

Life begins at 60: DTB and the new challenges ahead

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Today, it is hard to imagine the drug and therapeutics landscape of the UK 60 years ago. In 1962, statutory regulation of medicines would not be established for almost another 10 years, the *British National Formulary* was evolving from the former National War Formulary and still included a lot of traditional tonics and mixtures, and the concept of evidence-based medicine was decades away. However, in April 1962, the *Drug and Therapeutics Bulletin (DTB)* began to provide clinicians with vital, impartial and independent information on the harms and benefits of medicines at a time when there was very little else available.

Things have changed significantly over our 60 years. Evidence-based guidelines began to be developed in the late 1980s and the concept of evidence-based medicine was introduced in the 1990s. The development of the Cochrane Collaboration in 1993 exemplified the desire for a systematic approach to analysing clinical trial data to provide clinicians and policy-makers with reliable reviews of the effects of health interventions. In a ground-breaking development, the National Institute for Clinical Excellence (NICE) was set up in 1999 to create a national approach to decide what medicines and treatments the NHS should provide, and in 2003 it became a legal requirement for the NHS to fund interventions recommended by NICE's technology appraisals.¹ One of NICE's first acts was to determine that the antiviral, zanamivir, was not cost-effective and should not be provided by the NHS. In response, the chairman of Glaxo Wellcome reportedly threatened to move the company abroad if the decision was not reversed.¹

With the proliferation of information on medicines and treatments, and after two decades of NICE advice, you might consider that there is no longer a role for an independent drug bulletin. Nothing could be further from the truth. Independent scrutiny of national (and international) decisions on the development, licensing

and commissioning of medicines is as important as ever. In the Medicines and Healthcare products Regulatory Agency's (MHRA) current 2-year delivery plan, the authority makes it clear that it will work more proactively with the pharmaceutical industry to deliver 'what our customers want, as well as public health outcomes that benefit patients'.² In addition, NICE's latest strategy states that it has 'an important role in supporting the UK's ambition to be a major life sciences destination'.³ These shifts to closer collaboration with industry raise concerns about the ability of both agencies to remain independent and carry out critical evaluations of drugs and devices. NICE has also expressed interest, along with a number of agencies and several pharmaceutical companies, in joining the GetReal institute, which is focused on the use of real-world evidence in healthcare decision-making.⁴ Real-world evidence is a term that refers to the use of observational data that might be drawn from patients' electronic health records or disease registries. It is no surprise then that NHS Digital is currently overhauling general practice data to make it more available for research.⁵ Yet real-world data offer an inferior standard of efficacy data, and it is not yet clear if data from clinical systems will be sufficiently robust to monitor the safety of new drugs and devices.

The strategic direction of this trinity of the pharmaceutical industry, NICE and the MHRA, is highlighted by the government's Life Sciences vision document published in August 2021.⁶ In this document, the research, development and marketing of pharmaceuticals are seen as vital for the economy of the UK with the NHS as the testing ground for new innovative drugs, brought ever quicker to market and involving significantly lower investment on behalf of the submitting company.^{7,8} Integrated care systems will be legislated to have a duty to promote pharmaceutical research and regulators such as the General Medical Council will be required 'to embed research and innovation in standards for

registered professionals'.⁶ The MHRA will seek to steal a march on other regulatory bodies across the world by requiring less burdensome efficacy trial data and an acceptance of real-world data.⁷ Also included is an emphasis on the MHRA's use of novel biomarkers or surrogate markers in the licensing process.⁶ In short, we are seeing ever closer ties between companies that make medicines and organisations that regulate and sanction their use—commercialisation of a whole health system. This new world is further illustrated by the Innovative Licensing and Access Pathway, which involves the MHRA, NICE, the Scottish Medicines Consortium, the All Wales Therapeutics and Toxicology Centre and the NHS working together to 'accelerate the time to market' for certain medicines (eg, new chemical entities, biological products, medicines with new indications and repurposed medicines).⁸

Two examples illustrate the increase in commercial links between agencies. The first relates to the lipid modifying agent ▼ *inclisiran*. In a series of statements that read more like advertisements, NICE announced that the drug is a 'a potential game changer in preventing thousands of people from dying prematurely from heart attacks and strokes', and in a press release entitled 'NHS cholesterol-busting job to save thousands of lives', the Health and Social Care Secretary called it a 'ground-breaking new drug'.^{9,10} In November, a letter was issued on behalf of the Accelerated Access Collaborative and Commercial Medicines Directorate at NHS England informing local prescribing committees that they must approve *inclisiran* for use in primary care.¹¹ Such an approach has been challenged by clinicians over the lack of safety and efficacy data as well as concerns over clinical responsibility for prescribing *inclisiran*.¹² All this for a drug that NICE itself agrees has no evidence comparing it directly with other lipid lowering treatments and no long-term evidence on cardiovascular outcomes.¹³ The second example concerns a commercial agreement between NHS England and two

pharmaceutical companies who market direct acting oral anticoagulants (DOAC).¹⁴ Under the agreement, the companies will provide investment for 'Detect, Protect and Perfect Initiatives' based on the number of packs of their DOAC that are prescribed. Does this signal a major change in the way that the NHS commissions medicines and a greater role for manufacturers of medicines?

DTB supports innovation and the effective use of medicines that have clearly demonstrated that they improve clinical outcomes for patients. Nevertheless, we believe that there is a need to scrutinise both the introduction of new medicines and any commercial arrangements governing their use to ensure that they are in the best interests of patients, the health service and society. In the next decade, we can expect to see a significant increase in drugs coming into clinical use based on limited efficacy data and safety data that will be reliant on postmarketing surveillance and real-world data from clinical systems, as well as an increase in the number and scope of commercial arrangements with manufacturers. The need for independent scrutiny has never been more important.

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