SAGAR BEJALWAR, BD MEDICAL - PHARMACEUTICAL SYSTEMS

Sagar Bejalwar is a Global Marketing Manager at BD Medical – Pharmaceutical Systems, where his responsibilities include developing prefillable syringe solutions that most closely address drug, product manufacturer and clinician needs. Mr Bejalwar holds an MBA from Texas Christian University (Fort Worth, TX, US) and also a Bachelor's degree in Electrical Engineering from the National Institute of Technology, India.

Over the past three decades, BD has worked collaboratively with drug and product manufacturers to put solutions in place, avoid disruption to manufacturing and to ensure regulatory readiness. This approach has been highly successful and has earned BD a reputation for developing innovative technologies, which helps companies achieve ambitious time-to-market goals. BD's long collaboration with biopharmaceutical companies has allowed it to anticipate emerging needs, improve components and find solutions to complex delivery requirements.

In this interview, Mr Bejalwar discusses the product and clinician needs in delivering hyaluronic acid (HA) for cosmetic applications. He describes the problems that may arise when existing syringes are used to deliver HA, the substantial unmet needs, and what an optimal solution looks like.

Q Please could you give a brief overview of HA, what it is used for, and how and by whom it is typically administered?

A Hyaluronic acid is a naturally occurring substance in the body which is usually indicated to be used in dermo-cosmetics, intra-articular (IA), intra-ocular and vesico-ureteral reflux. HA in general is non-active and is not expected to have pharmacological and toxicological effects.

The viscosity of HA dermal fillers in cosmetic applications is found to be high. We are also observing that the viscosity of HA is increasing on an ongoing basis. Low reticulation dermal fillers may be used for hydration of skin and ageing prevention whereas a high reticulation may be used for dermal filling applications. Moreover, HA in cosmetic applications can have an effect in a week and may last for six to 12 months.

HA dermal fillers are usually administered by a dermatologist or a nurse depending on the country. It is normally delivered through a needle of around 27–30 G. Dermal fillers, being very viscous and having a gel type formulation, can exert a substantial pressure on the syringe tip and needle during administration. This pressure may challenge the connection of the syringe and needle leading to issues such as the needle popping off or leakage of HA.

There are different techniques for administering HA. For cosmetic applications HA may be delivered intradermally (ID) or through a subcutaneous (SC) route when the face or chin is to be restored and with a low angle of injection. The low angle of injection and high viscosity of HA makes administration of the product even more challenging.

Q What problems do users encounter when delivering HA dermal fillers with current devices?

A Current HA dermal filler products delivered through a syringe and needle may not be optimised to withstand the pressure that a viscous formulation such as HA exerts. One of the main problems that arises is rotation or disconnection of the Luer lock adapter (LLA). Rotation or disconnection of the LLA may lead to an insecure connection and may cause the needle to disassemble from the syringe. Rotating LLA and needle ejection can effectively lead to leakage of the HA product during administration.

45% of dermatologists have experienced leakage with HA syringes according to a recent international survey. The survey was conducted in February 2018 through a voice-of-customer (VoC) research survey of 87 dermatologists in the US, EU and Asia and was carried out by The MarkeTech Group (Davis, CA, US). Reducing the risk of this leakage thus represented a major unmet need. Ideally, we do not want leakages or spills in a clinical environment as this can expose a patient directly to HA and also cause disruption in the clinical work-flow. Leakages and spills may also portray an unprofessional image in a clinical setting adding to the patient's anxiety. In order to address the mentioned issues, it is necessary to ensure that the connection of the syringe with the needle is sufficiently robust and provides a secure delivery mechanism to the patient. A safely connected syringe and needle combination may enable the HA product to be injected optimally providing a safe and satisfactory experience to the patient.

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There is an increasing demand for more robust syringe delivery systems that can withstand the pressure the viscosity of HA exerts during administration.

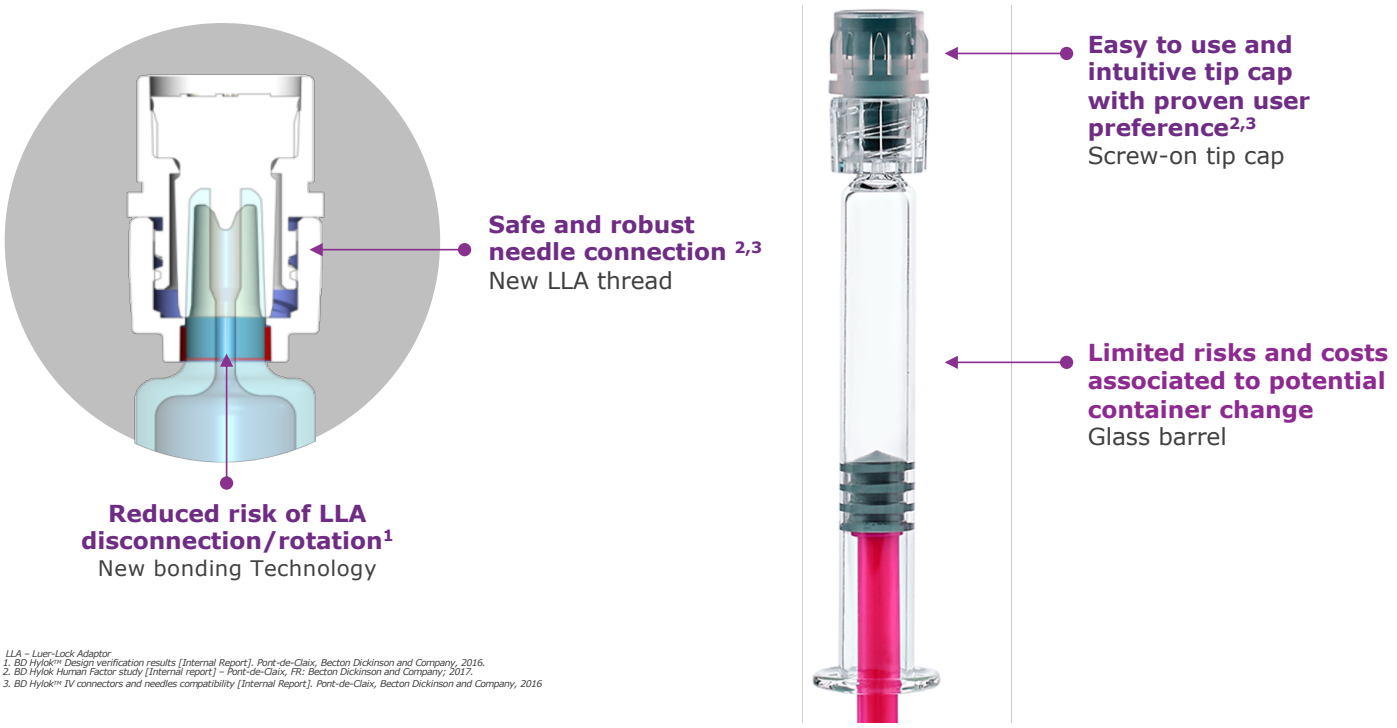

Figure 1: The BD Hylok™ syringe design.

Q Still focused specifically on the delivery of HA dermal fillers in cosmetic applications, what are the most important requirements HA product manufacturers have of prefillable syringes?

"Issues of leakage due to needle disconnection and LLA rotation are considered top priorities for HA manufacturers."

A Issues of leakage due to needle disconnection and LLA rotation are considered top priorities for HA manufacturers. This finding is based on VoC research conducted by The MarkeTech Group in November 2017 wherein 36 respondents including managers in manufacturing, quality, R&D, procurement, marketing and sales, and general management across the EU and Asia were interviewed.

We have come to realise that HA product manufacturers are primarily interested in sourcing a syringe that meets their filling and manufacturing requirements, and also addresses end-users' administration needs. Additionally, inertness of the syringe when storing and delivering HA has been found to be a need with HA manufacturers. In fact, 72% of decision makers in the HA industry expressed in an international study, a preference for glass over plastic. They favoured the material's inertness and resistance to steam sterilisation. The international study was based on the previously referenced survey conducted in November 2017.

Smooth and predictable gliding that is provided through a glass syringe is an attribute that is desired with the HA product manufacturers and end-users. Additionally, glass syringes are supplied by multiple suppliers with a large variety of configurations, enabling manufacturers to manage business-continuity risks. Glass may also appear aesthetically appealing when used in dermo-cosmetic applications.

Another requirement we have identified for HA manufacturers is syringe barrel resistance to steam sterilisation after the syringe is filled with the HA formulation. Steam sterilisation can be considered a standard by many when filling in HA or other compounds into the syringe. Therefore, it is critical to have evidence showing resistance of the syringe to steam sterilisation.

Q Can you tell us whether BD has a solution to address needs in HA dermal filler administration with respect to HA manufacturer and end-user requirements?

A Yes, we do have an optimal syringe delivery solution for HA delivery. The solution, BD Hylok™ syringe, has been commercially available since December 2018 and is currently available in a 1 mL format; the most commonly used format for HA delivery in dermo-cosmetic applications.

The BD Hylok™ syringe (see Figure 1) is a glass, prefillable syringe specifically designed to provide a robust needle connection through a patented, strongly affixed LLA during HA delivery. The LLA of BD Hylok™ is affixed using new bonding technology effectively reducing the risk of LLA rotation and disconnection during use. The syringe is designed with a New LLA thread that enables a safe and robust needle connection. Additionally, BD Hylok's intuitive screw-on tip-cap, is preferred by users over a standard clip-on tip cap as evidenced by a human factors study carried out internally by BD in 2017.

BD Hylok™ is resistant to steam sterilisation, is supplied with a technical data package to support HA manufacturer development and registration and is expected to be compatible with existing HA filling and packaging lines.

From a solution development perspective, we have been iterating BD Hylok™ over the past few years through end-user and HA manufacturer feedback and also through internal testing and validation studies. Solution developmental efforts have also been backed by qualitative and quantitative market research.

Q What performance validation has been conducted with BD Hylok™ for HA dermal filler delivery?

A BD Medical – Pharmaceutical Systems conducted a simulated-use human factors study to evaluate the usability of BD Hylok™ syringes among several routes of administration for injectable medications and products. This study aimed to assess that the connectivity of BD Hylok™ syringes is safe and effective when used by nurses and dermatologists injecting viscous product such as HA through the ID, SC and IA routes. The study also aimed to validate participant understanding of the BD Hylok™ product usage instructions in elation to optimally and securely screwing the needle on to the LLA of the syringe. The user population in this study entailed 15 nurses with experience using IV needles and IV catheters and 15 dermatologists with experience injecting patients with HA fillers for cosmetic purposes. The study design consisted of two phases, learning and validation and market peer comparison. The validation study results demonstrated that BD Hylok™ is safe and effective when used by trained intended users – nurses and dermatologists – and the intended uses, with viscous product such as HA as well as non-viscous products.

Based on performance of the BD Hylok™ syringe during the initial validation phase, no patterns of error for nurses and dermatologists during needle connectivity were observed. In the validation phase, a 100% success rate was recorded. In fact, BD Hylok™ syringe showed significantly lower failure rates compared to a market peer. LLA rotation was found to be the main cause of the significant difference between BD Hylok™ and the market peer.

In summary, in 859 injections that were performed by nurses and dermatologists in the human factors studies, no LLA rotation or disconnection was observed. And in 105 injections performed by nurses and dermatologists, no needle disconnection occurred when the needle was screwed in tightly.

Q How does BD Hylok™ perform relative to market peers after being subjected to different sterilisation modes?

A BD Hylok™ withstands both ethylene oxide (EtO) and steam sterilisation. Pull-out force – the force required to pull out the LLA – and rotational torque performance were tested after two EtO and two steam sterilisation cycles at 121°C, for 20 min. Market peers' performances were compared after one EtO and two steam sterilisation cycles at 121°C for 20 min. After EtO sterilisation, conditions were simulated in an environment where the glass syringe is prefilled with HA and the LLA subjected to forces/torque. After steam sterilisation, the resistance of pull-out force and rotational torque were calculated by subjecting the adapter to forces similar to those which it would be subjected to by end-users when screwing on the needle.

> "In 859 injections that were performed by nurses and dermatologists in the human factors studies, no LLA rotation or disconnection was observed."

Peer and competitor benchmarking showed that the BD Hylok™ LLA on average resists a pull-out force three-times higher than that of its peers (Figure 2). The rotational torque that BD Hylok™ can withstand is almost five times higher than that of its peers (Figure 3).

This robust LLA provides confidence to dermatologists and nurses to strongly screw on the needle without worrying about it disconnecting or rotating, or about consequent filler leakage and spillage concerns.

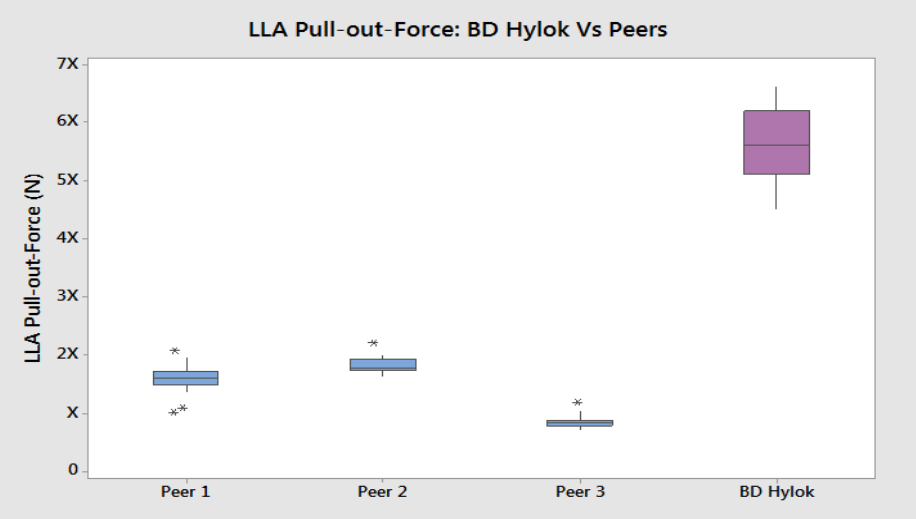

Figure 2: On average BD Hylok™ LLA resists pull-out forces three-times higher than that of its peers (BD Hylok™ and BD Hylok™ competitor syringes performance evaluation [internal reports] – Pont-de-Claix, FR: Becton Dickinson and Company; 2018).

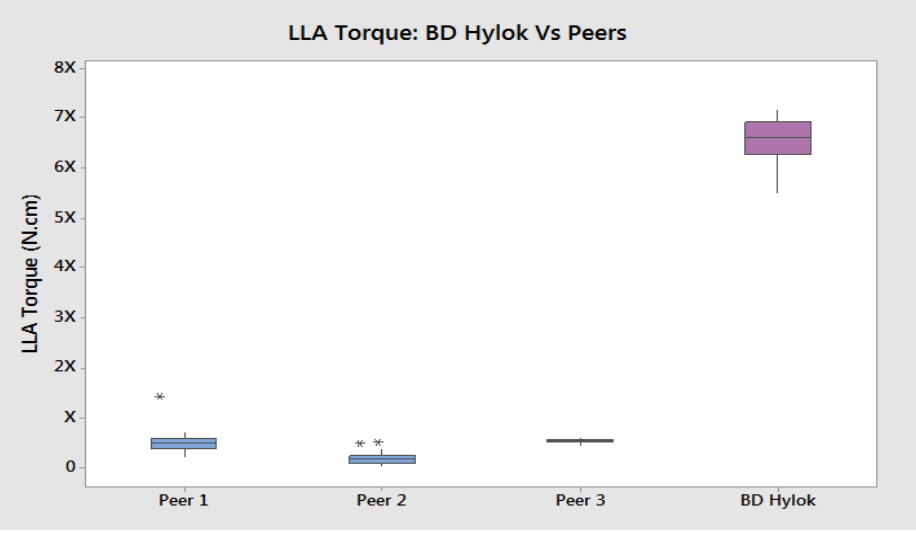

Figure 3: On average, the BD Hylok™ LLA resists rotational torque five times higher than that of its peers (BD Hylok™ and BD Hylok™ competitor syringes performance evaluation [internal reports] - Pont-de-Claix, FR: Becton Dickinson and Company; 2018).

Medical Support

- Non clinical and clinical data
- Human Factor Engineering (HFE) testing data

Regulatory Support

- Worldwide registration service
- Timely and accurate Regulatory Affairs package
- Consultative / training services
- Life cycle management strategy

Formulation and Analytics

- Extractable / leachable data set
- Analytical services

Distribution and Sales

- Logistics services deliveries
- Certificate of Analysis

Container / Device Selection and Customisation

- Early sample deliveries through BD Accelerate Program
- Compatibility with drug from mechanical and chemical standpoint
- Co-development partnering for customisation and rapid prototyping
- Functional test services
- Sample filling (Not For Human Use)

Filling, Assembly, Labeling and Packaging

- Technical support (machine and fill-finish)

Figure 4: BD's range of services complementing its product offering.

"BD's partners know that we have an extensive offering around regulatory, technical services and medical affairs, so they know that they will be provided with relevant data supporting the successful development and commercialisation of their products in BD Hylok™ syringes."

Q Thinking about the commercial development, what is the current status in terms of regulatory and technical data relative to BD Hylok™?

A As part of the offering to HA manufacturers, in addition to the BD Hylok™ product itself, we provide a robust, extensive data package to support development and registration.

The package includes but is not limited to: quality statements, human factors user studies summary, product usage instructions, performance assessment; and regulatory support to enable a smooth transition to BD Hylok™ from an existing syringe or enables adoption in case a new HA product is being launched.

BD's partners know that we have an extensive offering around regulatory, technical services and medical affairs (Figure 4). We are well positioned to provide our HA partners with relevant data supporting the successful development and commercialisation of their products in BD Hylok™ syringes, be that for initial container/device strategy or for lifecycle management.

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THE DIFFERENCE OF ONE DRUG DELIVERED

SECURE IN YOUR HANDS, SAFE FOR YOUR PATIENTS*[1,2] At BD, we're dedicated to improving the delivery of injectable drugs, one patient at a time. That's why we developed the innovative **BD Hylok™** glass prefillable syringe for hyaluronic acid. The BD Hylok™ glass prefillable syringe addresses end users' and manufacturers' concerns caused by the high viscosity of hyaluronic acid, such as needle disconnection and luer-lock adapter rotation. With its strongly affixed, patented BD Luer-Lok adapter for safe and robust needle connection,[1,2,4] the BD Hylok™ glass prefillable syringe delivers superior performance[5] for end users. Discover the difference of advanced technology. **Discover the new BD.**

*No needle disconnection, no BD Luer-Lok™ Adapter rotation or disconnection[1-3]

1 BD Hylok™ Design verification results [internal report]. Pont-de-Claix, France: Becton Dickinson and Company; 2016. **2** BD Hylok Human factor study [internal report]. Pont-de-Claix, France: Becton Dickinson and Company; 2017. **3** BD Hylok™ IV connectors and needles compatibility [internal report]. Pont-de-Claix, France: Becton Dickinson and Company; 2016. **4** Hallynck, Wools, Maritan, Devouassoux. 2016. Adaptor for a needleless device and method for connecting said device thereon. U.S. 2016/0158518 filed July 22, 2014, and issued June 9, 2016. **5** BD Hylok™ and BD Hylok™ competitor syringes performance evaluation [internal reports]. Pont-de-Claix, France: Becton Dickinson and Company; 2018.

Learn more at **bd.com/InnovativeSyringe**

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