PHARMACEUTICAL PHYSICIAN

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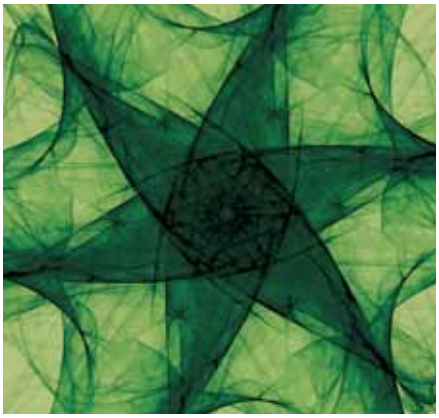

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PHARMACEUTICAL **PHYSICIAN**

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I TAKE EVERY opportunity to ask you, the readers, what you want to see in this journal. What would be interesting and relevant and help you at work? Recently many of you have mentioned a need for a simple update on current regulatory changes as there a number of key initiatives which impact our work as pharmaceutical physicians whether in R&D or marketing. The Early Access to Medicines Scheme (EAMS) being a good example of a cross cutting initiative. Hence, this issue focuses on a number of current 'hot topics' to which many of us will be expected to contribute in some shape or form by our companies.

I am delighted to be able to publish contributions from experts in their fields ranging from the Envigo team through to NICE and the EMA.

We often rely on the work that has already been done for a submission elsewhere to form the basis of a new submission. Senior management tends to think this will be quick and easy. It is not and from hard won experience needs careful thought and management. There are commonalities but you need to know where the differences arise and how to address them. The repurposing of regulatory submission documents is a topic close to the hearts of Louise, Michael and Sanjay from Envigo and I am delighted that they have written about this for us. Any new or aspiring medical directors should read this with care.

I am blown away by the potential of the PRIME (PRIority MEdicines) Scheme. Through PRIME, EMA offers early, proactive and enhanced support to medicine developers to optimise the generation of robust data on a medicine's benefits and risks and enable accelerated assessment of medicine applications. This will help patients to benefit as early as possible from therapies that may significantly improve their quality of life. And isn't making that difference a key driver for what we all do every day? I am looking forward to seeing how this scheme works out in practice and learning how we can work with the EMA to use the scheme effectively. The EMA has provided a simple overview of the scheme which should prove useful to tis readership.

Early Access to Medicines Scheme- we may be able to see medicines made available to patients 12-18 months before formal marketing authorisation. That is also exciting and will surely bring those working in clinical development, commercial, regulatory, pharmacovigilance and drug safety and so on, even closer together now 'as one team' as we strive to deliver on this. A great opportunity for patients -and for us to collaborate more closely with colleagues. Read what NICE has to say about this initiative.

I am grateful to those who choose to contribute to the journal on technical topics as above or to the lighter side, sending in "Coffee Break" reads, or personal views or book reviews. Thank you all.

Dr Madhu Davies

Dr Madhu Davies

SPECIAL FEATURE:

Repurposing Old Regulatory Documentation

By Louise Spencer, Regulatory Affairs Executive, Sanjay Jain, Principal Consultant - Biologics and Michael Edwards, Regulatory Consultant, Envigo, Cambridgeshire Business Park, Ely, Cambridgeshire, CB7 4EX, United Kingdom

KEYWORDS

Notice to Applicants (NtA), Code of Federal Regulations (CFR), Common Technical Document (CTD), Common European Submission Portal (CESP), Electronic Common Technical Document (eCTD), European Medicines Agency (EMA), European Union (EU), Food and Drug Administration (FDA), International Conference on Harmonisation (ICH), investigational new drug application (IND), guideline, marketing authorisation application (MAA), new drug application (NDA), marketing authorisation holder (MAH), dossier, Pharmacovigilance System Master File (PSMF) and Risk Management Plan (RMP), medicinal product.

Louise Spencer

Michael Edwards

Sanjay Jain

ABSTRACT

This article reviews the repurposing of old regulatory documentation, chiefly conversion of Notice to Applicants (NtA) style dossiers to the Common Technical Document (CTD) format following its introduction into all the International Conference on Harmonisation (ICH) regions. We look at the history of the CTD and the challenges, burdens and benefits that its introduction has had on the preparation of regulatory dossiers. We then discuss the various Modules of the dossier that require the most rewriting when converting from NtA to CTD, the key differences between both dossier formats, what documents can be carried over between the NtA and CTD format, and those documents that will require updating or creating together with additional data that the current CTD format requires. Finally, we consider the implications of electronic regulatory document requirements and the rework requirements.

INTRODUCTION AND BACKGROUND

MANY COMPANIES STILL face the challenge of converting old Notice to Applicants (NtA) style dossiers to the Common Technical Document[1] (CTD) format. The CTD format has its obvious benefits, but, for older products where the dossier was prepared in the previous NtA format, the implementation of the CTD requires extra work in some cases to convert the dossier to this format. Any variation submitted requires the relevant sections of the dossier to be updated to CTD; however, if desired a Marketing Authorisation Holder (MAH) can convert the whole dossier, although there is no obligation to reformat a dossier of an already licensed medicinal product[2]. Additionally when preparing for emerging market submissions and expanding territorial scope, reformatting of the dossier may be required, or conversion to electronic submission format.

HISTORY AND STRUCTURE OF THE CTD

An NtA dossier was presented in four Parts, and this format is still used for veterinary medicines applications in the EU[3]:

- Part I: Summary of the dossier (administrative data, product labelling, and expert reports)
- Part II: Chemical, pharmaceutical and biological documentation
- Part III: Pharmaco-toxicological documentation
- Part IV: Clinical documentation

The CTD became the mandatory format for MAAs in the EU from 1st July 2003, replacing the NtA dossier structure[2]. The CTD describes the organisation of Modules, sections and documents to be used by an Applicant for an MAA for a medicinal product for human use. The CTD is the internationally agreed format for the preparation of applications to be submitted in the three ICH regions of the European Union (EU), the United States of America (USA) and Japan. The CTD is organised into five Modules, of which Module 1 is region specific and is not strictly classified as part of the CTD, and therefore not defined by the ICH guidelines. Module 1 contains regional administrative and product information, whereas Modules 2, 3, 4 and 5 are intended to be common for all regions[1].

The ICH agreement to assemble all the quality, safety and efficacy information into a common format has led to harmonised submissions and eliminated the need to reformat the information for submissions to different ICH regions; which has several benefits:

- User friendly review
- Facilitates worldwide registration of products
- Ease of exchange of information
- Electronic submission

TABLE 1: Comparison of top-level structure of NtA and CTD formats

NtA	Data	CTD	Data
Part I	Summary of the dossier: administration (application form), product information, expert reports	**Module 1**	**Administrative, regional or national information:** administration (application form), product information, EU specific requirements for the administrative data Pharmacovigilance information and risk management plan
		Module 2	**Quality overall summary, Non-clinical overview/summaries and Clinical overview/summaries:** Expert reports included in Part I are replaced by Module 2
Part II	Chemical, pharmaceutical and biological documentation	**Module 3**	**Chemical, pharmaceutical and biological documentation** (quality overall summary Module 2.3)
Part III	Pharmaco-toxicological documentation	**Module 4**	**Pharmaco-toxicological documentation** (non-clinical written summaries Module 2.4, 2.6)
Part IV	Clinical documentation	**Module 5**	**Clinical documentation** (clinical written summaries Module 2.5, 2.7)

There is no difference between the CTD and the electronic version of the CTD (eCTD) in terms of scientific, technical and clinical content. Use of the eCTD is now mandatory for the EU centralised[4] and decentralised[5,6] submission procedures, and is actively encouraged for mutual recognition procedures (MRP) as use of the non eCTD electronic submission (NeeS) format will be completely phased out in the EU by 1st January 2017[6].

NTA TO CTD CONVERSION AND GRANULARITY

The CTD structure is made up of Modules rather than Parts and whilst the structure of the CTD and NtA format is quite different, the content and supporting data that an applicant must submit is essentially the same, with the addition of some information in the CTD format. It is therefore possible to convert (repurpose) a legacy application originally submitted in the NtA format to the CTD. *Table 1* left shows a top level comparison of the old NtA format and where the corresponding data appears in the CTD format - a more detailed correlation table is available in Volume 2B of the EU Notice to Applicants[2].

Continues on page 6 ▸▸

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In terms of converting an NtA format dossier (Parts I-IV) into the CTD format (Modules 1-5), the most rewriting of existing documentation is likely to be needed for Modules 1-3. As indicated in *Table 1*, the content of NtA Part I format is incorporated into Modules 1 and 2 in the CTD format, such that Part IA (application form and supporting documentation) and IB (proposed product information) are located in Module 1, and Part IC (expert reports in the CTD equivalent format) in Module 2. Quality data presented in Part II needs to be transposed into the CTD structure of Module 3, which differs in terms of ordering of information, and especially the clear distinction between active/drug substance (3.2.S) and finished/drug product (3.2.P) sections, as opposed, for example, to Part IIC (control of starting materials, including excipients and packaging) and Part IIF (stability) which incorporate information relevant to both.

Another aspect to consider, particularly with regard to Part II/Module 3 data, is the granularity of the CTD; in essence the degree to which single or multiple documents are required for CTD headings, and the possibility of presenting data in one section, or using individual sub-sections. Two obvious examples are Module 3.2.P.4 (control of excipients) and 3.2.P.5 (control of drug product), where an applicant could choose to present separate, or combined, sub-sections for each excipient and every presentation of the dosage form. Thus for excipients, and with a view to future variations, it may be advantageous to present separate sub-sections for each excipient, such that a subsequent change to one is confined to updating/replacing specific documents concerning only that excipient. Conversely, the use of combined sub-sections for finished drug product avoids duplication of details of analytical procedures (and their validation) across multiple strengths of a modified-release tablet presentation. Where a product contains multiple active substances, a separate 3.2.S section must be provided for each.

Concerning quality documentation for MAAs, the main concerns between the US and EU are directly linked to the different levels of detail generally required for each section of the application due to the different review processes in the two regions. Sponsors undertaking a global drug development programme would generally favour the parallel approach for the preparation of these modules. On the other hand, sequential preparation may be less resource-intensive and can therefore be more appropriate for a small company.[7]

Full details concerning granularity for non-region specific Modules 2 - 5 are provided in the ICH guideline 'Organisation of the Common Technical Document for the Registration of Pharmaceuticals for Human Use (M4)8 and a questions and answers document has also been produced[9]. In the event of an applicant having a preferred corporate format for their dossier, in terms of font and font size, it should be noted that the CTD recommends the use of Times New Roman, 12 point.

NEW ELEMENTS WITHIN THE CTD

A dossier presented in the CTD structure will also incorporate elements not specified in the old NtA format, in part owing to changes in legislation and guidance governing pharmaceutical registration. Examples for Module 1 in the EU include specific requirements for different types of application (Module 1.5), information relating to orphan market exclusivity where relevant (Module 1.7), and of course – in the context of recent changes in pharmacovigilance legislation – the summary of the pharmacovigilance system [Pharmacovigilance system master file (PSMF)] and Risk Management Plan (RMP) in Module 1.8. Although technically region-specific, there will be a number of global territories which require such documents, for example the RMP.

For Module 2, the NtA format expert reports are superseded by the CTD critical overviews, and written and tabulated summaries – thus the quality tabular formats and written summary for Part IC1 (expert report on the chemical, pharmaceutical and biological documentation) are replaced by the quality overall summary (Module 2.3), and there is no requirement in the CTD for a separate tabulated quality section. The non-clinical (as opposed to NtA 'pre-clinical' Part IC2) content is comprised of the non-clinical overview (Module 2.4) and written/tabulated summaries (Module 2.6), which differs from the NtA in that written toxicology summaries were not required in this format. Similarly, assessment of clinical data (NtA Part IC3) is covered by the clinical overview (Module 2.5) and written summaries with associated tables (Module 2.7). Guidance concerning the presentation and format of the CTD dossier (in the EU, Volume 2B of the Notice to Applicants) provides suggested non-clinical tabular formats and clinical summary tables; although the applicant can or may need to modify these according to their product and the type of application. Existing written summaries from an NtA dossier might serve as the basis for CTD documentation, depending upon their length and the level of detail presented.

CTD Modules 4 and 5, containing reports of completed non-clinical and clinical studies respectively, might require less rewriting when moving from the NtA format; although interestingly the EU Notice to Applicants does not recommend reformatting of the non-clinical and clinical documentation for products already authorised[2]. Study reports must be presented within the CTD structure; for example, any human metabolism and bioavailability studies presented in Part IIQ are re-located to the appropriate sub-section of Module 5.3. Where a product has multiple indications, a separate section 5.3.5 (Reports of efficacy and safety studies) is presented for each indication.

A comprehensive consideration of the requirements for all CTD sections is outside the scope of this article, and reference should be made to the appropriate regional presentation of ICH guidance.

CONSIDERATIONS FOR ELECTRONIC REGULATORY DOCUMENTATION

It has been over five years since the new EU Variations Regulation (EC 1234/2008)[10] was applied, and managing dossiers in eCTD is now mandatory in the centralised procedure (CP). There are still challenges in managing the preparation of eCTD variation lifecycle sequences and it is anticipated that the next version of the eCTD will address these issues. It will be interesting to see how variation lifecycles are handled when the mandatory use of eCTD for MRP dossiers is implemented in early 2017.[11]

The switch from paper-based to electronic submission of regulatory information has been advocated with the aim of helping the industry to move to eCTD working. As the implementation of eCTD has not taken place as anticipated, the Common European Submission Portal (CESP) is potentially the next step in the submission of regulatory dossiers and should save applicants considerable resource. The pros and cons between using CESP and agency portals (e. g., the UK Medicines and Healthcare products Regulatory Agency portal) need to be carefully considered before companies make full use of CESP. Mandatory eCTD submission for all regulatory applications might represent the ideal solution.[12]

Sponsors preparing a US investigational new drug (IND) submission can include Modules 2 to 5 of a CTD format dossier, in place of the previous IND format defined under Title 21, Part 312.23 of the US Code of Federal Regulations (CFR),[13] to assist with any future new drug application

(NDA) and create a broad history for the product. Submission of NDAs and certain INDs in eCTD format will become mandatory during May 2017 and May 2018 respectively.[14, 15] The US Food and Drug Administration (FDA) has issued a Comprehensive Table of Contents Headings and Hierarchy[16] for CTD format submissions, which also includes mapping tables for IND and NDA applications to match documents specified under a given CFR citation (or other source) to the relevant CTD module and sub-section. An understanding of IND content may be very helpful for non-US regulatory professionals when planning for an upcoming submission (e. g., MAA) based on this IND, and an IND in eCTD format would be much simpler to reuse during assembly for a submission. A comparison of FDA correspondence alongside European Medicines Agency (EMA) minutes to understand why regional differences arose during product development can be extremely supportive, for example, to explain the product history in Module 2 summary documents for other submissions world-wide. These could fast-track rapid repurposing and submission across various regions.[17]

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Additionally, many other regions, including Asia and the Middle East (e. g., Thailand and Saudi Arabia) are moving towards mandatory use of eCTD documents – these may only be available as hard copy in an older NtA dossier and will need to be converted to electronic and potentially text-searchable versions for reuse. In Japan, NDA (eCTD) submissions including electronic clinical data (CDISC) and eCTD will start from April 2016 with a two-year grace period.[18]

SUMMARY AND CONCLUSION

Use of the eCTD is now mandatory for EU centralised and decentralised submission procedures, and is actively encouraged for MRP, replacing the previous NtA dossier structure. There is no difference between the CTD and the eCTD in terms of scientific, technical and clinical content. However, there are regional differences in eCTD implementation between ICH regions. The switch from paper-based to electronic submission of regulatory information has been advocated with the aim of helping the industry to move to eCTD working. The ICH agreement to assemble all the quality, safety and efficacy information into a common format has led to harmonised submissions and eliminated the need to reformat information for submissions to different ICH regions. In general, the time required for compiling submissions such as those outlined above could be estimated depending on the amount of data in the package. However, the key message is that company resource will be required if repurposing of previous NtA regulatory submission are required.

This article has also been published by Envigo in their own publication, 'Pharma Consulting News', February 2016.

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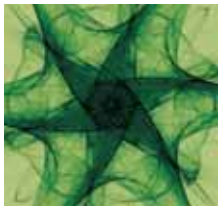
SPECIAL FEATURE:
Launch of PRIME

Paving the way for promising medicines for patients

From the European Medicines Agency.

New scheme supports European Commission priorities



ON 7TH MARCH 2016, the European Medicines Agency (EMA) launched its new PRIME (PRIority MEdicines) scheme to strengthen support to medicines that target an unmet medical need. The scheme focuses on medicines that may offer a major therapeutic advantage over existing treatments, or benefit patients with no treatment options. These medicines are considered priority medicines within the European Union (EU).

Through PRIME, EMA offers early, proactive and enhanced support to medicine developers to optimise the generation of robust data on a medicine's benefits and risks and enable accelerated assessment of medicine applications. This will help patients to benefit as early as possible from therapies that may significantly improve their quality of life.

By engaging with medicine developers early, PRIME aims to strengthen clinical trial designs to facilitate the generation of high quality data for the evaluation of an application for marketing authorisation. Early dialogue and scientific advice also ensure that patients participate in trials that are likely to provide the necessary data for an application for marketing authorisation, and help to make best use of limited resources.

"The launch of PRIME is a major step forward for patients and their families that have long been hoping for earlier access to safe treatments for their unmet medical needs, such as rare cancers, Alzheimer's disease and other dementias," says Vytenis Andriukaitis, EU Commissioner for Health and Food Safety. "Through enhanced scientific support this scheme could also help, for example, to accelerate the development and authorisation of new classes of antibiotics or their alternatives in an era of increasing antimicrobial resistance." The Commissioner also highlights that PRIME optimises the use of the current regulatory framework that can contribute to the European Commission's priorities in terms of boosting innovation, jobs, growth and competitiveness.

"Our goal is to foster better planning of medicine development to help companies generate the high quality data we need to assess quality, safety and efficacy of medicines," explains Professor Guido Rasi, EMA's Executive Director. "Patients with no or insufficient treatments could then benefit from scientific progress and cutting edge medicines as soon as possible."

PRIME builds on the existing regulatory framework and available tools such as scientific advice and accelerated assessment. This means that a PRIME medicine is expected to benefit from accelerated assessment at the time of an application for marketing authorisation.

"We want to ensure that breakthroughs in medicines reach patients quicker," says Dr Tomas Salmonson, Chair of the Committee for Medicinal Products for Human Use (CHMP). "By strengthening collaboration between the scientific committees, and by gaining and sharing knowledge on the medicine throughout the development, we will not only accelerate patients' access but also ensure an efficient use of available resources."

To be accepted for PRIME, a medicine has to show its potential to benefit patients with unmet medical needs based on early clinical data. Once a candidate medicine has been selected for PRIME, the Agency:

- appoints a rapporteur from EMA's CHMP or from the Committee on Advanced Therapies (CAT) in the case of an advanced therapy, to provide continuous support and help to build knowledge ahead of a marketing authorisation application;
- organises a kick-off meeting with the CHMP/CAT rapporteur and a multidisciplinary group of experts from relevant EMA scientific committees and working parties, and provides guidance on the overall development plan and regulatory strategy;
- assigns a dedicated EMA contact point;
- provides scientific advice at key development milestones, involving additional stakeholders such as health technology assessment bodies to facilitate patients' quicker access to the new medicine;
- confirms potential for accelerated assessment at the time of an application for marketing authorisation.

While PRIME is open to all companies on the basis of preliminary clinical evidence, micro-, small- and medium-sized enterprises (SMEs) and applicants from the academic sector can apply earlier on the basis of compelling non-clinical data and tolerability data from initial clinical trials. They may also request fee waivers for scientific advice. Since SMEs and academia often lack experience with the regulatory framework, they can benefit in particular from earlier scientific and regulatory advice.

STRENGTHENED REGULATORY TOOLKIT FOR MEDICINES ADDRESSING UNMET NEEDS

EMA has released guidance documents on PRIME as well as a comprehensive overview of the EU *early access regulatory tools,* i.e. *accelerated assessment, conditional marketing authorisation* and *compassionate use.* Revised guidelines on the implementation of accelerated assessment and conditional marketing authorisation are also published today. All these tools are reserved for medicines addressing major public health needs. The revised guidelines provide more detailed information based on past experience. They encourage early dialogue between the various stakeholders which is crucial to optimise use of these tools. Although PRIME is specifically designed to promote accelerated assessment, it will also help to make best use of other EU early access tools and initiatives, which can be combined whenever a medicine fulfils the respective criteria.

> "We want to ensure that breakthroughs in medicines reach patients quicker"

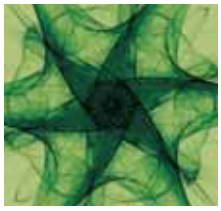
PRIME was developed in consultation with the Agency's scientific committees, the *European Commission and its expert group on Safe and Timely Access to Medicines for Patients* (STAMP) as well as the European medicines regulatory network. This network of national competent authorities and its many experts who conduct the scientific evaluations is key to the success of the new scheme.

The main principles of PRIME were released for a two-month public consultation in 2015 and the comments received were taken into account in the final version.

SPECIAL FEATURE:

A Note to describe procedures at NICE to support the Early Access to Medicines Scheme

Meindert Boysen, Elisabeth George & Jenniffer Prescott - Technology Appraisals Fay McCracken & Nick Crabb - Office for Market Access (National Institute for Health and Care Excellence Centre for Health Technology Evaluation)



INTRODUCTION TO THE EARLY ACCESS TO MEDICINES SCHEME

IN APRIL 2014, the Government announced the launch of the Early Access to Medicines Scheme (EAMS). EAMS provides an opportunity for important drugs to be used in UK clinical practice in parallel with the later stages of the regulatory process. It is anticipated that medicines with a positive EAMS opinion could be made available to patients 12-18 months before formal marketing authorisation.

Under the scheme, the Secretary of State for Health, acting through the Medicines and Healthcare products Regulatory Agency (MHRA) issues a scientific opinion on the benefits and risks of a new medicine or indication. This opinion provides additional information for clinicians and patients to assist in treatment decisions in areas of unmet medical need.

KEY STAGES OF EAMS AND NICE'S ROLE IN THEM

The following paragraphs outline the key stages of EAMS and NICE's role in them.

i. **Promising Innovative Medicines (PIM) designation and NICE Topic Selection –** A PIM designation gives an early signal that, based on the evidence to date, the medicine may be a possible candidate for the Early Access to Medicines Scheme and thus has the potential to be of value in areas of unmet medical need. The MHRA operates the process resulting in a PIM designation. Companies signal their intention to apply for a PIM designation and EAMS at an early stage by completing the relevant fields in UK PharmaScan. The MHRA advises NICE of the award of a PIM designation, subject to this information being treated as commercial in confidence unless and until the information is made public or otherwise disclosed by the company.

When NICE becomes aware of a PIM designation, the topic progresses through the usual NICE Topic Selection process (unless the technology is already covered in existing NICE guidance or is not within NICE's remit, for example a vaccine), except that products with a PIM designation are prioritised.

ii. **Joint scientific advice –** A PIM designation may be granted to products at an early stage in clinical development. It is strongly recommended that companies which receive a PIM designation seek joint scientific advice. This gives companies an opportunity to meet with both NICE and the MHRA to discuss their development plans at length from both a HTA and a regulatory perspective, and then to receive a bespoke written advice report addressing key questions. NICE Scientific Advice is offered on a not-for- profit fee-for-service basis.

iii. **Pre-submission meeting (MHRA) –** The MHRA holds one pre-submission meeting to ensure that all the information they need to reach an EAMS opinion is available before a company formally submits evidence for an EAMS opinion.

iv. **NICE EAMS meeting –** The NICE Office for Market Access offers

companies the opportunity to have a supplementary meeting with NICE to discuss the company's data collection plans during the EAMS period, in order to help ensure the company is well prepared for a potential Technology Appraisal (TA) or Highly Specialised Technologies (HST) evaluation. In some cases, data on clinical and cost effectiveness may need to be generated during the EAMS period to address the uncertainties in the clinical effectiveness evidence or anticipated resource use. These data will inform any subsequent submission to NICE. The NICE EAMS meeting aims to help companies gain insight into the NICE processes and evaluation frameworks, as well as to learn more about the option to develop and propose managed access arrangements and patient access schemes to support adoption following the EAMS period and NICE appraisal.

If a ministerial referral to NICE has already been made for the topic, a company may consider the standard TA decision problem meeting to be a sufficient forum to discuss plans for their submission to NICE, particularly if further evidence generation is unlikely to be feasible at this late stage. The decision problem meeting is a standard part of the NICE TA and HST processes and no charge is made for this meeting. A company may however believe that further evidence generation during the EAMS period would be both meaningful and feasible, and may ask for a separate NICE EAMS meeting.

Detailed procedures for NICE EAMS meetings are in the appendix.

v. Positive EAMS opinion – This is granted by the MHRA and is expected towards the end of the development process (typically at the end of phase III trials). It can exceptionally happen earlier. The EAMS opinion enables prescribers and patients to decide if the product might be suitable for an individual patient. Products with a positive EAMS opinion could be available to NHS patients 12-18 months before marketing authorisation is granted.

> "...medicines with a positive EAMS opinion could be made available to patients 12-18 months before formal marketing authorisation."

NICE EAMS meetings are optional and offered on a fee-for-service, not-for-profit basis. It should be noted that NICE EAMS meetings are not a substitute for joint NICE and MHRA scientific advice, where much more detailed engagement on prospective clinical development plans is offered.

In planning for the EAMS period, including potential additional evidence generation, an arrangement between the company and NHS England will be necessary. NHS England is invited to the NICE EAMS meeting to discuss the necessary arrangements.

The MHRA expect that EAMS products will be provided by the company to the NHS free of charge during this period.

vi. EAMS period and NICE TA or HST evaluation – NICE anticipates that before the EAMS period starts, all EAMS products will already have been selected as topics for a NICE TA or HST evaluation.

In order to develop timely guidance, NICE starts the TA or HST evaluation during the EAMS period (before marketing authorisation), and the company prepares its submission during this period. Any data collected during the EAMS period may be included in the company submission.

A NICE TA or HST evaluation of an EAMS product follows the normal published processes and methods. If NICE is notified of the PIM designation and positive EAMS opinion at least 12 months before expected receipt of marketing authorisation, these products are planned as a priority into the work programme so as to allow the first Committee decision to be published within 3 months of marketing authorisation, rather than 6 months under the usual process.

Prioritising EAMS products for evaluation may have the effect of

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Continues from page 13

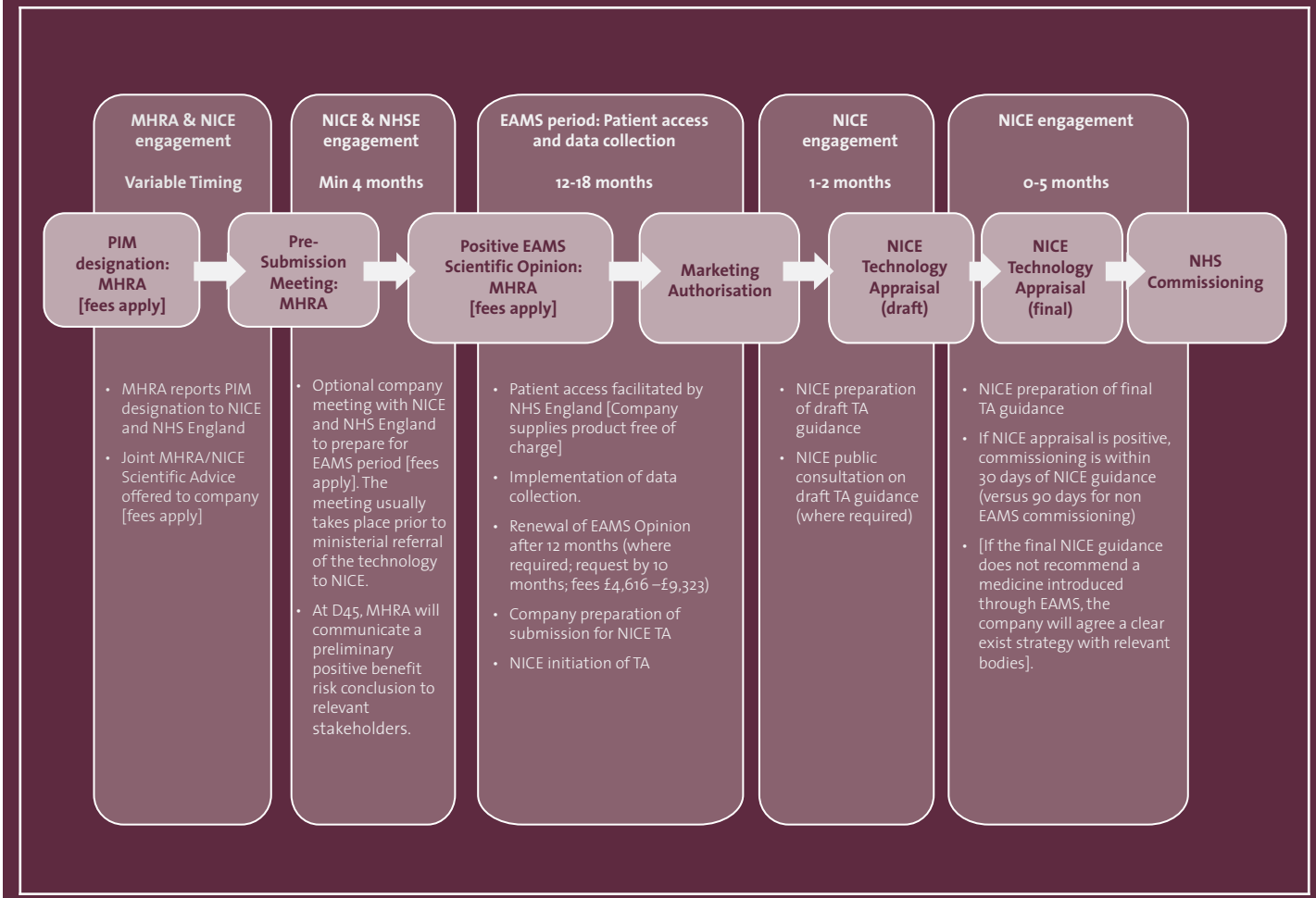
deprioritising other products if there are late changes in the regulatory timelines for the EAMS product.

VII. MARKETING AUTHORISATION AND NICE TA OR HST EVALUATION RECOMMENDATIONS – In line with standard processes, NICE issues preliminary recommendations for public consultation or final recommendations (where there are no issues requiring public consultation) as soon as possible after marketing authorisation.

If the Appraisal Committee or HST Evaluation Committee agrees that the product can be recommended, these recommendations are subject to the 2013 Regulations. These provide for a legal duty for NHS England, clinical commissioning groups and local authorities to make treatments recommended by NICE available to patients. The regulations normally require that products recommended by NICE are commissioned within 3 months of publication of the guidance. NHS England reduces this to 30 days for EAMS products.

The components of the EAMS process are outlined in *Figure 1*.

| FIGURE 1: EAMS



APPENDIX

Detailed procedures for NICE EAMS meetings

1. When NICE is notified that a PIM designation has been given and that the company has requested a pre-submission meeting with the MHRA, the NICE Office for Market Access offers the company an optional NICE EAMS meeting.
2. Companies wishing to take up the offer are advised to give the NICE Office for Market Access details about when the company anticipates engaging in the pre- submission meeting with MHRA. The NICE EAMS meeting is scheduled to align with the timelines provided for the MHRA pre-submission meeting. The NICE EAMS meeting usually takes place before Ministerial referral of the topic to NICE.
3. The company is asked to provide the pre-submission template submitted to the MHRA and to complete a NICE pro-forma to describe any plans for further evidence collection, for patient access schemes or flexible pricing.
4. The NICE Office for Market Access team considers the plans as set out in the pro-forma. Where evidence development during the EAMS period is likely to be important in reducing uncertainty prior to a NICE appraisal or evaluation, the Office for Market Access draws together a bespoke team of experts from NICE Scientific Advice, Technology Appraisals or the Highly Specialised Technologies programme as appropriate. The NICE EAMS meeting therefore provides an opportunity for tailored engagement and expert advice on plans for further evidence development.
5. The meeting is chaired by an Associate Director or Programme Director from the Centre for Technology Evaluation (CHTE).
6. Representatives from NHS England are invited to the NICE EAMS meeting. This enables NHS England to explore whether a commissioning circular would facilitate patient access during the EAMS period. It also allows discussion about arrangements that may need to be put in place to facilitate and coordinate data collection during the EAMS period. If a company does not wish to take up the NICE EAMS meeting offer, it may still wish to engage with NHSE separately.
7. Where there is likely to be high uncertainty at the point of NICE appraisal or evaluation, the NICE EAMS meeting provides an opportunity to discuss the options for 'managed access arrangements' after the EAMS period. This could take the form of continued data collection and the introduction of patient access schemes. In this case, the Office for Market Access draws in a representative of the Patient Access Scheme Liaison Unit to attend the NICE EAMS meeting.
8. NICE EAMS meetings are provided by the Office for Market Access on a fee-for- service, not-for-profit basis. Further details on fees are provided in the NICE EAMS meeting invitation letter to the company.

PERSONAL VIEW:

'He's not the Messiah, he's a very naughty boy': why Trump is searching for votes in the vestry

By Julia Davies

IT IS COMMON practice for politicians to seek support by appealing to their voters' greatest concerns. Wars, taxes, migration, the list goes on. In the May 2015 UK general election, politicians also took to subtly defaming each other, the opposition's policies; and slandering the opposition party's previous administrations. But notably absent from the claims that they were all normal, just like us, and definitely not at all posh, was an appeal to religion. Separate from politics in the UK religion may seem, but in the upcoming United States election one thing we can be certain of is the candidates relentlessly name-checking God and Jesus in their campaigns. Perhaps politicians in the sometimes damagingly politically-correct UK saw fit to steer clear of religion due to the havoc religious extremism is wreaking on the Middle East, and the growing concerns about ISIS incubating it with so called 'Trojan horses' in this very country. But across the pond in the US the response from some Republican politicians would almost certainly be to purport themselves as symbols of righteousness and Christianity in the face of barbaric Islamic extremism.

None more so than former Republican president George W Bush, who saw the War on Terror as the fulfilment of God's wishes. 'God would tell me, 'George go and fight these terrorists in Afghanistan'. And I did. And then God would tell me 'George, go and end the tyranny in Iraq'. And I did.' These claims of one-to-one communion with God would terrify the British electorate, and would probably result in the speaker being placed under psychiatric care; in the US they justified a war that still rages today, fourteen years on, with far greater repercussions than we perhaps realised even on 9/11. Suffering like this can prompt hard thoughts for us all. If God exists and would allow something like 9/11 to occur, who are we to say that he didn't speak directly to Bush? A God capable of allowing 9/11 is clearly capable of anything. The Guardian stated during Bush's time in office that he was 'one of the most overtly religious leaders to occupy the White House, a fact which brings him much support in middle America'. Bush, a born-again Christian, saw himself as 'on a mission from God', and Tony Blair, UK Prime Minister at the time and something of a religious zealot himself, is reported to have prayed with Bush in 2002 during the decision-making process for the War on Terror.

Whilst Bush isn't explicitly claiming to be the Messiah, some theologians aver that it is entirely conceivable that Jesus could have returned and been locked up in an asylum somewhere for claiming to be what he is. The idea that madness and messages from God are interlinked would surely horrify many believers, but several psychological studies have shown that schizophrenia can be brought on by stress, and sufferers report hearing God's voice after times of intense stress. Not that Bush has schizophrenia, but being the leader of the country targeted in an ultimately unprovoked and utterly horrific and devastating attack must have been unimaginably stressful on myriad levels; if hearing God's voice is triggered by stress it is perfectly understandable that Bush would feel that he had heard from God around this time.

Donald Trump, frontrunner for the Republican party's candidacy, (at the

PERSONAL VIEW:
'He's not the Messiah, he's a very naughty boy': why Trump is searching for votes in the vestry

time of writing), has stated that spreading his political message to large crowds has taught him 'how Billy Graham (a renowned Baptist preacher, who converted George W Bush) felt'. NPR has even called his rallies 'sermons' in which he preaches 'the gospel of Trump'. Such language, whilst seeming extreme, is appropriate, as the ostensibly Presbyterian serial adulterer and casino magnate is working hard to appeal to Conservative Christians. The two are made even less likely bedfellows in the face of his not being a regular churchgoer, and his historic support for abortion rights. Perhaps he has noticed the positive correlation in the US between devout or evangelical Christianity and the political far right, seeking its support for his own gain. Yet as we saw earlier, Bush's certainty that he was in direct conversation with God made him popular with even middle America, showing the extent to which religion shapes aspects of life for moderate Americans as well as those whose views are more extreme; though it could be argued that in the aftermath of 9/11 even liberals saw their views become more extreme and the whole country shifted to the right, making the August 2001 far right supporter the October 2001 moderate. Or perhaps the country, whilst foraging in the rubble of the Twin Towers for answers, was greeted by their leader, by the unshakeable image of his faith and the hope, no matter how vain, that Christian unity could end the horror.

Trump's political ambition suggests his desire to create a sort of cult around himself, and this, coupled with his overt flaws of character would, in Anglo-Saxon England, make him a prime contender for sainthood. Professor Janina Ramirez argued on BBC History Extra that Anglo-Saxon saints were like today's celebrities, and being flawed was requisite. She gave Diana, Princess of Wales, as an example. Trump may not have made such a splash in the UK as in the politically far right of the US populace, but, for those groups, he has perhaps aroused similar passions as Diana did globally. Whilst I am not suggesting that Trump is a saint, as this could not be further from my opinion, he has, perhaps unconsciously, modelled himself in the same mould as the Anglo-Saxon saints. Yet his demagoguery has caused concern in the more moderate UK, not on religious grounds but due to his vilification of, amongst others, Mexicans. His blatant racism is not Christian, flouting the teachings of Jesus imploring us to love our neighbours in the Parable of the Good Samaritan. As a US citizen, Trump's southernmost neighbour is Mexico, and his love for it, if it exists, is hidden under a thicket of bushels.

US Politicians are wise to target Christians, as America has the fourth highest rate of church attendance in the world, at 39%, with a total of 70% of the population of 319 million identifying as Christian. The church attendance statistics are somewhat skewed as Roman Catholic Malta records 52% of its 423,000 population attends church, whilst America, a behemoth in comparison, has no official state religion. Politicians such as Bush may also be invoking memories from history lessons of the god-given autocratic rule, or 'divine right', used by the Russian Tsars, and French Royal Family to prop up their crumbling 'ancien regime'. The Romanov dynasty fell in 1917, the French Revolution in 1789 saw to the end of monarchy in France. It seems ludicrous that the US, birthplace of Bill Gates and Steve Jobs, visionaries who have launched the world into the future, could be so downright backward.

So, when voting for either the Grand Old or Democratic party, voters must ask themselves some deep questions about just how far they want their leader's 'moral conscious' to dictate

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PERSONAL VIEW:
'He's not the Messiah, he's a very naughty boy': why Trump is searching for votes in the vestry

Continued from page 17

policy. Ultimately, we can't be surprised by the United States' god-fearing political slant. Even United States citizens who are not devout Christians can act as though they are, slavishly obeying a set of laws cemented at a large delegates' council, so heavily amended they bear little resemblance to the original; and above all venerate the lawgiver. God bless America.

Sources - guardian.com, npr.org, photo credits npr.org

Note: This article reflects the personal views of the author. BrAPP has no view on the topic.

COFFEE BREAK:
What fresh hell is this?

by Katie L. Chain MS (a nom de plume)

THIS TIME I thought I might share some word encounters I have had that are humorous and sometimes even may make you think.

Let's get started with a fresh collision - "deleveraging" or the reduction of the leverage ratio or the percentage of debt in the balance sheet of a single economic entity. Got it? That may work for you if you run a top government department but when you hear at a very modest marketing strategy meeting – puleeeeeze. I think my wordy (and very up his own arteries) friend was referring to some kind of ploy to back–off on dubious core product claims against the competition. In the same meeting we heard about "project creep" - was that about slipped timelines or the guy who just talked about "deleveraging"? I suspect the latter, especially when he went on to use the unword "generability". This sort of stuff really "grinds my gears". To paraphrase Allen Butler's poem of 1858, "he was a self-made man who worshipped his creator".

I love typos – I have to as, with dyslexic fingers, I make many myself. However, they can sometimes give you fresh insights. For example, I received an email proposing plans for a "screwing questionnaire". Thinking my Market Research colleagues were getting a tad too close to the bone, I received an apologetic return email about the planned "screening questionnaire". Shame - I might have learned something.

Musing during a review session on drug X's latest adverse event data, my mind wandered (mindfully) at the mention of "signal detection" to earlier that day. Driving to work late, I was desperately trying to see the opposing traffic lights so I could race away from the line when mine turned greenish. My contribution to the meeting was, unsurprisingly, not great that day.

Acronyms can flaw you. My builder recently explored the illegal possibility (bless him) of avoiding what he affectionately called the "Vodka and Tonic "(VAT to you and me). I never avoid the latter and certainly not the former.

Then there are "Vs and Bs". Time is money to management consultants, so when they pitch (free of charge) you'll get this sort of jargon. However, when they are charging you, time expands to meet their "Values and Behaviours" as well as their fees, with the added "Vodka and Tonic" of course.

The flow of meetings seldom run true. One top management meeting I sadly missed was apparently full of fireworks. I loved my friend's summary of it all when she said in hushed tones in the car park later that day - "they couldn't even agree on what they disagreed about". Top management!

And finally, some useful quotations I stumbled across which I am sure will help with the latest ABPI Code 2016 version:

"Scepticism is the beginning of faith" - Oscar Wilde. It's the way I review all promotional material for ABPI Code compliance.

"I'd rather have lucky generals than good ones" – Napoleon. Don't share this marketing as a guide to product claims.

Quoting from Dorothy Parker (20th Century poet, author, critic and her sort of girl) Katie engages with her Microsoft pal (not 10) to share more real life interactions with the English language, but not necessarily as we know it.

"If you cross [the line] enough times it disappears forever" – film, The Rainmaker. That may be true in life in general but definitely (!) don't try this with the PMCPA.

Happy word-hunting

INC Research and CISCRP Announce Strategic Collaboration to Focus on Patient Awareness

FIRST-OF-ITS-KIND partnership underscores the importance of creating awareness of clinical trials and the vital role patients play in participating in clinical research

INC RESEARCH HOLDINGS, Inc. (Nasdaq: INCR), a leading, global Phase I to IV contract research organization, has announced a strategic collaboration with the Center for Information and Study on Clinical Research Participation (CISCRP), a non-profit organization dedicated to engaging the public and patients as partners in the clinical research process. Through this collaboration, INC and CISCRP will jointly develop and implement educational initiatives designed to bring greater awareness to the importance of clinical trial participation in advancing public health.

"Continuing to make patients valued partners in the clinical research process is vital to accelerating the delivery of new medicines to market," said Clare Grace, PhD, Vice President, Site and Patient Access. "CISCRP has been doing great work in this area for more than a decade and INC Research is proud to support their efforts to further increase awareness of the critical role patients play in clinical research and the value that this research brings to the development of new therapies. By furthering the connection that patients have with the clinical research community, we can better understand their perceptions about clinical research and the barriers that are potentially preventing them from participating in trials for which they may be suited."

"Without clinical trial participants, new medicines and discoveries simply wouldn't be possible," said CISCRP Founder Ken Getz. "It is essential that we engage patients and their local health care community as partners in the drug development process. We are very excited about entering into this collaboration with INC Research to raise public awareness about clinical research, to educate the patient community and to ultimately strengthen patient engagement."

As a main component of the strategic collaboration, INC Research and CISCRP will co-host a ground-breaking event in September 2016 called the "Inspiring Hope" Ideathon. This unique event will bring together industry leaders and pioneers along with advocacy groups and is designed to generate new ideas and discuss innovative ways to help raise awareness of clinical research. To register interest in participating or for more information on the event, please email InspiringHope@incresearch.com. In addition, INC Research will sponsor CISCRP programs and events, such as AWARE for All and Medical Heroes, throughout the year as well as collaborate on the development of future patient awareness events. The Company will work with CISCRP to leverage findings from the 2015 CISCRP Perceptions & Insights survey to improve awareness of volunteer perceptions, motivations and experiences with clinical research/inform strategies that incorporate the patient voice into trial design.

For the last two years, INC Research and CISCRP have co-chaired Patients as Partners in Clinical Trials, an annual conference designed for clinical trial executives in pharma and biotech, directors in patient advocacy, patients involved in clinical trials, academia, government and service providers who are looking to incorporate the patient perspective throughout the clinical trial process.

About CISCRP

The Center for Information and Study on Clinical Research Participation (CISCRP) is a first-of-its-kind nonprofit organization dedicated to educating and informing the public, patients, medical/research communities, the media, and policy makers about clinical research and the role each party plays in the process. CISCRP provides free education and outreach to the general public and patient communities. Visit www.CISCRP.org for more information or to support CISCRP.

About INC Research

INC Research (Nasdaq: INCR) is a leading global contract research organization ("CRO") providing the full range of Phase I to Phase IV clinical development services for the biopharmaceutical and medical device industries.

BOOK REVIEWS

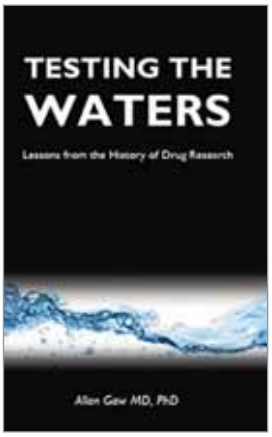
CALL FOR REVIEWS: PLEASE WRITE A SHORT REVIEW OF C 400 WORDS OF A BOOK THAT HAS MADE AN IMPRESSION ON YOU. THIS CAN BE ANY SORT OF BOOK BUT ONE THAT MADE YOU PAUSE FOR THOUGHT- AND SAY WHY. PLEASE SEND YOUR COPY FOR MADHU'S ATTENTION, C/O LIZ@BRAPP.ORG

TESTING THE WATERS Lessons from the History of Drug Research

ALLAN GAW.

SA Press. March 2016. ISBN 13: 978-0-9563242-5-2

Available from www.amazon.co.uk as a Kindle book download. £6.31



"TESTING THE WATERS" is the third in a series. I always find it slightly unnerving to be sent the latest book by someone whose work I have previously thoroughly appreciated. What if I don't like it this time? -Those of you who have been reading "Pharmaceutical Physician" for a while may recall positive reviews of some of Allan Gaw's previous publications: happily on this occasion too, I wasn't disappointed.

I am fascinated by history on several levels, ranging from just how different yet how similar the lives of those who came generations or even millennia before us are to our own lives today, through to the big question 'and what do I learn from this?' As Andrew Marr put it: "History is either a moral argument with lessons for the here-and-now or it is merely an accumulation of pointless facts.'

We work in a cutting edge, endlessly innovative industry where the marriage of science and speed dominates. But sometimes, just once in a while, whilst forging relentlessly ahead we could benefit from a period of thoughtful reflection on what those who pioneered drug research are trying to tell us across the intervening years.

Allan is a fluent and compelling author who gently and painlessly draws the reader into the stories making the book a pleasure to read. After some illuminating quotations which frame the topic of the book very well, Allan asks "Modern medicine, and indeed modern life, is difficult to imagine without the ready availability of well-researched and effective medications, but think for a moment: what would our world look like if there were no drug treatments?" What indeed?

Taking a necessarily selective approach to an otherwise vast subject, the reader is taken on a voyage of discovery calling in on Venice two thousand years ago, where highly analytical individuals were able to devise reasonable approaches to the evaluation of new drugs, to Ancient Rome, Persia and an doctor living in rural England by way of the battlefields of Europe, and the laboratory benches of a successful chemical company on the cusp of transforming itself into the beginnings of the German pharmaceutical industry.

Luck played its part as always, so did serendipity and good timing- as well as bad. And most of you are aware of the pivotal role played by a seemingly helpful and desired sleeping tablet in shaping modern drug regulation. The vignettes are compelling and memorable, evoking images of our ancestors and their interest and enthusiasm for science and research, although for many that would have been heavily punishable if expressed in such terms.

Although I know it is the modern way, I struggle with e-books: something to do with a feeling that my computer /tablet is for 'work' whereas I read for pleasure, perhaps. Nonetheless, despite the electronic format, reading this book was certainly not work. I cannot recommend it highly enough: even if you read nothing else about the origins of drug research and what it can (should?) teach us, read this. Even if you 'learned to hate history' as one medic recently described the influence of his school days to me, read this. I cannot improve on Dr Gaw's own summary: "In each case we can enjoy the narrative as an interesting historical vignette, but these stories are included for more than simple entertainment. Each teaches us a lesson that is relevant and resonant today. For the most part these stories are about people long dead, from other worlds, but we should not forget that they were in many ways no different from ourselves. They were adults and children, healthy and sick, good and bad. What happened in each case, like a pebble tossed into a lake, sent ripples across the years. Those ripples still lap against the shores of the present, inviting us to catch them, dipping our fingers and testing the waters."

This is a 'buy'.

Madhu Davies