Medicines & Healthcare products Regulatory Agency

MHRA

Point of Care manufacture – proposal for a new regulatory framework

18th March 2021

A. Summary

Technology is enabling the creation of new medicinal product types that have features such as very short shelf lives, in the range of 15 seconds to a few hours, necessitating manufacturing at the point of care (POC) and / or other products that are highly personalised. Product types seen to date span a wide range of dosage forms, such as blood products, gaseous products, Advanced Therapy Medicinal Products (ATMPs) and small molecule products, driven in large part by the development of separation device technologies. These products do not fit the current 'standard model' of manufacture and supply, which typically features centralised manufacture of large batches of stable products at a few manufacturing sites.

A new regulatory framework is required to enable the development of POC manufacture and supply, which provides control measures equivalent to those currently in place for medicinal products, so ensuring that POC products have appropriate quality, safety, and efficacy attributes. Although the POC framework will be new, it will be based on and link to current regulatory control systems including inspection, clinical trials, marketing authorisations and pharmacovigilance. Products manufactured at POC will not replace products manufactured in more traditional factory-based locations, they will enlarge the spectrum of products and supply models to meet widening therapeutic needs.

The work to create the new POC regulatory framework is contained within the Second Sector Deal of the UK's Life Sciences Industrial Strategy as one of the 'innovative regulation' projects. The MHRA's involvement in an Engineering and Physical Sciences Research Council (EPSRC) funded project to evaluate manufacture through the Redistributed Manufacturing in Healthcare (RiHN) network and the resulting white paper provided valuable insights into manufacture at POC.
A proposal for the new regulatory framework that balances control of these products but will not result in unnecessary regulatory barriers is a system based on modification to precedents that exists in medicines legislation including the plasma master file (PMF) system.

B. Issues and regulatory challenges

Information obtained from requests for regulatory and scientific advice, borderline classification opinions and the presence of some products in clinical trials demonstrate that there is a wide range of medicinal products that can only be manufactured at POC. The main features of POC manufactured products that makes progress for such products difficult and in some cases impossible under the current regulatory framework include:

- Short shelf life.
  Some of these can be in the order of hours, minutes or less, which has two major implications:
  - There is only time for local supply of the finished product, which therefore compels manufacture to be in very close proximity to the patient.
  - There may be no time for end of manufacture Quality Control testing and Qualified Person certification prior to supply.

  Conventional products typically have a shelf life of 2 to 3 years, which allows for a relatively long period for end of manufacture Quality Control testing and, where appropriate, Qualified Person certification of each batch followed by national or global distribution. These cannot occur with such short shelf life products and need to be replaced by equivalent measures that

provide assurance of the quality of products during manufacture, concurrent assessment and rapid decision to either supply and administer or to reject the product.
In addition, manufacture will typically be of single units for immediate administration, which is similar to some radiopharmaceuticals, and may mean that there will be no or limited finished product for reference and retention materials. Flexibility will be needed to include materials from other stages of the process.

- Manufacture at a large number of sites.
  This is a further consequence of a very short shelf life with the requirement for close proximity to the patient. Manufacture at commercial scale will be by 'scale out' rather than the conventional approach of 'scale up'. Depending on the product type, the ability of patients to travel, availability of specialist clinical expertise and clinical facilities, there may be some concentration or focal points in the provision of such products. An application currently at clinical trial stage is projected to involve approximately 200 POC sites in the UK, which would manufacture a total of about 12,000 products per year.
  This contrasts with the current scale up manufacturing models where any one product is typically manufactured in a few global locations, usually in the range of one to three sites, each at large scale.
  There are some specific regulatory challenges that arise from manufacture at a large number of manufacturing sites:
    - The need for personnel named on a manufacturer's licence. Traditional manufacture involves named quality control, production management and certification personnel responsible for the product.
    - Control, consistency and availability of product that complies with manufacturing and Clinical Trial Authorisation (CTA) and Marketing Authorisation (MA) requirements across a large number of POC sites.
    - The life cycle demands for POC manufactured products must be included in a development plan through clinical trial phases to accumulate evidence of comparability needs.
    - Marketing Authorisation: MAs currently name each site of manufacture and the MA is varied when a new site is added or an existing site withdrawn. This requirement will be a heavy administrative burden and costly, potentially prohibitively, given that site changes are anticipated to be relatively frequent. A similar requirement exists for CTA, where the finished investigational medicinal product (IMP) manufacturing site is named in the CTA. Each new manufacturing site will also need to be inspected, authorised and comparability demonstrated

  The fact that some products are in clinical trials means that the need for regulatory change in this area is current rather than at a future point.

- Intermittent nature of manufacture.
  The main driver for manufacture at POC sites will be the occurrence and clinical need of individual patients, so is likely to be intermittent. The potential concentration of focal points in the provision of specialist clinical services could result in campaign manufacture. This contrasts with most conventional manufacturing operations that have full time manufacturing operations and support staff, which facilitates the retention of operator skills, routine supply of raw and starting materials and consumables, and routine maintenance of equipment and utilities.

- Novel and wide range of manufacture location types.
  Depending on the nature of the treatment delivery, some manufacturing locations that are unusual in comparison with conventional sites will be used. These will range from pharmacies, hospital wards, operating theatres through to mobile settings such as ambulances and

vehicles converted to provide mobile manufacturing units. Some regulatory advice enquiries have been received for manufacturing sites such as in the home of patients: these may serve to define one of the limits to the new regulatory framework.
These manufacturing locations contrast with the 'standard model' of manufacture, which is typically factory based (centralised) sites, either dedicated to specific products or with manufacturing on a campaign basis.

- Wide range of product types.
  An assumption is often made that POC manufacture only applies to new types of product. While this is partly true in that some types of ATMPs are manufactured at POC, applications have also been seen for some types of blood products, medical gasses and some small molecule products. In addition, while some of these products are not patient specific, such as medical gasses, others are autologous, meaning that they are derived from and must be returned to the same patient.

Further regulatory considerations for products manufactured at POC:

- Terminology.
  As with many new developments, POC manufacture has a range of terminology including 'de-centralised' manufacture, redistributed manufacture and 'GMP in a box', which can create uncertainty.

- Classification.
  Many products manufactured at POC involve the use of device technologies for:
  - Generating and isolating gasses that act pharmacologically (e.g. nitrous oxide).
  - 3D printing (additive manufacture) and which can be
    - small molecules (single Active Pharmaceutical Ingredient [API], multi-layered, multi-compartment) or
    - ATMP manufacture, referred to as bioprinting.
  - isolating tissues and cells (e.g. adipose or mesenchymal stem cells)
  - isolating blood components (e.g. platelets).

  However, since the intended purpose of these products is achieved by pharmacological, metabolic, or immunological action, they do not fall within the scope of medical device legislation and will be classified as medicinal products.

  It has been argued that, as the 'product' placed on the market is a 'piece of equipment' (or device) which does not incorporate a medicinal product, that the medical device directive can be applied. In some cases, where the generating device also delivers the medicinal product, it could be CE marked as a medical device using the appropriate classification rules and conformity assessment procedures. However, there is currently no formal mechanism for the involvement of a medicines authority to evaluate the quality, safety and efficacy of the medicinal product that is produced by a medical device so CE marking alone is not sufficient or appropriate.

  A general principle of regulation of products and systems that comprise combinations of medicines and medical devices is that they do not have to fulfil the duplicate requirements of medicines and medical device legislation, instead the two regulatory regimes should complement each other. For example, the conformity assessment of the generator/manufacturing equipment under medical device legislation could form part of the dossier supporting the medicines Marketing Authorisation Application (MAA) and also form part of the GMP controls of the device if used as an item of manufacturing equipment.

Product manufactured by a medical device can fulfil the definition of a medicinal product. A precedent exists for radionuclide generators, which only produce the medicinal product very shortly before use. These were specifically provided for in the directive 2001/83/EC, as they were in established use at the time of drafting; however, new POC cases will need to be provided for.

- Future proofing.
  Given that scientific and technological advances are on-going, the new regulatory framework will require a degree of flexibility to accommodate further product types. This is intended to be achieved by being principles based and supported by interpretive guidance in areas such as GMP, GCP, CTAs and MAAs, which can be updated as needed.

A new regulatory framework is therefore required for the proportionate control of these types of products, but which links to the existing regulatory controls, such as CTAs, MAAs and pharmacovigilance requirements, to maintain the levels of quality, safety and efficacy seen with current products.

C. Outline regulatory proposal

Many of the measures introduced here are adapted from precedents in current use in the regulation of medicinal product manufacture, blood component, and tissue and cells processing. These measures include adaption of concepts in GMP (e.g. those used in current short shelf life products such as radiopharmaceuticals, real time release testing and parametric release, Product Quality Reviews), the master file systems (e.g. those used for plasma and active pharmaceutical ingredients), and also the hub and spoke model used in the regulation of tissue and cells collection and processing.

The Control Site concept.

The regulatory system is proposed to be based on a Control Site, which will be the primary focus of regulatory controls by MHRA. The Control Site will be a physical site and will oversee all aspects of the POC manufacturing system including the individual manufacturing locations and their activities.

The Control Site will be responsible for a range of activities including the assessment and establishment of new sites through an ‘onboarding’ process, decommissioning and removal of manufacturing sites. Other activities that the Control Site will be responsible for include but are not limited to: training of central and local staff, oversight of the pharmaceutical quality system, provision and control of manufacturing equipment, raw and starting materials and consumables used in manufacture, systems to capture and supply information from local sites to the Control Sites on production activities, provision of Qualified Person (QP) oversight, traceability information, provision of a system or systems to capture and report incidents, issues, out of specification or compliance events, serious breaches and serious and adverse event reporting, change control and periodic audit of systems and sites.

Arrangement for QPs to certify product will need to be developed, which will usually be after the product has been administered. There will most likely be a system of local verification based on compliance of equipment with qualification criteria, the process with validation criteria and the manufacturing process with key criteria.

In conjunction with CTA and MAA processes, 'criteria for release' may be needed which could be different from the 'product specification'. Other considerations could be the need for routine product, or surrogate, testing for product and process consistency monitoring, rather than batch release processes. Where it is possible to test each product or batch after administration this could be an alternative to confirm that the dose was acceptable. In all cases, actions would need to be taken if the products or batch was out of specification.

This reporting system and its degree of sophistication in exchanging information between the Control Site and each manufacturing site, plus other sites such as any used for testing, will need to be commensurate with factors such as the number of sites and the need for immediacy of reporting. Reporting systems from POC sites to the Control Site could allow assessment of data in or near real time.

The Control Site will also be required to compile, maintain and supply to MHRA:

- A **POC Master File**, POC MF, this will be the key source of information on the POC system. It will need to be kept up to date and supplied on a routine basis to MHRA for review and assessment of the degree of compliance with the different areas of good practice such as GMP, GCP and GPvP. The frequency of reporting is most likely to be on an annual basis and will be linked to the routine re-inspection of the POC manufacturing system.
- Notices of significant events and issues on an as -needed basis when significant individual events or emerging trends are apparent through the current interim compliance report system.
- The POC MF is aimed at simplifying the tasks of all parties in the manufacture, applications for authorisations and regulation. In the initial stages of development, the POC MF will only support one CTA and one MAA, however by analogy with the Plasma and Vaccine Antigen Master File systems, the POC MF could support more than one CTA and more than one MAA.

Details of the contents of a POC Master File are to be determined but it will:

- Capture and maintain information that will be used to inform any MHRA Good Practice inspection:
    - GMP inspections - the Control Site would be subject to regular inspection along with selected manufacturing sites. The frequency of inspections of the control and POC sites has not been determined but as for MHRA's current GMP inspection programme it would be based on risk. This could be an annual GMP inspection for the Control Site and sufficient exemplar POC sites to provide assurance that a satisfactory level of control is exercised by the Control Site over the manufacturing and any testing sites. Each POC site would have nominated individual who would be accountable for complying with the established POC procedures.
    - GCP inspections – the POC MF could be part of GCP planning and risk-based inspections with the Control site forming part of an investigator site inspection and be reviewed for GCP aspects, together with sponsor oversight of the process. The inspection planning would determine where GCP and GMP aspect start and stop, or where GCP can review some of the POC GMP aspects (as agreed) at the investigator site which would help inform/support the GMP manufacturing site knowledge and intelligence
    - GPvP inspections - VRMM would agree a risk management plan (RMP) with the MAH and it is likely that HCPs would need to be given educational materials on the administration of the product, as well as around the reporting of adverse events

experienced by the patient at the POC. In addition to adverse events, other special situations such as medication errors, overdose, occupational exposure, etc., represent important information for pharmacovigilance purposes. There may be other risk minimisation activities required and these would be detailed in the RMP. As for any authorised product, the MAH would need to establish a pharmacovigilance system which would need to be described in the pharmacovigilance system master file (PSMF); this system could be subject to a GPvP inspection.

- Be a stand-alone document which will be separate from the dossier for clinical trial or marketing authorisation and it will provide relevant information for these purposes.
- Require regular re-certification to demonstrate that requirements of both MA and GMP continue to be met.

Other considerations:

- CTA/MAA
    - The requirements for the supporting documentation for a CTA or MAA will need to be adapted:
        - Details of the control site will need to be included but there will be no need to specify each individual manufacturing site;
        - The process by which new sites would be 'onboarded' will need to be described, with particular focus on how comparability would be established between product manufactured at different sites;
        - Process development and control sections of the dossier could be captured as a POC Master File component (or as an appendix to the IMPD) and submitted for scientific and technical evaluation as part of the MAA or a CTA;
        - Data requirements for finished product testing, batch analyses, stability testing and labelling will be dependent on the nature of the product and the shelf life; these could differ significantly from conventional pharmaceuticals and may need to be agreed on a case-by-case basis.
- VRMM
    - The RMP would need to be agreed on a case-by case basis depending on the nature of the product and its clinical use. A key element would be traceability and it may be beneficial to use patient registries to support ongoing evaluation of the benefit-risk balance.

D. Next steps.

Powers now exist under the MMD Act to make regulatory changes including those for manufacture and supply at point of care. The main steps and indicatives time are below:

- External event:
    - 18th March
    - Collate feedback – 3 weeks
- Preparation for public consultation:
    - Further development of this POC document
    - Initial engagement with Government legal services on legal text changes

- Impact Assessment development
- Public consultation
    - consultation during the summer
    - Further engagement events during the consultation
    - Analyse comments, publish response
- Parliamentary process:
    - Finalised legal text for submission in late 2021
- Operational requirements:
    - Development of regulatory guidance documents in GMP and other regulatory areas will start in the second half of 2021.

E. Glossary

- API (AS) Active Pharmaceutical Ingredient (Active Substance)
- ATMP Advanced Therapy Medicinal Product
- CAPA Corrective and preventive actions
- CT Clinical Trial
- CTA Clinical Trial Application
- GCP Good clinical practice
- GLP Good laboratory practice
- GMP Good Manufacturing practice
- GPvP Good pharmacovigilance practice
- MA Marketing Authorisation
- MAA Marketing Authorisation Application
- PMF Plasma Master File
- POC Point of care
- POC MF Point of care Master File
- QC Quality Control
- QP Qualified Person as set out in Regulations 8 and 41 , role defined in Schedule 7 of HMR 2012
- RMP Risk Management Plan