HOSPITAL PHARMACY EUROPE

ADVISORY BOARD REPORT

What price can you put on safety?

Funded by SUN PHARMA

Sun Pharmaceuticals has developed a range of ready-to-administer (RTA) products, including intravenous (IV) gemcitabine bags and 50ml midazolam syringes for use in intensive care units (ICU). Eight Directors of Pharmacy from six European countries met in Amsterdam to share their experience of RTA products and to consider what the future might hold.

If licensed RTA products were freely available, most hospital pharmacies across Europe would be using them, on the grounds that they guarantee quality and stability, enhance patient safety by minimising the possibility of compounding and administration errors and increasing aseptic unit capacity.

But, of course, they cannot be free, and so their procurement becomes a trade-off between their direct cost and their direct and indirect benefits.

Where and how that line is drawn, and the role of international, European and local guidance in the decision-making process were the focus of discussion of this gathering of European Directors of Pharmacy.

They began with a critical appraisal of RTA 50ml midazolam syringes.

RTA 50ml midazolam ICU syringes

Who are the stakeholders and what is the procurement process?

Across the EU, procurement is discussed/decided between ICU pharmacists and intensive care departmental medical chiefs (cost), with nurses playing a crucial advisory role.

In Spain, there is a regional tender for syringes, with a centralised expert and technical committee establishing requirements and offering the final decision, ratified by the regional healthcare government. A hospital committee proposes, analyses and decides for devices not included in the tender.

In the UK, ICU pharmacists and clinicians (anaesthetists and intensivists) are the major stakeholders, with pharmacy procurement designing any framework/contract.

Costs/Benefits

- The benefit is not to minimise the cost, or to save nurses' time, but to minimise the risk to the patient by preventing administration errors; there is unfortunately no price tag on that, but there was consensus that this is the only way forward.
- If a company has a licensed RTA product with a long shelf life that is terminally sterilised, that would be a winner. As phrased by one delegate: if we can buy it, then we buy it.
- In the interest of patient safety, it is not possible to overstate the importance and benefit of proper labelling and barcoding on syringes and primary packaging. This is an area in which the benefit of industry-prepared RTA syringes can easily be sold. As regards colour coding, this is perceived to be fraught with danger, unless one can be assured of EU-wide uniformity.
- Calculations can be deceiving. One of the delegates from Germany cited the example of 50ml KCl syringes: his hospital's ICUs prepare 700 KCl syringes every day, which, at one minute per »

> When we are so pushed for capacity, why would you make something when there is a suitable licenced alternative at a reasonable cost?
> **Alison Beaney, UK**

DELEGATES

Alain Astier
Formerly Head of Department of Pharmacy and currently Emeritus Professor of Clinical Pharmacy and Biotechnology, Henri Mondor University Hospital, Paris, France

Alison Beaney
Quality Assurance Specialist Pharmacist and Visiting Professor, University of Sunderland, UK

Robert ten Broeke
Head of Pharmacy, Catharina Hospital, Eindhoven, The Netherlands

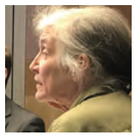
Martin Hug
Chief Pharmacist, University Medical Centre Freiburg, Germany

Irene Krämer
Director, Pharmacy Department at the University Medical Center, Johannes Gutenberg-University, Mainz, Germany

Antonio Lalli
Director of Pharmacy, Hospital San Giovanni di Dio, Naples, Italy

David Lopez
Vall d'Hebron University Hospital, Barcelona, Spain

Andrea Machiavelli
Director of Pharmacy, ASST Cremona, Italy



Theresa Saklatvala
Chair, Content Director, Cogora

Where are the 50ml syringes compounded?

	ICU	Pharmacy	Other
Spain	✓	✓ (if a hazardous drug)	
Italy		✓	
Germany (Mainz)		✓	
Germany (Freiburg)	90%	10%	
Netherlands	Low volume, short shelf life	High volume, long shelf life	
France	✓		
UK			Trust buys the RTU product (to avoid risk and release nurse time). Entire content of 50mg/50ml vials is drawn up in a syringe and infused via a syringe driver

syringe, consumes 700 minutes of nursing time every day (not to mention the risk of miscalculation). But industry must charge €5 per syringe to cover its cost, which the hospital is unwilling to pay – because it is so 'easy' to prepare in house.

Other benefits of RTA 50ml syringes of midazolam include:
– They save preparation time (of between 50 seconds and nine minutes per syringe, according to one delegate)
– They enhance patient safety, as there can be no compounding errors
– They minimise needlestick injury
– They guarantee quality and sterility
– Their 24-month shelf life minimises waste and facilitates stock management
– They do not require refrigeration space
– No re-programming of syringe drivers is required
– Their clear labelling facilitates easy identification (benefit of tall man lettering was singled out)
– They release capacity in aseptic units. On the wards, two nurses are involved in the in-house preparation: one nurse (or pharmacy technician) to prepare and another to check calculations

Barriers to buying
- In the past ten years, the rate of drug shortage has multiplied 20-fold. To guarantee patient treatment, hospitals must retain the capability to prepare products in house where practicable and safe.
- Hospital pumps that are programmed for one company's syringe may need to be re-programmed should the decision be taken to use a different supplier's syringe, lest there be calculation errors introduced.
- Ward storage space and refrigeration, when required, favour the selection of vials over syringes. So, while storage is a barrier, the fact that RTA 50ml midazolam ICU syringes do not require refrigeration is a benefit.
- Diversion is a potential problem, especially for 2mg/ml syringes of midazolam, and they would best be stored in a safe room.
- Misconceptions of the 'affordability' and 'reasonable pricing' of an RTA product may be predicated on a miscalculation in its in-house preparation
- Re-programming of pumps can be perceived as a barrier. However, modern pumps can be re-programmed to accommodate RTA syringes as required, and are therefore not a barrier
- If specific syringes are not on a regional tender, they cannot be procured
- Within ICU, you have automatic machines for dispensing, and the placing of high-volume syringes in these machines is problematical.
- The delegates were of one mind when considering the advantages and disadvantages of two concentrations of the 50ml midazolam syringes. They unambiguously stated that having the choice of two concentrations invited administration errors and recommended only 1mg/ml be available throughout the hospital, and that only 2mg/ml be available in ICU, where the higher concentration would mean you would have to replace syringes less often. Smart pump libraries would have to be rationalised accordingly.

> The benefit is not to minimise the cost but to minimise the risk for the patient
> **Alain Astier, France**

Criteria for new candidates for ICU RTA syringes
- First, we need to look at the nature of the products and at what is currently available, to see where we should be targeting resources.
- Products to be considered for ICU RTA syringes include those that are:
– High risk in terms of either complex preparation, complex calculation or microbiological risk (risk calculation as to be found in the UK defined by National Patient Safety Agency, NPSA 20)
– High volume (e.g. 50ml KCl)
– Anything used in ICU (in standardised concentrations)

RTA IV oncology bags

Who are the stakeholders and what is the procurement process?

Across the EU, it is the hospital pharmacist who exercises decision-making authority, with price negotiation support on offer from purchasing groups.

Decisions are taken on the advice and influence of nurses (usability), clinicians (including heads of speciality units) and the Pharmacy and Therapeutics Committee.

In the UK, the main stakeholder/driver is NHS England, driven by the use of dose banding tables, the minimisation of waste through financial incentives,

Commissioning for Quality and Innovation (CQUIN) points rewarding the purchase of dose banded products and the increased capacity within Trust aseptic units resulting from outsourcing. Contracting sits with regional procurement specialists, and the Trust decides whether or not to take part.

Bag design, connecting sets and saline priming

The delegates were invited to put their artistic skills to work, by way of describing to their colleagues the configuration of IV connecting sets in their countries. In the Netherlands, the bag is accessed with a simple spike (bag will have a spike port), or with a male Luer Lok (bag will have a female Luer Lok, as illustrated below).

In describing configurations in their own countries, the delegates were directed to focus on: Views on saline priming, and preference for spiked port or Luer Lok.

Regarding saline priming, it was pointed out that it takes a substantial amount of time to flush, and that there are no advantages to priming, assuming that you have the correct administration system to assure nurses that there will be no 'contamination' droplets. It is always easy to expel air from the drip chamber of any administration set, now made super easy with the use of a wing valve (CODAN) at the top of the drip chamber. There was 100% consensus that saline priming was unnecessary – the delegate from the Netherlands committing to checking with his pharmacy the following day to learn if wing valves had been adopted.

There was also 100% consensus that spike ports (spikes, not needles) or Luer Loks would be equally acceptable for bag access, and industry was encouraged to equip bags with both spike ports and Luer Loks, so as to service all markets.

Dose banding vs fixed doses

Fixed dose refers to the absolute dose of medicine that meets the respective indication, regardless of body mass index (BMI) or body weight. Dose banding is a series of standardised doses at intervals of BMI or body weight.

The dosing regime may not solely be determined by the SmPC, but also by the prescribing physician: the doctor prescribes the fixed dose, and the pharmacist calculates the individual dose (software) and rounds to the band. Doses may be adjusted (on the authorisation of the physician) to fit pre-filled drug bags so, in this sense, the terms 'fixed dose' and 'dose band' become interchangeable in practical terms.

In the UK, it was suggested that the reason that dose banding is incentivised is because it is seen to save money. As fixed dose gemcitabine bags are available in several volumes, there will always be one concentration that falls within the acceptable 5 – 6% range and, as such, they are used in the UK.

In the Netherlands, dose banding is not allowed. As in Italy, the two main fixed dose 10mg/ml gemcitabine bags are 1,400mg and 1,600mg. This means less of a storage issue, and you use vials for those patients that use other doses.

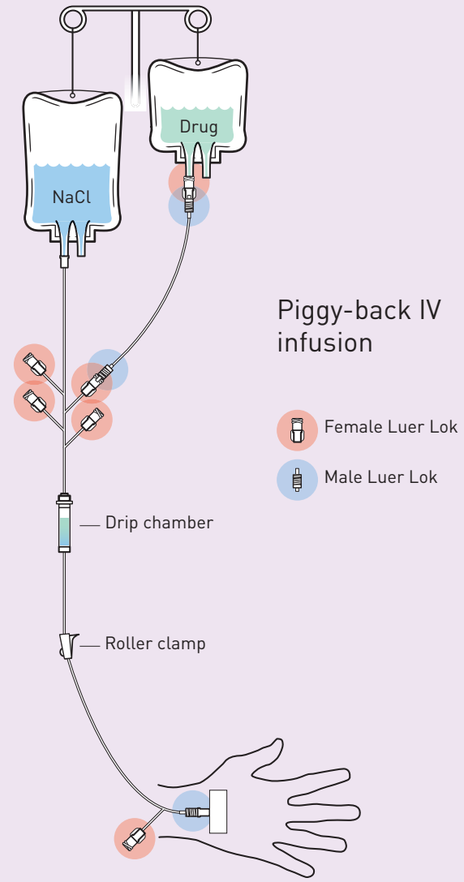
It follows, therefore, that, when Industry is looking to license new products of this type, they might want to look at what dose bands there already are. The key is, above all, to administer the right concentration.

Costs/Benefits
- RTA IV oncology bags improve capacity within pharmacy by decreasing the number of preparations in the compounding unit and decreasing the time in processing each task. So capacity is released within the aseptic unit, at a time when everybody's aseptic unit is under stress.
- RTA IV oncology bags free up robots to get on with other tasks.
- Other benefits of RTA IV oncology bags include:
– There is no waiting time for patients, doctors and nurses
– Medication errors are eliminated
– Quality and sterility are guaranteed
– Risk of exposure to potentially hazardous drugs is greatly reduced
– Risk of needlestick injury is diminished
– Capacity is increased and stress is reduced in compounding units
– Use of medical disposables is reduced
– Waste is reduced

> I prefer to use these special administration systems where I don't have to prime the line
> **Irene Krämer, Germany**

Barriers to buying
- In the past ten years, the rate of normal drug shortage has been multiplied by 20. And that means that hospitals must retain the capability to prepare products in house where practicable and safe.
- Germany pharmacists are incentivised by Health Insurers for compounding gemcitabine bags for outpatients, at a rate of €49 per bag, i.e. an incentive not to use licensed RTAs. This is a major barrier to

Piggy-back IV infusion (Netherlands)



innovation, and needs to be changed in their reimbursement system. There were no reports of similar incentives from other countries.

- Unless the RTA product is supplied in concentrations that are within the acceptable range of a hospital's dose banding, the commercial product will not be used.
- Pharmacists are required to buy and store several RTA bags rather than, say, a single vial: storage is a real problem

Is existing guidance fit for purpose?

Status, standards and advocacy

Throughout the day, mention was made of the two guidelines that internationally inform the choice between licensed RTA/RTU products and unlicensed equivalents made within the hospital: the European Statements of Hospital Pharmacy (European Association of Hospital Pharmacy) and the Standards of Practice. Safe Handling of Cytotoxics (International Society of Oncology Pharmacy Practitioners). Both advocate that, before pharmacy manufacture or preparation of a medicine, the hospital pharmacist should ascertain whether there is a suitably commercially available pharmaceutical equivalent. And it is a sound principle that, if there is a licensed/authorised product that fulfils your needs and that comes at a reasonable price, then you shouldn't be making it yourself, for all the safety and capacity reasons above.

National and local guidance may have greater influence. In the Netherlands, for example, it is illegal to make a medicine if there is an RTA/RTU equivalent on the market, whereas in Germany, you are allowed to manufacture for your own hospitals.

But the situation is not at all clear cut for the sorts of product we are dealing with here. In the UK, for example, the Medicines and Healthcare products Regulatory Agency Guidance Note 14, which is their interpretation of the Medicines Act (1968), says that you should not be using something for which there is a licensed equivalent, but these products are specifically excluded from the scope of that document. Add to this grey area the fact that hospitals that do not make/source their own products are increasingly finding themselves in very difficult situations in the event of drug shortages.

Let us look at midazolam syringes. They are marketed/soon to be marketed across Europe. Hospital pharmacies are already preparing them – the identical product. If the only reason to continue to prepare is to save money, then something is clearly wrong with the guideline. And what if your hospital's pumps are programmed for syringes other than that being marketed? That's always a big problem for companies coming to market with a special syringe.

> The problem is to define what kind of drug must be or should be prepared in an RTA form
>
> **Alain Astier, France**

Existing guidance is insufficient. What is needed is a published consensus, led by pharmacists and founded on a critical analysis of the literature, that aligns with the special situations surrounding these sorts of product (e.g. what concentration, what formulation), defining drugs that should be furnished by the hospital and those that should be manufactured by the company, for example, in an RTA syringe.

Conclusion

There are clearly many situations in which commercially available RTA products are preferred to those manufactured internally. Industry must continue to listen to the needs and opinions of their market, and promote and develop their products accordingly.

For their part, and in co-operation with Industry, pharmacists should lead the way in developing fit-for-purpose guidance.

There is always more that can be done to improve patient safety, regardless of cost, and one tool is clearly the continued development of RTA drugs.

Recommendations

In Germany there is the aim to standardise concentrations of products for use in ICU, with the involvement of the Society of Anaesthesiology and The German Society of Intensive Care Medicine. But this is not enough: what is needed is standardised concentrations all over Europe – otherwise, Industry will have a problem choosing which products to prepare. What we need is a consensus between all countries as to which products they need, in which concentrations, to make it more efficient for Industry to produce – then perhaps they will become more affordable.

Meticulous barcoding and labelling on syringes, bags and primary packaging of all RTA products is a significant driver of their use as they minimise the likelihood of administration error. There is a call for standardised barcoding across the EU.

RTA gemcitabine bags would be very useful in outpatient clinics, where patients and staff are currently often kept waiting for hours for Pharmacy to provide in house.

Existing guidance is insufficient. What is needed is a published consensus, led by pharmacists and founded on a critical analysis of the literature, that aligns with the special situations surrounding these sorts of product (e.g. what concentration, what formulation), defining drugs that should be furnished by the hospital and those that should be manufactured by the company, for example, in an RTA syringe.

There was also 100% consensus that spike ports (spikes, not needles) or Luer Loks would be equally acceptable for bag access, and industry was encouraged to manufacture both types, so as to service all markets.

There is preference in some quarters to have RTA 10mg/ml gemcitabine bags available in fewer volumes – 140ml and 160ml seem to be preferred – because having currently six from which to choose is too complicated and takes up too much storage space. This means less of a storage issue, and you use vials for those patients that use other doses.

Products to be considered for ICU RTA syringes include those that are:

- High risk in terms of either complex preparation, complex calculation or microbiological risk (risk calculation in the UK defined by National Patient Safety Agency, NPSA 20)
- High volume (e.g. 50ml KCl)
- Anything used in ICU (in standardised concentrations)

Products recommended for RTA availability include:

- 1 unit per ml insulin in 50ml syringe
- Cisplatin
- Oxaliplatin
- Epinephrine and norepinethrine (syringe)
- Amphotericin (stability issues nonwithstanding)
- Piperacillin and tazobactam (if made in house, nurses will draw up before fully dissolved)