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Regenerative Medicine

Comparability: manufacturing, characterization and controls, report of a UK Regenerative Medicine Platform Pluripotent Stem Cell Platform Workshop, Trinity Hall, Cambridge, 14–15 September 2015

This paper summarizes the proceedings of a workshop held at Trinity Hall, Cambridge to discuss comparability and includes additional information and references to related information added subsequently to the workshop. Comparability is the need to demonstrate equivalence of product after a process change; a recent publication states that this 'may be difficult for cell-based medicinal products'. Therefore a well-managed change process is required which needs access to good science and regulatory advice and developers are encouraged to seek help early. The workshop shared current thinking and best practice and allowed the definition of key research questions. The intent of this report is to summarize the key issues and the consensus reached on each of these by the expert delegates.

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A stakeholder workshop was held in Trinity Hall, Cambridge University, on the 14–15 September 2015 to discuss comparability in cell therapy manufacturing. The focus of the workshop was on human pluripotent stem cell derived therapies.

Comparability is the regulatory requirement to demonstrate product equivalence (highly similar) after a process change [1,2]. Such process changes include a media component change, a donor/starting material change, a manufacturing platform change and the introduction of a new manufacturing site. A recent publication by current and former members and experts of the Committee for Advanced Therapies, EMA has emphasized that demonstrating comparability maybe "difficult for cell-based medicinal products" [3].

The workshop aims were to share the EU regulatory position, understand the significance of comparability and approaches to achieving comparability, and to define challenges to the community with the intent to communicate these more widely in order that they can be addressed by stakeholders perhaps precompetitively and to help developers proactively address these issues.

It was attended by more than 50 cell therapy development professionals from around the world with a wide range of backgrounds and reflecting a wide perspective. It was held under the auspices of the UK Regenerative Medicine Platform (UKRMP) and its cell biology, differentiation and manufacturing hub, The Pluripotent Stem Cell Platform with the intent that it would also inform the research of the hub.

This note summarizes the substance of the presentations and discussions at the workshop as below and references to related guidelines have been added. Some of the presentations and a preworkshop briefing paper [4] can be found at [5]. We are grateful to Dr Louise Bisset of the UK Medicines and Healthcare products Regulatory Agency (MHRA) for

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an introduction to the problem of comparability from a regulatory perspective. This set the context for the workshop: the need for manufacturing process change is accepted, is inevitable and there are mechanisms to address it; presently the 'product is the process' since "a biological medicinal product cannot be fully characterized;" significant changes observed in the product characteristics after manufacturing process changes may require further nonclinical and clinical studies to investigate any impact on efficacy and safety.

To ensure that pluripotent stem cell products get to market, there are some key translational issues which need to be addressed including manufacturing. Living cells add particular complexities, which need to be addressed in manufacturing system design and within manufacturing protocols. Change management protocols [6] describe specific changes that an organization would like to implement following product approval and how these would be prepared and verified and are important to manufacturers and product developers as well as the regulator. They provide a record, and later, part of a regulatory submission of the strategy adopted by a manufacturer in order to manage post-approval changes including for example, comparability issues. The submission needs to be in a form that permits the regulator to assess and approve or challenge the adequacy of the strategy. Without being able to demonstrate comparability it is hard to carry out process improvement, and particularly to transfer a product to a second manufacturing site – such a as a Contract Manufacturing Organization (CMO) or additional manufacturing sites. This is an instance of the requirement for practical interchangeable manufacturing (see Box 1) where a product specification includes limits of critical attributes related to function and the key problem is the control of variation within these limits [7]. The goal of the comparability exercise is to ensure the quality, safety and efficacy of drug product produced by a changed manufacturing process, through collection and evaluation of the relevant data to determine whether there might be any adverse impact on the drug product due to the manufacturing process changes [1]. Manufacturing experience in other sectors has shown that manufacturing variability can be reduced by automation of a manual process but emphasizes that mechanization (see Box 1) of the process gives more significant gains.

Justification of product specification & limits

Product testing strategies are at the heart of product specifications, process development and understanding. Product release specifications do not establish full characterization of the product and therefore whilst ensuring product consistency, form only part of the evidence required to demonstrate comparability. Comparability protocols consequently must consider the risks associated with any proposed process change and must prescribe the way in which any such evidence will be gathered. In doing so attention must be paid to the process instructions (including standard operating procedures), critical process parameters, in-process controls and critical quality attributes (CQAs) in addition to the product specification to ensure and demonstrate comparability (see Box 2).

When deciding on whether to make changes, an approach based on risk should be taken and practical limitations must be considered. Prior to undertaking a comparability study, it is important to understand what is expected and this will depend on the nature of the change and the stage of the product's lifecycle. Historical data and process development data should be used to set comparability acceptance criteria for selected CQAs and all data analyzed following the comparability data-gathering exercise to support a claim of comparability at the quality level. Any differences should be explained, in terms of potential effect on safety/efficacy. Where the effect on safety/efficacy cannot be predicted then further nonclinical or clinical data may be required.

Assays which enable the detection of variation as a result of any change are useful to inform conclusions. Assays should be shown to be capable of detecting quality changes. Potency and mode of action assays – which are often the most complex – are the most critical when trying to assess comparability.

It is important to ensure that the product and process platform is correct at the start of the process and to not rush into the clinic too early, in order that changes can be made as process improvements rather than process alterations. Organizations can also record information on changes which occur during early product development in nonmandatory documents such as a cell history file [10]. Where significant changes need to be made to the manufacturing process, it is advisable to make these before pivotal clinical trials. Process improvements to an established/authorized process can be made if they do not trigger a marketing authorization (MA) variation, in other words, where they do not relate to a specification or manufacturing method registered in the clinical trial authorization or MA. These changes are conducted under good manufacturing practice (GMP) change control in accordance with the principles of quality risk management [11,12].

By the very nature of the starting materials, variation is inherent in these products. Wide upper and lower acceptance limits can be established where validated (i.e., upper and lower limits do not adversely affect the quality of the product) and quantity permits so that future manufacture of these products could therefore accommodate or control this variation. Specifications

Box 1. Learning from conventional manufacturing.

- Interchangeable manufacturing [8] – interchangeable parts are parts (components) that are, for practical purposes, identical. They are made to specifications that ensure that they are so nearly identical that they will fit into any assembly of the same type. One such part can freely replace another, without any custom fitting (such as filing). This interchangeability allows easy assembly of new devices, and easier repair of existing devices, while minimizing both the time and skill required of the person doing the assembly or repair. Interchangeability was an eighteenth century Enlightenment ideal [8] as was the metric system. Practical interchangeability is distinguished from theoretical interchangeability by the application of limits related to product function. A critical step in the realization of interchangeability in conventional manufacturing, in particular the ability to manufacture the same product at a number of sites, was the development of systems of gauges that allowed measurements that could be related to function
- Six Sigma [9] – is a set of techniques and tools for process improvement. It was introduced by engineer Bill Smith while working at Motorola in 1986 and based upon the principles of statistical process control. Jack Welch made it central to his business strategy at General Electric in 1995. Today, it is used in many industrial sectors. Six Sigma seeks to improve the quality of the output of a process by identifying and removing the causes of defects and minimizing variability in manufacturing and business processes. It uses a set of quality management methods, mainly empirical statistical methods, and creates a special infrastructure of people within the organization, who are experts in these methods. Critically process capability is measured and understood to drive conformance to specification. Each Six Sigma project carried out by a team within an organization follows a defined sequence of steps and has specific value targets, for example: reduce process cycle time, reduce pollution, reduce costs, increase customer satisfaction and increase profits
- Automation vs mechanization – it is important to distinguish between the automation of a manual process, the replication of a manual process by a machine typically to make it more repeatable, reduce risk or enhance cleanliness by removing humans from the manufacturing environment or reduce recurrent costs; and the mechanization of a process where the machine achieves better than human performance typically for example, by being more powerful and/or precise

for starting materials are often difficult as it is difficult to establish quantitative acceptance criteria. Where materials are available in small quantities, unless absolutely necessary some tests could waste material, for example, material obtained from a human biopsy. In such a case the size and appearance may be sufficient as controls. Additional controls over clinical collection techniques and practices may be required. Specifications should be set considering manufacturing process requirements.

The problem of variation in starting materials is significant, but the desire or ability within the field to control it does not appear to be increasing over time. Also, it may not be possible to control the variability of starting materials.

Most currently applied statistical tools use normally distributed data, however input variation for cell-based therapies tends to be non-Gaussian in form and therefore there is a need for appropriate statistical tools that allow for the disproportionate effect of the kurtosis. Under such circumstances the probability of an outlier is higher and more serious in impact than in conventional settings and statistical process control methods may break down.

It should also be recalled for therapeutics that outliers cannot be excluded as each outlier represents an individual patient requiring a treatment. Also as result of the wide range of variability between patients, any individual patient is poorly characterized by the mean. Further the nature and character of the cells will only be one parameter on which the success of the product can be measured. Most cell therapies are not first-line treatments and it is likely that a cell therapy may only be one component of a patient's treatment. Asymmetrical specifications are problematic from the perspective of a developer and in particular ranges of failure at the lower limit of the specification must be carefully considered. Where the underlying data distribution is asymmetric, manufacturers need to take this into consideration when setting limits so that the probability of staying within the specification is the same for both upper and lower limit.

Markers currently being used for cell identity are determined on a largely empirical basis and therefore future discoveries about the true mode of action may render their use in release criteria inappropriate in the long term. Consequently there is more work to be done to ensure we are measuring quality meaningfully.

Qualification of the starting cells will, where supply allows, be critical to help understand and reduce input variation. Automation of assays can be used as a tool to reduce variation, but only if the automated platforms are validated and their contribution to variation is understood. Automation is expensive to implement and should be deployed at points in the process where it will exert the most influence on control of product quality. There is an opportunity for the manufacturing community to share experience of what can be achieved with respect to process variation and its control.

Box 2. Glossary of pharmaceutical development terminology.

- CQA – a physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality
- CPP – a process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality
- A pivotal clinical trial is that which provides the most significant data used to support the marketing authorization application. Usually this is the Phase III trial
- Comparability protocol – US FDA guidance for industry defines "a comparability protocol is a well-defined, detailed, written plan for assessing the effect of specific CMC changes in the identity, strength, quality, purity and potency of a specific drug product as these factors relate to the safety and effectiveness of the product. A comparability protocol describes the changes that are covered under the protocol and specifies the tests and studies that will be performed, including the analytical procedures that will be used, and acceptance criteria that will be achieved to demonstrate that specified CMC changes do not adversely affect the product. The submission of a comparability protocol is optional" [15]

CMC: Chemistry, manufacturing and control; CPP: Critical process parameter; CQA: Critical quality attribute.

Product characterization & assays

Product characterization is a fundamental part of manufacturing that poses particular challenges to the demonstration of comparability in the context of cell therapy medicines.

There is consensus that for specifying cellular products satisfactorily a selected number of key characteristics should be measured by quantitative assays that identify cellular identity and function with a high level of sensitivity; it is desirable to use orthogonal assays to measure key characteristics. However, variability that could affect a comparability assessment can arise from multiple sources in manufacturing with biological, process and analytical variability the most important ones. Delegates agreed that some of the biological variances cannot be controlled due to the intrinsically complex nature of cells. Nevertheless, in principle it is possible to design controllable characterization assays for cellular products so that reproducibility of assays is increased and meaningful biological discrepancies can be assessed.

Variability of analytics is a particular issue for cell therapy products as they differ from other biologics in the lack of established standard references to aid the construction of robust assays. The workshop recognized the need for the establishment of a framework for reproducible analytics (currently a topic of discussions led by the National Institute of Standards and Technology [MD, USA] and the National Institute for Biological Standards and Control [Hertfordshire, UK]) for cell therapy with the involvement of academia, industry and national and international standards organizations that could provide criteria and tools to facilitate the transition from research-grade to industry-grade characterization.

Case studies of common characterization techniques (such as gene expression) revealed that variability arises with each step but can systematically be reduced via automation of manual procedures and standardization of data analysis. Several techniques, such as fluorescence-activated cell sorting, are already moving in this direction with new platforms and reference systems suited for comparability between laboratories and equipment. However, many parameters currently used to assess cell culture quality are still qualitative and subjective based on operator expertise, often via manual optical microscopic inspection. The inclusion of quantitative software based live cell imaging coupled with predefined thresholds within algorithms is encouraged for characterization during development.

Understanding the mechanism of action of the product underpins the development of potency assays required for in-process and release testing, a complex process that has to be tailored to each specific drug product. A number of challenges are associated with every phase of potency assay design including: robustness, time to develop and perform the assay, availability of reference material and performance. Developers recommend screening a matrix of potency assays during product development that would be later narrowed down to a panel of key, often multi-parameter assays. Utilizing multiple potency assays would also help to risk assess the product and cross validate assays.

Furthermore, potency assay development is a dynamic process that needs to be linked to clinical data, which are critical to correlate safety and efficacy of the product to the product characteristics. Overall, a pragmatic approach to product characterization is one that would define a 'window of system behavior', with particular attention to the definition of the limits, so that a level of biological variability is tolerated but the process as a whole is under control.

Principles of comparability & risk assessment approaches

Although the International Council for Harmonisation (ICH) of Technical Requirements for Pharmaceuticals for Human Use Q5E document on Comparability of Biotechnological/Biological Products Subject

to Changes in Their Manufacturing Processes [1] is specifically for proteins and small molecule biologics, the principles apply to products using pluripotent stem cells. The main 'overarching' regulatory guideline 'guideline on human cell-based medicinal products' [13] contains a section on comparability which makes reference to ICH Q5E. For planned changes, a risk-assessment approach should be followed to establish the focus of the comparability study, assess the change(s) and the impacts on the product CQAs also taking into account the fact that changes might have a cumulative effect on the product. The comparability study depends on the extent of the change and the stage in the products development when the change takes place (for example pre- vs post-pivotal clinical trials).

It is important to realize that it is not sufficient to rely on routine specification tests (i.e., the release criteria) when seeking to demonstrate comparability following a process change, data from in-process controls, extended characterization and stability studies will also be required comparability protocols should be designed to consider all outcomes and acceptance criteria must be prespecified. Ideally the data generated from product characterization and in-process checks (i.e., quality data) would be sufficient to provide the evidence of comparability without resorting to further non-clinical or clinical bridging studies, but where changes are identified and effect on safety or efficacy cannot be predicted or 'ruled-out' further non-clinical or clinical studies may be required. A risk assessment approach should be used to focus and define the experimental program; address issues critical-to-development; and identify and justify key putative process changes, for example using risk assessment methods and principles as outlined in ICH Q9 [11], or other suitable methods.

Importantly from a regulatory perspective, non-clinical studies (remembering the 3R principles [14]) and clinical trials used to demonstrate comparability must be sufficiently statistically powered to show that the product is within the tolerance limit, recalling the regulatory perspective that the mode of action is verified in the pivotal clinical trial (see Box 2). Crucially, where manufacturing changes are made to the product, following pivotal clinical trials, the product must be shown to be sufficiently comparable to the clinically tested material. Some level of comparability needs to be conducted, commensurate with the degree of change, whatever stage of the development lifecycle the change is made, including early changes.

Manufacturing control & process modeling

There is a requirement to control manufacturing processes to ensure that the product is equivalent after a change. Controlling the process may be achieved by passive control by setting process limits, and by active control involving feedback loops. Ideal manufacturing control development will take the fastest route to the process knowledge (operating limits, control precision) to allow informed process design to meet objectives and manage process risk – the greater the process knowledge, the lower is the risk of change.

Well-designed manufacturing controls are especially important when there is a large parameter space with very complex interactions, poor control relative to the allowable limits, insufficiently developed measurement capability and the process dynamics are very complicated. There is an advantage to developing models of cell manufacturing process protocols in order to predict those experiments that should be performed in order to confirm impact of the proposed change upon the manufacturing process. Such models might be useful if used to reduce the parameter space for experiments, rather than to replace them and if the model predictions are subsequently validated using appropriate experimental studies

Comparability plans & protocols

One of the reasons for the lack of resources spent on developing comparability and control tools is that the developers of these products are often academia, hospitals and small–medium enterprises who are unable to afford regulatory expertise, regulatory support structures or funding. Early engagement with MHRA in the UK or other regional regulator is needed. The product characterization associated with different manufacturing protocols is frequently squeezed to a late stage in the development process.

Examples where a demonstration of comparability post-marketing authorization would be required include: change of starting materials/reagents, introduction of a new manufacturing process step and the introduction of a new site. Practice differs between the US and the EU, although the intention is similar: to provide confidence in the continued quality, safety and efficacy of the product after the change. In the USA the comparability protocol describes, prospectively, the planned change to the manufacturing process in the form of a prior approval supplement which, when reviewed by the US FDA, will determine whether the planned change can be reported in a category lower than that required without a full comparability protocol. The comparability protocols will be acceptable only if certain conditions have been met: the product can reasonably be expected to satisfy the required quality criteria, the process and plant have been qualified and the analytical assays that are required in order to demonstrate comparability have been developed and validated. In such cases, the regulator will expect that

the identity, strength, quality, purity and potency of the product must be verified as part of the comparability protocols. Process improvements may also invalidate assays by changing the background impurity profile on which the assays were validated.

The comparability protocols must relate a robust concept of the mechanism of action for the product to the product quality attributes. The putative process changes must be listed along with the historical data (both release and in process characterization). The comparability protocols must set out prescriptive decision-making criteria together with the data requirement.

In the EU there is a mechanism by which the manufacturer of the licensed product can submit a comparability plan for approval by the regulator, before the actual study is carried out. The manufacturer submits what is called a 'post-approval change management protocol' as a variation [16], which details the comparability plan. The comparability study is performed and the data/results are then submitted as a further more 'minor' variation for the final conclusion on comparability. This approach is often used by manufacturers for larger manufacturing process changes (e.g., introduction of a new site). Changes to manufacturing processes post licensing usually occur many times during a products life-cycle. These changes are submitted to the regulator as variations (usually for biological products these are type II variations) and some form of comparability assessment will be required, the extent of which depends on the nature of the change. Changes which occur prior to approval and during historical product development should be documented in the manufacturing process development sections of the dossier (both drug substance and drug product).

Future therapeutic landscape, induced pluripotent stem cell & haplobanking

Taking a forward look at the therapeutic landscape, transplantation of allogenic therapies is difficult due to the requirement for either a suitable match or immunosuppression. The Global Alliance for iPSC Therapies (GAiT) [17,18] project aims to create international banks of stem cells which are selected to be immunologically compatible with a large proportion of the potential recipient population by covering a wide range of haplotypes for ABO and HLA antigens. Though these banks of cells are to be the starting material for the final therapeutic, the concepts of comparability need to be applied. There are potential differences between cell lines derived from different donors, different tissue sources, different methods of isolation and different methods of inducement of pluripotency and different expansion and banking techniques. To achieve comparability between banks, the alliance is working toward developing guidelines for a global production process and critical quality control (QC) tests, defining common QC techniques, common specifications of the banks and engaging with regulatory bodies to ensure that the validation packages being developed are acceptable to regulatory bodies in different jurisdictions. The alliance is also examining reference materials to compare the banks to validate comparability between banks. The variability in the banks is expected to be large due to the high-biological variability, variability between manufacturing sites and operator variability for manual processes.

Plenary summary & conclusion

The plenary session considered the current limitations to, and best practice for, process development for a new cell therapy. The main emphasis in discussion was on the relationship between the features of the process (critical process parameters) and confidence that measurable characteristics of the product (CQAs) are genuinely responsible for efficacy and safety within its micro-environment and for the target indication and patient population. A key outcome of this session was a summary of lessons for developers as shown in Table 1.

The session included key informal input from developers. Developers emphasized the value of an approach based on risk management and that there is a need start the risk assessment as early as possible. In view of the limited resources of many small–medium enterprises in the sector the careful and early application of a risk-based approach to product characterization is most important. An early dialog with the relevant regulators should be part of this work to ensure that the strategy is adequate and rational.

A balance must be struck between obtaining sufficient characterization data with strong links to the putative mode of action (demonstrated or based on prior knowledge) and measurement of excessive numbers of features simply because of a lack of confidence. Novel assays may be required, these can be used provided they are shown to be suitable and are validated.

An important point is to start the development of the potency assay early. Without this assay it is very difficult to satisfy the regulatory requirement to demonstrate control of product 'strength'. An understanding should also be gained of which components of the product should be classed as impurities, although, with a product consisting for example of a mixture of cell types, this may not always be possible and the drug substance may have to be defined in terms of the spectrum of cells present. Biomarkers should not be accepted uncritically for this purpose because some may not be indicative of product quality, safety or efficacy, will be an ongoing production cost burden and may lead to unnecessary investigations should variation be found batch-to-batch.

Table 1. Lessons for developers.

Number	Lesson
1	Talk to the regulators in your jurisdiction about proposed changes as early as possible
2	Be clinically specific and have a well-defined product and process understanding
3	Understand variation; understand allowable operating limits; control variation
4	Developers should focus on the key steps of: (1) process transfer; (2) product and process comparability
5	Measure the right process parameters and intermediates as well as the final product to establish a baseline: product and process knowledge will require measurements over and above product release criteria
6	Use a risk-assessment approach to define the experimental program necessary for comparability and start as early as you can; use the analysis as a mechanism to direct resource
7	Key stage gates and value inflection points are pivotal preclinical work, and pivotal clinical trials – key studies need to be done before these
8	Recall that in the EU Phase III clinical trials are intended to verify putative modes of action
9	Use historical analytical and process data to help set limits
10	Be careful with the definitions of active substance, strength and product and process impurities
11	Characterize as much as you can as early as you can, characterization will be product specific. Do not confuse identity with potency; question the value of your biomarkers
12	Understand your assay and equipment; use appropriate and sustainable equipment and technology to future proof in case you need to reproduce the technique beyond the lifetime of more bespoke instruments
13	All assays used should be validated for the intended use. For licensed products this means conformance to International Council for Harmonisation Q2(R1) [19]. Different assays would normally be used for identity, purity and potency testing.
14	Use assays that are able to detect the change you aim to execute
15	You may have to run processes 'side by side' (rather than comparing the changed process to retained samples)
16	Academic developers require regulatory support in manufacturing scale-up

Wherever possible the chosen assays should be simple, and consideration should be paid to the likely continued availability of reagents/consumables. Assays should be validated for use. For licensed products this means conformance to ICH Q2(R1) [19]. Different assays would normally be used for identity, purity and potency testing. Developers suggest that assays are based upon protocols published in peer-reviewed journals, however given the pace of change in this area may be new and unique to an organization.

It is important not to do analytical experiments out of curiosity but only after clarifying the purpose, risks of conducting them and the scope of the work. This is because the results must be followed up if unwelcome effects are found. It is preferable to do the tests that are needed and to make sure that the risks of the outcome are understood and managed.

The quality, safety and efficacy of the drug product may be affected by events that take place in 'the last one hundred yards'. As far as possible it is desirable to control the administration of the product by developing dosage forms and delivery vehicles that are able to maintain the drug product within an acceptable envelope of parameters such as temperature, time and fluidic stress or rate of delivery.

Some of these concerns are legitimate research topics, 'measurement of biology' for instance is not a solved problem and developers need to be clear on those areas that remain research issues. Research should be funded in methods that permit better interpretation of the significance of biomarkers. The current guidance is helpful but does not provide sufficient information to drive method development. There are a number of decision-making tools available that enable the developer to decide at what points they should conduct analysis of measurable features that exercise the most influence over product properties. Everyone needs viability assays and the community should start by creating robust comparable protocols for these.

Discussions at the workshop emphasized the need to address the requirements of comparability and security of supply simultaneously and that situations where a compa-

rability protocol may be required must be identified and addressed early in the development process. Key value inflection points for addressing comparability issues are before pivotal preclinical work and before pivotal clinical trials. Exchanges at the workshop also identified that there is still a need for the manufacturing community to convince other stakeholders of the value of the application of automation and mechanization approaches to control variation. A recurring theme of the workshop was the need to keep unpicking complexity and variation in cell therapy manufacturing, variation sources (biological, technical and operator) and the consequences of variation and how to address/control them. There is an opportunity to put mechanisms in place to share learning on the variation encountered by developers.

The key precompetitive activity arising from the workshop was the need to develop a framework for comparative analytics including methods of data presentation. This could include criteria for application of methods and tools; precompetitive interlaboratory comparisons and assay development; and analytical reference materials.

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