Council of Europe resolution CM/Res(2016)2: a major contribution to patient safety from reconstituted injectable medicines?

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Received 20 August 2018
Revised 21 December 2018
Accepted 31 December 2018
Published Online First 16 February 2019

EAHP Statement 3: Production and Compounding.

To cite: Beaney AM, Le Brun P, Ravera S, *et al*. *Eur J Hosp Pharm* 2020;**27**:216–221.

ABSTRACT

This article focuses on the reconstitution of parenteral medicines and the work that has been carried out at the European level to improve patient safety. Reconstitution may occur in a clinical area, for example, ward, theatre and so on, or within pharmacy. The quality of reconstituted medicines should ideally be the same, regardless of where reconstitution takes place. However, in practice, risks are greater when reconstitution is carried out in clinical areas. Although ideally all reconstitutions should be carried out within pharmacy aseptic units, capacity is generally not available to allow this, so a risk assessment approach must be taken to enable the healthcare establishment to decide which products must be reconstituted in pharmacy and which, with appropriate safeguards, can be reconstituted in clinical areas. Although guidance on reconstitution has been established in some countries, this is not the case across much of Europe. The Committee of Experts on Quality and Safety Standards in Pharmaceutical Practices and Pharmaceutical Care (Council of Europe) (hereafter: Committee of Experts) has undertaken work to develop quality and safety standards for reconstitution in the different locations within healthcare establishments, taking a risk-based approach. In June 2016, the Committee of Ministers of the Council of Europe adopted Resolution CM/Res(2016)2 on good reconstitution practices in healthcare establishments for medicinal products for parenteral use. Drafted by the Committee of Experts, the Resolution recommends implementation measures for best practices for the reconstitution of injectable medicines for administration to patients. This article summarises the rationale behind the Resolution, its drafting process and main chapters. There is no justification for patient safety with respect to reconstituted medicines to be variable across the Member States of the Council of Europe. Implementation of Resolution CM/Res(2016)2 will enable risk reduction in healthcare establishments and is a major contribution to patient safety from injectable medicines at the international level.

RISKS TO PATIENTS

Before administration to patients, parenteral medicines must be in a ready-to-administer (RTA) form, that is, presented at the required concentration and volume, in the final container (syringe, infusion bag or elastomeric device) for administration. To be in an RTA form, unless so provided by the pharmaceutical industry as a marketed, authorised product, the medicine must usually be reconstituted. This reconstitution may take place in the clinical area (ward, theatre and so on) or within pharmacy.

Reconstitution is defined as manipulation to enable the use or application of a medicinal product with a marketing authorisation in accordance with the instructions given in the summary of product characteristics (SmPC) or the patient information leaflet. This definition is based on consensus among the Member States signatory to the Convention on the Elaboration of a European Pharmacopoeia (Ph Eur Convention).[1]

The quality of reconstituted medicines should ideally be the same, regardless of where reconstitution takes place. However, risks of microbiological contamination, incorrect product composition, health and safety issues, and so on[2–6] are greater when reconstitution is carried out in clinical areas. When patient health is already compromised, medication errors are associated with increased morbidity and mortality.[7] Medication errors are particularly prevalent for parenteral medicines, with serious consequences for patients.[8–10] Hence, the implementation of safe reconstitution practices is critical to ensure appropriate patient safety in Europe.[11–17] Patients in countries outside Europe, notably the USA, have also been harmed by parenteral medicines following incorrect reconstitution.[18–20]

Although guidance on reconstitution has been established in some countries, for example, the UK,[21] this is not the case across much of Europe. This article focuses on the reconstitution of injectable parenteral medicines and the work carried out at the European level to improve patient safety for reconstitution.

BACKGROUND TO RESOLUTION CM/RES(2016)2[22]

The European Directorate for the Quality of Medicines and HealthCare (EDQM), a Directorate of the Council of Europe (CoE), traces its origins to the Ph Eur Convention. The 38 Member States and European Union (EU) that have signed the Convention are committed to achieving harmonisation of the quality of medicines throughout Europe and beyond.

The EDQM provides the technical secretariat to the European Committee on Pharmaceuticals and Pharmaceutical Care, which is responsible for the EDQM's activities in the area of safe use of medicines, supported by its subordinate Committee of Experts on Quality and Safety Standards in Pharmaceutical Practices and Pharmaceutical Care (Council of Europe) (hereafter: Committee of Experts).

A working party of the Committee of Experts was formed, chaired by HS (coauthor). This working party involved delegations from Austria, Norway and Switzerland. In 2008, it issued a survey on quality and safety assurance standards for the preparation of medicinal products to the different countries belonging to the CoE with the aim of establishing whether these standards for preparation of medicines in pharmacies were harmonised throughout Europe. The results[23] showed that there was significant variation between respondent countries. Additionally, there was a gap in standards between preparation of medicines in pharmacies and those manufactured by the pharmaceutical industry. The survey[23] also identified a lack of regulation of reconstitution.

Consequently an Expert Workshop,[24] with representation from professionals from 21 European countries, was held that led to a Resolution[1] on pharmacy preparation, adopted in January 2011. This Resolution[1] included a paragraph (9) on reconstitution of parenteral medicines in healthcare establishments. This paragraph was further elaborated by a new working party, resulting in guidance on good reconstitution practices.[22]

WHAT IS SPECIAL ABOUT RECONSTITUTION?

As explained previously,[2] reconstitution is different from industrial manufacture and also from 'regular' pharmacy preparation because the starting material is an authorised medicinal product. Legally, therefore, reconstitution is in a special position, and hence a separate paragraph (9) was written about it in the Resolution on pharmacy preparations.[1]

Although ideally all reconstitutions would be carried out within the controlled environment of a pharmacy aseptic unit, in practice capacity is generally not available for this. Hence a risk assessment approach is required to enable the healthcare establishment to decide which products must be reconstituted in pharmacy and which, with appropriate safeguards, can be reconstituted in clinical areas.

The need for further work on standards for reconstitution was identified in the abridged survey report.[23] At the time, legislation concerning reconstitution of parenteral medicines was missing or insufficient in most countries of the CoE. The Resolution[1] recommended that national authorities should develop, in cooperation with relevant professional bodies, specific legislation or guidance taking into consideration the factors stated in Paragraph 9 of the Resolution.[1]

Subsequently, to provide greater clarity on the requirements for reconstitution, the Committee of Experts was entrusted with developing additional guidance. Following approval in June 2016, this additional guidance was published as Resolution CM/Res(2016)2,[22] and the parent Resolution CM/Res AP(2011)1[1] was updated and reissued.[25]

Although, in contrast to EU Directives, implementation of CoE Resolutions is not legally obligatory, it is a statement of political will, and Member States are strongly encouraged to adapt their legislation in line with the provisions of these Resolutions.[22 25]

NATIONAL RESPONSIBILITIES

National authorities are required to develop specific legislation and guidance on reconstitution. This should be developed in cooperation with all stakeholders, for example, relevant professional bodies.

Sufficiently detailed, practical information is not always available for a medicine to be reconstituted into a RTA form, in compliance with its marketing authorisation. A national parenteral manual (injectable medicines guide), explaining how to handle injectable medicines, including reconstitution, is recommended and is a responsibility of the professional body. (The required contents are outlined in the Resolution[22].) This document, or database, should be available in pharmacy and in all clinical areas of the healthcare establishment.

RESPONSIBILITIES OF MANAGEMENT WITHIN INDIVIDUAL HEALTHCARE ESTABLISHMENTS

Within individual healthcare establishments, management is responsible for ensuring there are systems for safe reconstitution, for example, by authorising the parenteral manual within its organisation. They should also decide which parenteral medicines should be reconstituted in pharmacy and which can be safely reconstituted in clinical areas. This documented decision should be based on risk assessment, which has led to the development of a hierarchy of parenteral medicines, ranked in order of their reconstitution risk for that specific healthcare establishment.

If the residual risk remains high for any products after risk reduction methods are in place, or if the minimum standards for reconstitution in clinical areas (table 1) are not maintained, the management of the healthcare establishment should ensure that injectable medicines are appropriately reconstituted elsewhere and are available for patients, for example, purchasing them as RTA products, preparing them in pharmacy.

The management of the healthcare establishment is responsible for ensuring that risk review of reconstitution is regularly undertaken and for considering the results of these in the context of their own organisation.

Appropriate training of health professionals, for example, nurses, in line with national professional regulation, is a prerequisite of safe reconstitution. The management of the healthcare establishment is responsible for ensuring adequate resource is available for safe reconstitution to be implemented, including provision of adequate training for staff in clinical areas. The qualifications and competence of all personnel involved in reconstitution should be documented,

Table 1 Minimum requirements for reconstitution in clinical areas[22]

	The quality system in the clinical area needs to encompass reconstitution. Particular attention should be given to ensuring that the following issues are comprehensively addressed in a document that is available to the personnel involved:
1	An overall procedure for reconstitution that covers general aspects such as aseptic handling, hygiene, any special clothing requirements, policy on independent checking, requirement to use immediately and so on.
2	Detailed instructions for the safe reconstitution of each medicinal product, for example, the leaflet authorised by the regulatory authority , the parenteral manual.
3	Procedures for labelling of each reconstituted medicinal product, if it leaves the hands of the person who has reconstituted it, to ensure that the prescription, the product (active pharmaceutical substance, dosage, time of administration of the reconstituted medicinal product) and the patient's identity (given and family names) information match, and the reconstitution procedure is traceable (identity of the person who has reconstituted it).
4	A system for documenting individual reconstitutions, including calculations performed, as applicable.
5	A list of medicinal products (generic name and trade name, where applicable, strength, container, dosage) which can be reconstituted in the clinical area under these minimum requirements.
6	Documented evidence of the competency of personnel to reconstitute medicinal products (qualification document for each person involved in reconstitution, approved by the management of the specific clinical area).

with particular emphasis on their knowledge and skills in performing calculations, hygiene and in aseptic handling techniques.

The management of each healthcare establishment is required to appoint a 'designated person' to be responsible for reconstitution within their organisation. This may be their entire role, or it may be in addition to another function. It is also acceptable for the designated person to create a reconstitution team which they coordinate. The designated person should develop a quality management system for reconstitution, including preparing documentation, ensuring training of personnel involved in reconstitution and approving standard operating procedures. A key responsibility is to approve the decision as to which products are suitable for reconstitution in specific clinical areas. It is, therefore, essential that the designated person has a clear mandate and direct access to the management of the healthcare establishment. They should preferably be a pharmacist, but if not they should have suitable training and appropriate experience to perform this role.

HANDLING RISKS OF RECONSTITUTION IN CLINICAL AREAS

The Resolution[22] gives minimum requirements for reconstitution in clinical areas (table 1). If these are not met in a specific clinical area, reconstitution should not take place there.

There should be a risk management system[26] across the organisation to minimise risks to patients from injectable medicines reconstituted in clinical areas. This involves risk identification, risk assessment, risk management, risk acceptance and risk review.

To aid implementation of the Resolution,[22] a checklist (table 2), taking into account the most relevant risk factors, is provided for the identification, assessment and reduction of risk for reconstitution of medicines in clinical areas. Prospective and retrospective risk analyses are also advocated[22] to provide managers with a more complete and balanced picture of risks.

The risk of microbiological contamination is increased if the method of reconstitution is complex (involving more than five aseptic non-touch manipulations, or involving a complex technique, for example, syringe-to-syringe transfer, filtering and so on). Risk is also increased if the reconstitution requires an open system, where the sterile medicine is exposed to the external environment. The consequences of any microbiological contamination introduced during reconstitution are more severe if the product is susceptible to microbiological growth, for example, propofol, or if it is not used immediately (table 1).

The risk of incorrect composition is increased with a concentrate (which requires further dilution before administration), or where a complex calculation is involved (any calculation with more than one step for reconstitution, eg, double or series dilution, or to prepare for administration, eg, mg/kg/hour).

Other situations with increased risk of incorrect composition are those involving the following:

- Dose unit conversion, for example, mg to mmol, % to mg.
- Complex fractions or decimal places.
- Consideration of a displacement value.
- Powder requiring dissolution during reconstitution. (Risk that the powder does not dissolve completely before administration, causing incorrect composition and risk of particulate contamination of the reconstituted medicine.)

Where use of a part vial or ampoule, or of more than one vial or ampoule, is required, the risk of incorrect composition also increases, as measurements of volumes are required.

Some injectable medicines, due to their inherent pharmacological activity, pose a significant risk of patient harm if not used as intended, for example, insulin and opiates.

This is not an exhaustive list of risk factors and, although there is space on the checklist for any other risks to be recorded, for example, reconstitution procedure longer than usual and unstable active pharmaceutical substance requiring special precautions, each reconstitution should be assessed individually. Similar medicinal products may be assessed as a group to reduce workload. (The feasibility of this depends on the medicine and the situation in the specific clinical area.)

To minimise the risks posed by medicines reconstituted in clinical areas, the Resolution[22] contains some general principles. It requires risks to be assessed for staff carrying out reconstitution. The reconstitution of medicines that are hazardous or pose a safety risk for the staff performing reconstitution, for example cytotoxics and certain biologicals such as monoclonal antibodies, or those that require special attention at the time of reconstitution (filtration, products with slow dissolution, monoclonal antibodies that are fragile and so on) should take place in an environmentally controlled area within the pharmacy or under the full responsibility of a pharmacist. This may also apply to other products, for example, certain biologicals and gene therapy products, depending on the level of risk they pose to operators. Some risks are sufficiently great to dictate that the product cannot be reconstituted in the clinical area and must be provided in RTA form.

The Resolution[22] also states that injectable medicines should ideally be reconstituted as close as possible to their time of administration or use in clinical areas. Medicines reconstituted in clinical areas should be handled and stored as required in the SmPC. (If expiry periods longer than those in the SmPC are allocated, this is outside of the manufacturer's responsibility.)

The use of the risk assessment checklist (table 2) is recommended to identify high-risk products being reconstituted in clinical areas to target them for pharmacy preparation. Alternative risk assessment methods are allowed, however, as long as they apply the same rigorous criteria.

The Resolution[22] requires 'residual risk' to be assessed, after risk reduction measures currently in place have been taken into account. Irrespective of the results of the risk assessment, the aim is to reduce risks associated with reconstitution in all cases. The checklist published as part of the Resolution[22] (table 2, part II) gives examples of possible risk reduction methods that may be relevant.

The Resolution[22] gives practical advice on how to use the risk assessment checklist (table 3). At the end of the checklist, a decision should be made as to whether the product is suitable for reconstitution in the clinical area. A brief justification for the decision should be recorded.

Identification of all risks relevant to a specific reconstitution procedure should be carried out for each product (or group of products), and all risk reduction measures (as in part II of the checklist, table 2) should be considered and implemented where possible. There then remains a 'residual risk' for the specific reconstitution. Parenteral medicines requiring reconstitution should be ranked according to their residual risk (with any relevant risk reduction methods in place). Those higher in the ranking, that is, with the greatest residual risk, should not be reconstituted in clinical areas, and alternatives should be sought, for example, provision of an authorised RTA product (if available) or by preparation in pharmacy. The final residual risk should be acceptable to the healthcare organisation. If necessary, the residual risk may warrant the reconstitution of a

Table 2 Checklist for the identification, assessment and reduction of risk posed by the reconstitution of medicinal products in clinical areas

Product:	Clinical area:	Assessment completed by:	Date:

I. Risks	Assessment
Product-related risks	
A Microbiological contamination	
A1 Is the reconstitution *complex*? ► *More than five aseptic non-touch manipulations involved in the procedure.* ► *Reconstitution includes a complex technique such as syringe-to-syringe transfer, filtering.*	Yes □ No □
A2 Is the product *susceptible to microbial growth*? *For example, propofol.*	Yes □ No □
A3 Does reconstitution involve an *open-system* procedure?	Yes □ No □
A4 Is the medicinal product to be stored, that is, not used immediately?	Yes □ No □
B Incorrect composition	
B1 Does reconstitution involve use of a *concentrated medicinal product*? *For example, slow bolus injection is not advised.*	Yes □ No □
B2 Does reconstitution involve a *complex calculation*? ► *Any calculation with more than one step for preparation (eg, double or series dilution).* ► *Any calculation with more than one step to prepare for administration (eg, mg kg/hour [excludes weight-based calculations where the calculation is part of the prescribing stage]).* ► *Dose unit conversion required (eg, mg to mmol or % to mg).* ► *Complex fractions or decimal places involved mg/hour or mg/day delivery for syringe drivers, for example, in palliative care.* ► *The need to consider a displacement value.*	Yes □ No □
B3 Is the dosage form of the medicinal product to be reconstituted *a powder, lyophilisate, suspension or emulsion*?	Yes □ No □
B4 Does reconstitution involve use of *a part vial or ampoule*, or use of more than one vial or ampoule? *For example, 5 mL required from a 10 mL vial or four times 5 mL ampoules required for a single dose.*	Yes □ No □
C Risks for the staff	
C1 Is the product *cytotoxic*? *For example, overall procedure for reconstitution that covers general aspects such as aseptic handling, hygiene, any special clothing requirements, policy on independent checking, requirement to use immediately.* ► *Documented evidence of the competency of personnel to reconstitute medicinal products (qualification document for each person involved in reconstitution, approved by the management of the specific clinical area).*	Yes □ No □
C2 Is the product *hazardous in any other way*? *For example, biologicals*.	Yes □ No □
D Risks related to the pharmacological activity of the medicinal product	
D1 Does the medicinal product carry a specific therapeutic or pharmacological risk? *For example, insulin and opiates.*	Yes □ No □
E Any other risks not recorded above	
E1 Reconstitution procedure longer than usual.	Yes □ No □
E2 Unstable active pharmaceutical substance requiring special precautions during reconstitution or handling of the medicinal product (*eg, monoclonal antibodies).*	Yes □ No □
E3	Yes □ No □
II. Risk reduction methods currently in place	
a Ready to administer or ready to use product available in clinical area?	Yes □ No □
b Simplest range of concentrations/strengths/forms of parenterally administered medicinal products in use?	Yes □ No □
c Most appropriate vial/ampoule size and concentration in use?	Yes □ No □
d Using a device to convert an open system into a closed system?	Yes □ No □
e Independent second check from another person and/or the use of dose-checking software in place?	Yes □ No □
f Dose calculating tools available, for example, dosage charts for a range of body weight?	Yes □ No □
g Additional guidance available on higher risk parenteral medicines?	Yes □ No □
h Protective equipment available? *For example, an isolator.*	Yes □ No □
i Preprinted format of labels available?	Yes □ No □
j Locally approved protocols available for off-label or unlicensed use of the product?	Yes □ No □
k Infusion monitoring form or checklist in use?	Yes □ No □
l All requirements of handbook fulfilled (SmPC, leaflet)?	Yes □ No □
III. Product suitable for reconstitution in clinical area:	
Justification of the decision:	Yes □ No □

RTA, ready-to-administer; SmPC, summary of product characteristics.

particular product being recognised on the organisation's risk register.

The Resolution[22] states that all remaining risks should be regularly reviewed (annually is suggested) to ensure that the healthcare establishment's decision on the most appropriate location for the specific reconstitution to take place remains acceptable. Since the previous risk review, additional risk reduction methods may have become possible. Some examples of these are the following: a new RTA formulation may have been developed by the pharmaceutical industry and authorised by the regulatory authority, a new system may have been developed to convert an open procedure into a closed one, and the healthcare establishment may have become aware of risk reduction measures in use in other establishments that they could implement in their organisation. Hence it is important to regularly review residual risk to optimise patient safety.

Table 3 Use of the risk assessment checklist[22]

1	All risks associated with the reconstitution of a particular medicinal product (or group of similar products) in a particular clinical area should be identified by ticking 'yes' if they apply.
2	On the basis of the risks identified and the risk reduction methods in place, that is, the residual risk, the manager of the clinical area involved and the designated person should agree whether or not the product is suitable for reconstitution in that specific clinical area, and the reason for this decision. This should be recorded on the checklist (see Resolution[22] section 5.4 - Risk Acceptance).
3	A pharmacist should complete steps I–III of the checklist, and should sign 'assessment completed by' and insert the date into the fields at the top of the page.
4	The checklist should be signed by both the manager of the clinical area and the designated person overseeing the assessment.
5	A date when the risk assessment should be reviewed (suggested at least annually) should be added to the completed checklist (see Resolution 22 Section 5.5—Risk Review).
6	The completed risk assessment checklist should be kept on file in the clinical area. Superseded completed risk assessment checklists should be clearly marked as such but retained for audit purposes.

IMPLEMENTATION OF CM/RES(2016)2

The CoE aims to achieve greater unity between its Member States, among others, by the development and adoption of high-quality, common standards in the public health field. The CoE and its EDQM acknowledge the right of patients to equally safe parenteral medicines and encourage harmonisation of requirements for medicinal products. Reconstitution of medicinal products in healthcare establishments is a core competence of Member States and is not, in practice, harmonised throughout Europe. Therefore, implementation of the Resolution[22] at the national level is strongly recommended to rectify this situation for the sake of patient safety and to ensure that patient needs are fully met.

Although implementation of this Resolution[22] by national authorities requires investment of resource by their healthcare establishments, there are significant benefits to these organisations in terms of reducing harm to patients from the reconstitution of injectable medicines. Support from medication safety organisations within Member States could play a role in facilitating implementation of the Resolution[22] at the national level.

In the UK, the concept of risk assessment of injectable medicines in clinical areas is well established. A risk assessment tool[27] was published in 2005 which became the basis of a Patient Safety Alert[21] requiring risk assessment of practices and individual injectable products reconstituted in clinical areas. There is an ongoing requirement[21] to audit injectable medicines practices in clinical areas. In fact, the principles of the Resolution[22] have been built into the recently updated standards for National Health Service pharmacy aseptic units[28] to ensure that the product profile of these units is based on risk. (Risk assessment allows prioritisation of products of higher risk for pharmacy preparation to make best use of the limited capacity in pharmacy aseptic units.) These standards[28] are implemented via the national audit programme.

Even for those products whose reconstitution is assessed as low risk, pharmacy has a role to play in the training of nurses to raise awareness of the risks to patients from reconstitution of injectable medicines in clinical areas and to give advice on 'non-touch' techniques. Advice has been published in the UK for a nursing audience on this topic.[29] This could also aid implementation of the Resolution[22] in other Member States.

In the Netherlands, a Safety Programme started on 1 January 2008 with the aim of improving patient safety in Dutch hospitals in five years. The Programme includes two pillars: (1) reducing avoidable accidental damage through ten current themes and (2) introduction of a safety management system.

One of the themes was the development of a professional guide 'High Risk Medication: preparation and administration of parenterals'. Experts, on behalf of the Safety Programme, have formulated interventions to improve the preparation and administration of parenteral medicines on the basis of available literature, existing guidelines and national 'good practices'. A new version of the practical guide is in preparation and will include recommendations of the Resolutions.[22 25]

Efforts around the improvement of the reconstitution process are also ongoing in other European countries (eg, Armenia, Czech Republic and France). Nevertheless, further work needs to be done with a view to implementing harmonised measures to guarantee that best practices are in place in healthcare establishments for the reconstitution of medicinal products.

CONCLUSION

There is no justification for patient safety to be variable across the CoE Member States with respect to injectable medicines. In response to the lack of legislation and/or guidance on reconstitution of parenteral medicines within these countries, the Committee of Experts has taken the initiative of developing Resolution CM/Res(2016)2.[22] Implementation of this Resolution[22] enables risk reduction in healthcare establishments and is a major contribution, at the international level, to patient safety from reconstituted injectable medicines.

What this paper adds

What is already known on this subject

- Improper reconstitution of injectables can cause harm to patients.
- The Council of Europe Committee of Ministers has adopted Resolution CM/Res(2016)2 on good reconstitution practices in healthcare establishments for medicinal products for parenteral use.

What this study adds

- A summary of the rationale behind Resolution CM/Res(2016)2, its drafting process and its main content.
- Encouragement to use risk assessment tools to evaluate reconstitution in healthcare establishments.
- Measures to aid implementation of the Resolution that will improve patient safety from reconstituted injectable medicines and enable risk reduction in healthcare establishments across Europe.

Acknowledgements The authors would like to thank the delegations of the Member States participating in the Committee of Experts CD-P-PH/PC, the European Association of Hospital Pharmacists (EAHP) and the European Federation of Nurses Associations (EFN). The authors would also like to thank Dr Sabine Walser (former staff member of the EDQM, Council of Europe), Dr Neerup Handlos (Capital Region Pharmacy, Herlev, Denmark) and Mrs Elizabeth Adams (Chair of the European Nurses Association), who were involved in the drafting process for Resolution CM/Res(2016)2.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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