified Bodies. As a consequence, where the use of any medicine also involves the use of such a device, close communications are encouraged from an early stage in the development of products, to ensure that there is an appropriate exchange of information to preclude delays once an application has been submitted – this early contact is encouraged at both the EMA and the MHRA as evidenced by the interview reports.

Notified Bodies undertake the evaluation and testing of devices according to the appropriate standards for that device. For any tests which have been developed to identify the nature of bacteria, the test would have to be scientifically justified and validated according to requirements for sensitivity and specificity.

The regulatory agency for medicinal products would take the results into account when evaluating its potential use in conjunction with antibiotics, so that appropriate information could be included with the Summary of Products Characteristics (SmPCs).

The situation is different for individual Member States where some of the agencies responsible for medicines are also responsible for MDs and IVDs e.g. MHRA in the UK.

Status of Proposed New Legislation

Over recent years MDs and IVDs have been controlled through European Commission Directives. However, in 2012 a communication on "safe, effective and innovative medical devices and in vitro diagnostic medical devices for the benefit of patients, consumers and healthcare professionals" was published by the Commission with proposals to establish two new Regulations for MDs and IVDs. A private communication from EUCOMED indicates that the Regulation for MDs is currently progressing through European Council (EC Revision of the Medical Device Directives, 2014). The Regulation for IVDs will follow and may be in place by 2016.

For the latter Regulation, there is a new definition for IVDs, a 'risk-rule based classification system', involving: reinforcement of clinical evidence requirements: alignment of international requirements: reinforcement of oversight by Notified Bodies; joint assessments by experts from other Member States and the Commission; and conformity of assessment procedures with IVDs intended to be used as companion diagnostics. There will be a consultation procedure with the pharmaceutical industry, EMA and National Competent Authorities within Member States; so that there is an awareness of the proposals and interested parties are alerted to consider how they should interface with the new Regulations and consequential procedures. In addition, vigilance and market surveillance will be strengthened to reinforce post-market safety assessment. To further strengthen harmonisation amongst the Member States, there will be a Medical Device Coordination Group similar to that for Clinical Trial Coordination across Member States.

In September 2012 the European Commission issued proposals for a new Regulation to replace the current Directive, which includes:

- New risk classification – genetic tests and companion diagnostics subject to pre-market scrutiny by Notified Bodies
- Clarification for evidence about clinical validity
- Clarification of status of Laboratory Developed Tests (LDTs)
- Definition of companion diagnostic products.

In the 2009 Work programme, the Agency recognised the need for "a more intense interaction between the authorities in charge of diagnostics and medicines during the clinical development of medicinal products" (Work programme for the EMA – 2009). Also, the interests of NICE must be considered, too, creating the need for tripartite interactions across EMA, Notified Bodies (NBs) and Health Technology Assessment (HTA) bodies).

In view of these proposed changes and consultation procedures, there is benefit in maintaining an awareness of progress over the coming years to ensure that proposals for IVDs to be used in conjunction with antibiotics are fit for purpose.

2.7 Scientific Advice and Protocol Assistance

Various Articles of the European Parliament and Council Regulation (EC) 726/2004, allowed the Agency / CHMP to set up administrative structures and procedures to establish the Scientific Advice Working Party (SAWP) with the remit of providing scientific advice and protocol assistance to applicants for Marketing Authorisations. Scientific advice may be sought on issues relating to quality (details of manufacture and quality control), pre-clinical

and clinical topics. These provisions apply for all classes of medicinal products including antimicrobials.

Within these procedures, the EMA and the MHRA have always encouraged applicants, particularly for new innovative products and those where there is a public health or unmet medicinal need to contact the agency as early as possible. This approach is beneficial not only to the applicant but also to the agency, since it allows an early warning of where either new, or updates of existing, guidelines might be required. This approach allows companies to have dialogue with the regulators on matters which may have arisen during the development of the product well before submission of a dossier, and thereby minimise the risk of issues being raised late in the assessment of dossiers which delay the review procedure and decision on the application.

To do so, the Agency also offers pre-scientific advice meetings for preparation in advance of formal scientific advice and protocol assistance (SA/PA) meetings (see 2.8).

In cases where new or innovative products are being developed by the industry – SME or otherwise – such as antimicrobials, vaccines and diagnostic tools, evidence has shown the benefits in seeking such advice. The 2010 Annual Report from the EMA, published in the January edition of the Journal of Clinical Pharmacology (Liberti et al, January 2010), reported on the impact of scientific advice on the outcome of marketing-authorisation applications.

The EMA and the FDA have set up a procedure for the provision of parallel scientific advice.

The EMA in 2010 initiated discussions between national agencies HTA bodies in the E.U. The objective was to encourage collaboration regarding clinical trial design in advance of the submission and evaluation of applications for marketing authorisations and minimise the risk of non-acceptance of the regulatory decisions by HTAs. Parallel scientific advice is now available in the U.K. between MHRA and the local HTA - National Institute for Health and Care Excellence (NICE)

2.8 Adaptive Clinical Trial Design

In certain cases studies may be planned with an adaptive design involving design modifications based on the results of interim analysis. Using this approach has the potential to speed up the process of drug development without lowering scientific and regulatory standards. The EMA – EFPIA (European Federation of Pharmaceutical Industry Associations) had a joint workshop on the methodology for adaptive designs in confirmatory clinical trials in December 2008 (EMA - EFPIA Workshop of adaptive designs in confirmatory clinical trials, 2007).

2.9 Pre-submission Meetings in Advance of Marketing Authorisation Submissions

There are opportunities for applicants to have pre-submission meetings to discuss regulatory, quality, safety, efficacy, risk management plans relating to imminent submissions (EMA - Pre-submission meetings, 2000-2014). The EMA provides an opportunity for companies to:

- Present their proposed development programmes to coordinators and EMA staff and receive observations
- Obtain guidance on a range of other matters including how to gain scientific advice, seek regulatory understanding on the legal basis for a submission, GMP / GCP /GLP related issues etc.

This engagement permits a good understanding of the process and procedures to be followed and a refinement of the company's strategic plan for submission of the dossier.

2.10 Options Available for Marketing Authorisations

Submissions to the EMA through the centralised procedure mainly follow the standard process which is cited on the EMA web-site: the CHMP opinion needs to be given within a period of 210 days. However, within that process a number of other options may be used where specials conditions occur. These options include the use **accelerated assessment** (Article 14 (9) of Regulation (EC) No 726/2004), **conditional marketing authorisation** under Commission Regulation (EC) No 507/2006 and **marketing authorisations granted under exceptional circumstances** (Regulations (EC) No 726/2004). Another possibility is **compassionate use** which is a treatment option that allows the use of an unauthorised medicine.

These special circumstances afford a degree of flexibility in the amount of data that is acceptable dependent upon each, which seriatim require:

- Accelerated assessment – "When an application is submitted for a marketing authorisation in respect of a medicinal product for human use which is of major interest from the point of view of public health and, in particular, from the viewpoint of therapeutic innovation, the applicant may request an accelerated assessment procedure. The request shall be duly substantiated." This procedure can reduce the review time from 210 to 150 days, depending upon the content of the individual application. These facilities apply to both human and animal products.
- Conditional Marketing Authorisation – A conditional marketing authorisation may be requested by the applicant or proposed by the CHMP. This request should contain justifications to show that the medicinal product falls within the scope and requirements cited within Regulation (EC) No 724/2004 and Regulation (EC) No 507/2006. This means that the product belongs to at least one of the following categories:

    - Seriously debilitating or life-threatening disease
    - Medical products to be used in emergency situations
    - Orphan medicinal products

    It may be necessary to grant a marketing authorisation on less complete data than is the normal case but the authorisation would be subject to specific obligations. For example, certain requirements need to be fulfilled, namely:

    - The risk-benefit balance of the product would need to be positive
    - It is likely that the applicant would be able to provide comprehensive data. By way of specific obligations, the holder of the authorisation would be required to complete ongoing studies, or conduct new studies with a view to confirming the risk-benefit balance being positive.
    - Fulfilment of unmet medical needs
    - The benefits to Public Health of the immediate availability would outweigh the risks inherent in the fact that additional data are still required.

    In addition, the applicant should indicate the proposals for completion of ongoing or new studies, or collection of pharmacovigilance data.

    Because of the reduced data package the development time for the product may be reduced thought the assessment of such applications is not easy. An estimate of the reduction in development time up to the grant of a marketing authorisation is not feasible due to the inherent variability through the process.

- Exceptional circumstances – Products for which the applicant can demonstrate that comprehensive data (in line with the requirements laid down in Annex 1 of Directive 2001/83/EC, as amended) cannot be provided (due to specific reasons foreseen in the legislation) might be eligible for marketing authorisation under exceptional circumstances. The reasons include:
    - the indications for which the product in question is intended are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence, or
    - In the present state of scientific knowledge, comprehensive information cannot be provided, or
    - It would be contrary to generally accepted principles of medical ethics to collect such information,

  And therefore a marketing authorisation may be granted subject to certain specific obligations.
- Compassionate use – such programmes are for patients within the European Union who have a disease where there is no suitable authorised therapies or where they cannot enter a clinical trial. This can apply to patients with a chronically or seriously debilitating disease or whose disease is considered to be life-threatening and who cannot be treated by an authorised medicinal product. The approach is intended to facilitate the availability of new treatments which are still under development. Records of the use of such products are kept by the EMA / CHMP

    - MHRA colleagues highlighted an initiative taken by their Agency. It is an Early Access to Medicines Scheme (EAMS) introduced in April 2014, aimed at providing patients with life threatening conditions or seriously debilitating conditions with access to medicines that do not yet have a Marketing Authorisation, when there is a clear unmet medical need. It was stated that the scheme could be used after Phase II or during Phase III clinical trials – essentially, the Agency can provide an 'accelerated opinion' before the grant of the Marketing Authorisation.

Such special circumstances provide flexibility for the regulators to recommend a positive opinion, according to the legislation and the supportive guidelines. This flexibility is exemplified by the grant of conditional marketing authorisations for each of Sirturo, an antimycobacterial drug against multi-drug resistant tuberculosis (March 2014) and Deltyba an antimycobacterial drug against multi-drug resistant tuberculosis (April 2014).

2.11 Rolling Review

In planning on how to deal with an influenza pandemic, the Agency prepared a crisis management plan (EMA Crisis Management Plan, 2006). When this was activated in April 2009, it was soon realised that to speed up the review of dossiers for vaccines, and thus the grant of Marketing Authorisations, it was necessary to review data in a step-wise manner as they became available from the individual manufacturers. Between April and September whilst seed viruses were prepared by WHO laboratories, manufacturers prepared the vaccines and review was undertaken by regulators in a proactive and iterative manner. By introducing, for the first time, a rolling review procedure, this enabled the regulators through the CHMP to review and recommend a positive opinion (circa 26th of September 2009) which allowed the European Commission to grant the Marketing Authorisation six days later. The total time for both tasks of: manufacture, control by the industry; and review by the regulators to a CHMP opinion; was 153 days.

The flexibility of this form of review is likely to be activated again for the review of any Ebola vaccines which may be submitted for assessment (Ebola - Possible use of a rolling review procedure, 2014).

2.12 Evolution of the Review of Dossiers

The review of dossiers for Marketing Authorisations has evolved over the years starting with the review of primarily quality, safety and efficacy with little post-authorisation monitoring in the early 1980's. It was recognised however that it was important to obtain feedback from physicians regarding any adverse drug reactions (ADRs) arising from the use of medicinal products. Over the subsequent years, more and more information was gained from ADRs, thus strengthening post-authorisation data. The review of dossiers has evolved and matured so that through the beginning of this century between 2000 and 2009 the review includes not only that of quality, safety and efficacy but, also, the inclusion of Risk Management Plans (RMPs).

In parallel and with the advent of the Regulation on Advanced Therapy Medicinal Products (ATMPs), it was clear that both the size of the clinical trials and the corpus data for review would be smaller, but that the use of such products would have much closer monitoring by specialist physicians / healthcare workers before and after treatment. This further, significantly strengthened post-authorisation control. It also stimulated reflection on the balance between the data submitted to support an application for an MA and post-authorisation control with emphasis on benefit risk judgements at the CHMP These same factors may require consideration in the context of narrow-spectrum AMs. The situation would be similar and the patient data base / corpus of data for review would also be reduced. In such situations, the patients would have much closer physician monitoring which might allow more permissibility regarding a smaller data base as reflected in the guideline issued by the EMA in 2009 and finalised in 2012 (CPMP/EWP/558/**95 Rev 2**).

Another factor influencing the review process is the structure and capacity within a regulatory agency (Cone, M& Walker S, 2005) (Liberti, L et al, 2013). The Centre for Innovation in Regulatory Science (CIRS) Workshop on regulatory review incorporated international regulators and multinational pharmaceutical company representatives to focus on the best practices that underlie regulatory decision making, thereby facilitating the transparent, timely, procedurally predictable and good quality evaluation of new medicines. Key points made in the report were:

- A good quality review of a marketing authorisation dossier is dependent upon the processes use by the agency and its quality management system (QMS). Regulatory agencies require clear and defined processes and consistent application supported by well-trained personnel.
- The review of dossiers is science driven – a good quality review depends on two aspects, the quality of the review and the quality of the decision making. (Eichler H G et al, 2008)
- A decision framework should be established to ensure good quality decision-making (Liberti L et al , 2013). Agencies should continuously evolve their processes and practices to ensure implementation of optimised tools and techniques.

3. Recent Regulatory Initiatives (2009 – 2014)

3.1 Further Evolution of the Review of Dossiers

In addition to the initial comments on the evolution of the review of dossiers in point 2.11, steps were taken by the EMA to study in detail benefit – risk methodology (EMA Benefit Risk Methodolgy Project, 2009 - 2014). The mission was "the development and testing of tools

and processes for balancing multiple benefits and risks as an aid to inform regulatory decisions about medicinal products". One of the key tasks of a regulatory agency is the review of dossiers throughout the life-cycle of a product and to balance the benefits (desirable effects) of the product against the risks (undesirable effects). This task is multi-factorial and thereby complex. However, regulators have to bring together all of the available evidence provided by experts and evaluate the corpus of data. Though expert judgement may be feasible for specific aspects, integrating these evaluations and deciding on the overall balance of benefit and risk is not easy. The objective of this project, therefore, was to move towards a more structured approach by examining various models for benefit / risk (Honig et al , 2007). When the results of the 5th and final work package is finalised the Agency plans to initiate public consultation and provide a workshop to seek views before adoption of a final position from the Agency. The outcome of this project will further strengthen regulatory decisions by refining the benefit / risk methodology.

3.2 Scientific Advice and Protocol Assistance in Parallel with Health Technology Assessment (HTA) Bodies

In the development of medicines, the EMA has promoted early dialogue between regulators and HTA bodies. When new topics arise, workshops are arranged to bring together all of the interested parties – regulators, HTAs and developers - to share their views and, hopefully, plan how to deal with any issues which may arise (EMA - HTA workshop on parallel scientific advice, 2013) (EMA - THA Workshop Report, 2013). The primary objective was to facilitate speedier access to new medicinal products for the public. A key step is the provision of parallel scientific advice between the regulators and the national HTA's (EMA - HTA Guideline, 2014). A workshop will be held at the EMA on parallel scientific advice in drug development on the 26th November 2014. In addition, the EC established a European HTA Network, which is a voluntary step to bring together the competent authorities responsible for HTA.

The ultimate aim will be to minimise delays in access to medicines, arising from different views and decisions between regulators and HTAs. At this point in time, it has to be achieved nationally due to different health policies and funding models amongst the member states.

3.3 Development of Scientific and Clinical Guidelines (2009 – 2014)

Many guidelines have been developed in Europe and through the International Conference on Harmonisation (ICH) which has allowed the generation of regional and international guidelines. These have resulted in a growing global understanding of data requirements between the industry and regulators and reducing, to a degree, some of the uncertainty in product development. Most of these guidelines are generally applicable to the development of medicinal products, whilst others are more specific addressing particular needs of certain products and potential public health matters.

In the context of AM products, additional clinical guidelines have been prepared by the EMA and experts from member states. These include:

- Guideline on the evaluation of medicinal products indicated for treatment of bacterial infections (CPMP/EWP/558/95 revision 2), which came into effect in January 2012 and
- Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections (EMA/CHMP/351889/2013), which came into effect in May 2014.
- Concept Paper on revision of the points to consider on pharmacokinetics and pharmacodynamics in the development of antibacterial medicinal products

(CHMP/EWP/2655/99) and conversion to a CHMP guideline. The consultation period ended in May 2014.

The EMA held a workshop on AMR in November 2013 entitled "Best use of medicines legislation to bring new antibiotics to patients and combat the resistance problem". (New Antibiotics Workshop - Best use of medicines legislation, 2013)

The report of the workshop provided information on the major issues discussed and recommendations (Antibiotic Workshop Report, 2013), namely:

- the approval process for new antibiotics in Europe and whether the new requirements in the guidelines cited in this section are considered adequate for fostering rapid development of new antibacterial agents;
- encouraging appropriate use of antibacterials as one of the tools to reduce the speed at which antimicrobial resistance develops;
- aspects of research and development, including agreement on the importance of efficient and early dialogue between industry and the EMA to facilitate medicine development (Extract from EMA Web-page November 2014)

Many very useful presentations were given in the workshop. There is great value in reflecting on one such presentation of views expressed in relationship to the new guidelines highlighting important features of core guidelines:

- "If the PK/PD analyses are convincing, it may be possible to completely omit clinical dose-finding studies
- A single pivotal study may be acceptable to support an indication
- Adult efficacy data in some indications can be extrapolated to children
- Guidance for SmPC sections most pertinent to antibacterial agents
- Simplified section 5.1 on microbiology, resistance mechanisms, pathogens treated in clinical trials, others expected to be susceptible
- Regarding rare infections / pathogens (e.g. some MDR pathogens) efficacy data can be collected in standard RCTs and / or separate targeted studies
- Studies that enrol patients with well-documented infections regardless of which body site(s) is / are affected may be the only way forward
- When only limited data can be obtained randomised study designs are preferred but may not need to be powered for inferential testing
- Minimum number of treated cases to support a specific claim for treating certain MDR pathogens to be judged on a case-by-case basis." (Extract from EMA Web-page November 2014 - Dr Mair Powell – MHRA)

From the foregoing information in guidelines and the tools generally available for the submission of applications for Marketing Authorisations (Section 2 of this report), there is clear evidence of the evolutionary and ongoing responsiveness of regulators to current needs.

3.4 Adaptive Licensing

According to the EMA entry on its web site "Adaptive licensing is an approach to the authorisation of human medicines that is currently being discussed and developed" (Eichler H G et al , 2012). Essentially, it involves the staggered or progressive licensing of a medicinal product, where it may be used in a restricted population and then, through an iterative process, more evidence is gathered and the marketing authorisation may be adapted to allow access to a broader patient population. Thus, there is growing scope to provide medicines for serious and unmet medical needs (Eichler H G , 2014).

Just like the multitude of interested parties involved in AMR, there is a similarly wide range of colleagues involved in adaptive licensing. These include:

- EMA and other medicines regulators
- Patient and consumer organisations
- Pharmaceutical industry
- HTA bodies
- Organisations issuing clinical treatment guidelines – Public Health Bodies
- Healthcare professionals
- Researchers
- Academics

Others at the Escher Project have expressed views on adaptive marketing authorisations, indicating that it "may, in some cases, replace the binary regulatory decisions on drug approval with a progressive reduction of uncertainty about the benefit-risk profile of a drug through iterative evidence gathering and evaluation" (Jong, Jean Phillipe de, 2013).

In addition to this approach and considering the evaluation of antimicrobials in particular, there may be different requirements depending upon the nature of the products concerned i.e. a narrow rather than a broad spectrum product as shown in 2.5 and 2.11. The advent of adaptive licensing may further promote this approach.

4. General Observations

4.1 Overview on the overall analysis of current regulatory systems and their impact on business models for antibiotics

The findings in this report are based on interviews with staff of the EMA and the MHRA and are similar regardless of the agency. The time period covered was 2000-2014. Information was also gleaned from their web-sites and the review of related publications.

In reviewing the regulatory systems over the last 14 years and how they have evolved in two time-slots 2000 to 2009 and 2009 to 2014, it is clear that additions have been made to the armamentarium available to the regulators. Sections 2 and 3, of the report, respectively, describe each of the new tools along with information on its purpose, how they may be used, rewards and possible limitations. Considering the desirability of speeding up the development and marketing of new medicinal products, many of the facilities can be used either alone or in combination with others to achieve that objective. These additions in various ways can promote the earlier grant of marketing authorisations and, thereby, access of medicinal products to patients.

4.2 Impact on business models

To evaluate their impact on business models for antibiotic development is not easy to quantify. The evaluation is complex due to various inter-dependencies within individual tools and across a number of them. The primary determinants in the development of antibiotic products, which is not unlike many other medicinal products, will be the:

- speed of development by the manufacturer and applicant (SME or otherwise) for the marketing authorisation
- nature (special conditions which may be applicable) of the application and quality of the dossier submitted to the regulator
- review and benefit risk evaluation by the regulators

Taking the points seriatim, the first two items are dependent upon the applicant, who could use one or a number of tools to speed up development. Should it be an SME, then it could

use 1 to 8 and the benefits of 14 and 15. Points 9 to 13 could only be used, too, if applicable. Key to the understanding and use of these tools, in preparing an integrated strategic plan for development, will dictate the impact of these measures on any business model. In general, a good plan will provide an aggregated saving in the development and review phases. However, it is not possible other than in one or two cases to quantify the time saved. *These are "accelerated assessment" where the review time could be reduced from 210 to 150 days. Depending upon the nature of the product the "rolling review" could afford a similar reduction.* However, the rest of the items are dependent upon other factors including the quality of the dossier on which there may be uncertainty. Should the company be a standard pharmaceutical company, then point 1 would not be applicable; all others could be used. Inevitability, the quality of the dossier would be expected to be significantly better than from a small company with limited resources. This latter point in itself is likely to reflect a higher quality of development and strategic plan for submission and, thereby, a speedier review and approval.

1. Small and medium-sized enterprises
2. Innovative Task Force
3. Orphan Drugs
4. Development of scientific and clinical guidelines
5. Medical devices and In-vitro medical devices
6. Scientific advice and protocol assistance
7. Adaptive clinical trial design
8. Pre-submission meetings
9. Accelerated assessment
10. Conditional marketing authorisation
11. Exceptional circumstances marketing authorisation
12. Compassionate use
13. Rolling review
14. Evolution of the review procedure
15. Adaptive licensing

In the report, the third point on the review, and benefit risk evaluation by the regulator, evidence has been provided on the progress made over the last 14 years. New opportunities are available for the applicants and the regulators to work proactively on the development of new products through ITF, Scientific Advice and pre-submission meetings and the special conditions for SMEs and ODs with fee reductions / exemptions. In addition, the evolution of the review of dossiers over that period of time enhanced the approach to benefit-risk assessment, culminating in the concept of adaptive licensing. Provided applicants contact the regulators early in development of an antibiotic and establish a sound strategic plan, taking into account the opportunities available, for development and submission of the application for a marketing authorisation, then the time for development can be reduced significantly. However, again because of the multiplicity of parameters to be considered in development, it is not possible to quantify the reduction in development time accorded to the individual points, with the exception of possibly "accelerated assessment" and "rolling review".

4.3 National

For the National situation, systems are in place at MHRA to facilitate the development, submission and review of applications for marketing authorisations for all medicinal products, including antibiotics. MHRA is responsible for medical devices and, therefore, has the capacity to link the review of a medicinal product with a medical device or IVD. They also provide for the Early Access to Medicinal scheme, as well as those in the European legislation cited in this report.

4.4 Regional

For the European / Regional situation, systems are in place at EMA to facilitate the development, submission and review of applications for marketing authorisations for all medicinal products, including antibiotics. The Agency has systems in place to work with those in Europe who are responsible for medical devices and IVDs.

4.5 Global

In addition to the European Regulations other regional jurisdictions globally have their own legislation and administrative procedures to deal with the review of dossiers for Marketing Authorisations within their jurisdictions. Having recognised the difficulty faced by the pharmaceutical industry in satisfying regulatory requirements from so many different regions (in the 1980's), where data requirements could vary significantly causing problems in licensing and the manufacture of medicinal products, three regions – Japan, United States and Europe - and the pharmaceutical industry collaborated to harmonise the regulatory requirements for Quality, Safety and Efficacy through the International Conference on Harmonisation (I.C.H.), which was set up in 1990. As time has passed, other global regions including Brazil, Russia, India and China - the BRIC countries - have now expressed interest in becoming involved in such harmonisation, because of the global market in pharmaceuticals.

During the last 24 years there have been other drivers for harmonisation. The two major agencies, the Food and Drug Administration (FDA) and the European Medicines Agency (EMA), are often faced with similar tasks at the same time e.g. reviewing dossiers, inspection of global manufacturing sites or dealing with Pharmacovigilance and Public Health issues. To deal with this effectively, agreements were put in place between the European Commission and the United States administrations (2003) to share and exchange information to facilitate the work in all of these areas and others as they arise. Agreements were reached to share even early drafts of guidelines to bring together the concepts and philosophies. Discussions have been undertaken in relationship to antibiotic guidelines etc. as exemplified in the TATFAR report (US EU TATFAR Report, 2011). The philosophy of review by both agencies is similar, though detailed processes differ due to legislation and administrative procedures, so the outcomes from the review of dossiers may not be the same. However, in the event of new antibiotics being developed and submitted for review, presumably the industry would value having parallel scientific advice between the FDA and the EMA during the early stages of development to reduce the risk of having to meet different requirements from the agencies.

In 2001, WHO outlined a global strategy for the containment of AMR. Now a comprehensive report entitled "Antimicrobial Resistance – Global Report on Surveillance" (April 2014) has been published drawing attention to the "need for an improved and coordinated global effort, including wider sharing of surveillance data, for public health actions in relationship to AMR".

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