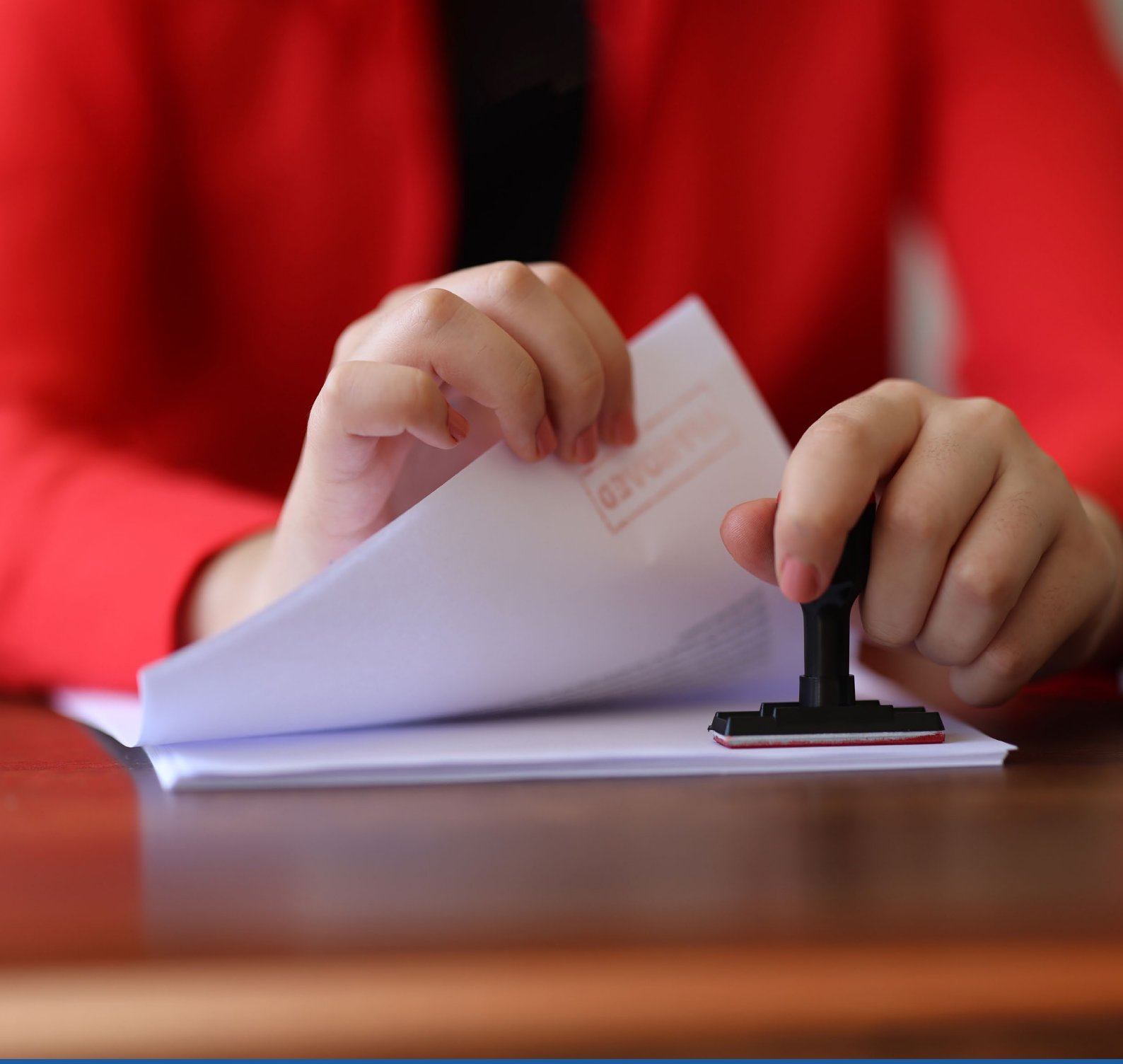

Excellence in pharmaceutical distribution and the critical role of Good Distribution Practice (GDP)

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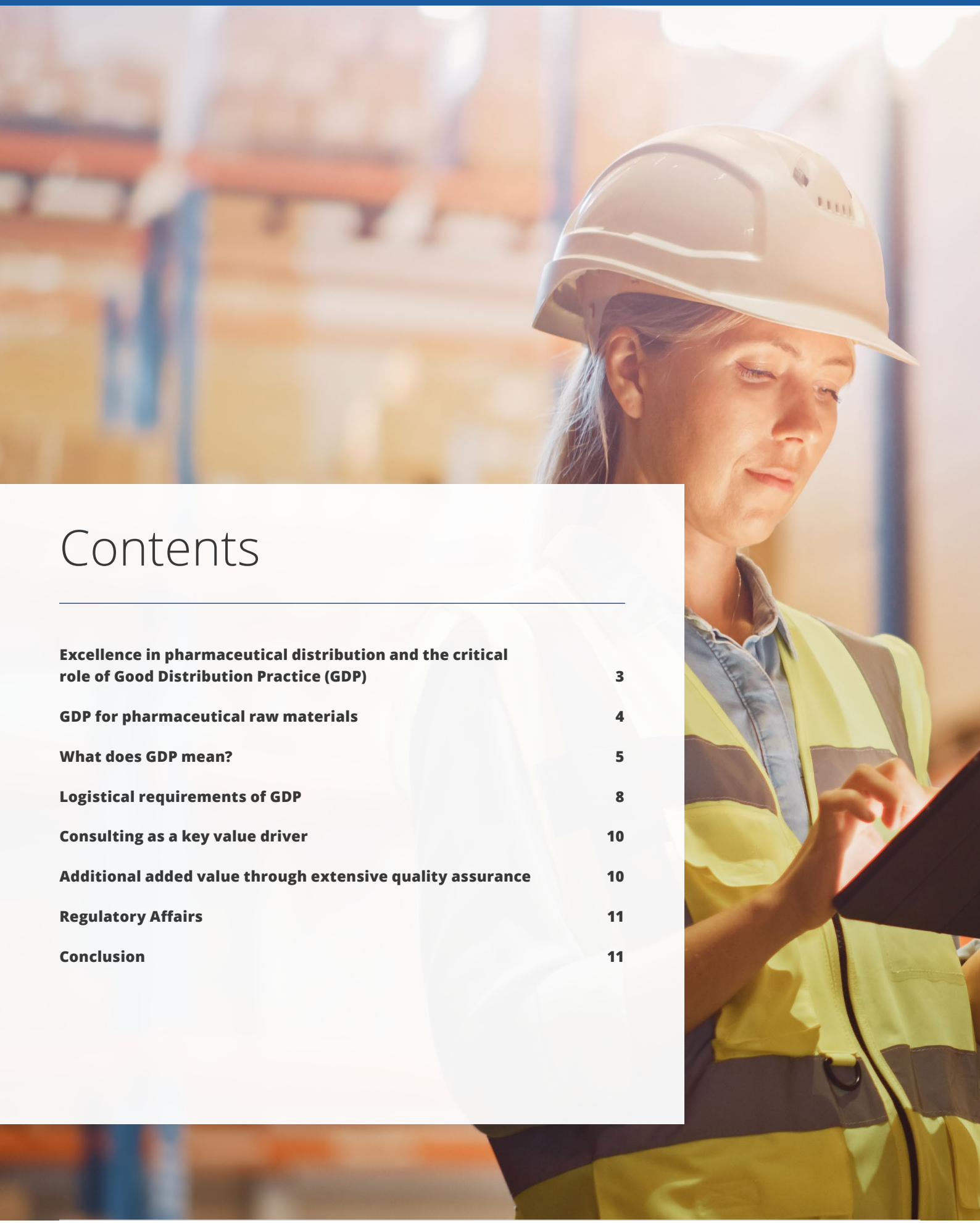

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Distributors play a key role in the supply of raw materials to the manufacturing industry. Particularly in the heavily regulated pharmaceutical industry, their role extends far beyond the simple legal function of the purchase and sale of raw materials. In addition to logistical efficiency and cost optimisation, quality assurance and technical support must also be provided. Thus, distributors make a vital contribution to securing production processes and fulfilling high quality standards.

For the manufacturer, the distributor is a multiplier enabling it to supply a much larger number of customers. Above all, however, a professional distributor takes ownership of the goods and thus accepts responsibility for the quality of the products it handles, which is especially crucial in the distribution of pharmaceutical raw materials.

Andreas Lekebusch, Global Business Director at Biesterfeld, explains what makes a distributor of pharmaceutical raw materials into a valuable partner:

"It's about fulfilling a role that involves more than simply processing business transactions. You must accept a responsibility both to the manufacturer and to the customer. By making the fulfilment of market-specific regulations and GDP guidelines, as well as support and consulting throughout the distribution process, a natural part of your business processes, you can offer your business partners even greater added value."

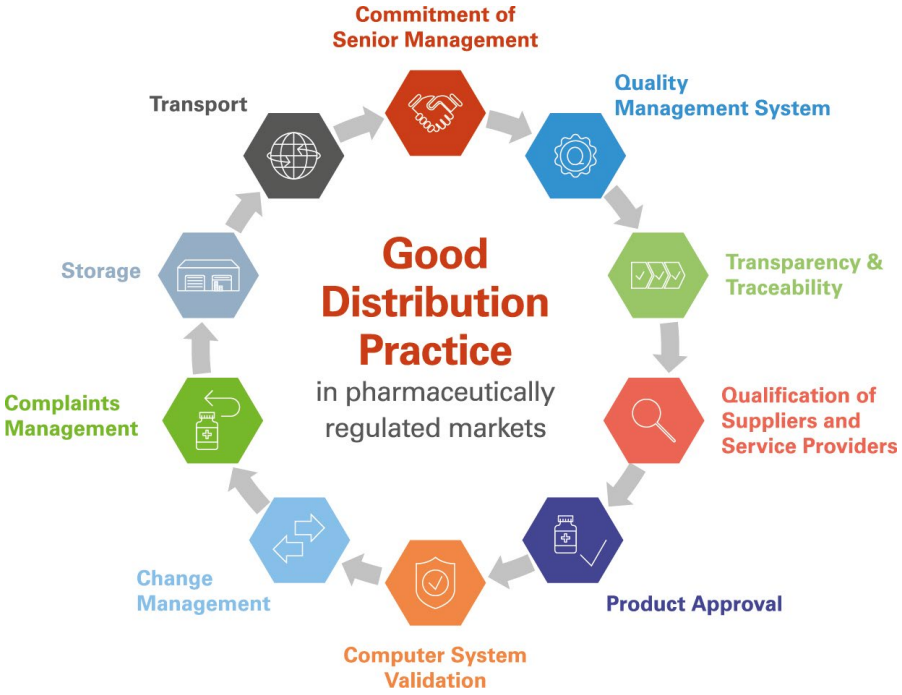
Core tasks:

- **Economies of scale and logistical efficiency:** Distributors handle large purchasing quantities and source multiple products from manufacturers, allowing them to set better prices and reduce freight costs by combining shipping volumes.
- **Risk management:** Distributors maintain an inventory of stock. This increases product availability, reduces lead times and ensures punctual delivery even when supplies are required at short notice.
- **Quality assurance and compliance:** In the distribution of pharmaceutical raw materials, distributors ensure that the quality and integrity of the delivered materials is maintained and the required flow of information is assured – all in accordance with the standards of Good Distribution Practice (GDP).
- **Technical support and consulting:** Distributors use their extensive practical expertise to advise customers, so that they can supply the right products and solutions for the customer's requirements from their extensive portfolio.

Nowadays, many distributors are already very well set up with respect to GDP. However, some still have room for improvement. This makes it all the more important to pay attention to quality and regulatory processes when choosing a distributor for pharmaceutical raw materials and active ingredients. Distributors which serve multiple industries, in particular, should emphasise the special status of pharmaceutical products in their business operations.

This paper outlines the critical and quality-assuring function of distributors in supplying the market with pharmaceutical raw materials. Taking the example of Biesterfeld, one of the leading international distributors of products and solutions in the specialty chemicals and pharmaceutical industries, it describes how GDP requirements are implemented and what additional measures the company takes to offer genuine added value to its customers and partners.

GDP for pharmaceutical raw materials



Historical background:

In 2022 and early 2023, there were multiple cases of contaminated cough and fever syrups, which resulted in the deaths of hundreds of children. As had occurred in previous cases, glycerine with a high proportion of toxic components had found its way into the supply chain to drug manufacturers. In spite of contradictory information being provided, the manufacturers relied on the container labels and the analysis certificates supplied and failed to carry out the required tests on the raw materials.

Because there is a long history of incidents of this type, in 2004 the World Health Organization (WHO) published the "Good trade and distribution practices for pharmaceutical starting materials" (GTDP). These are aimed at members in the supply chain for pharmaceutical raw materials and also serve as a template for industry-specific guidelines and/or legally binding regulations for industry associations and government agencies.

Legal background:

Since the amendment of the EU Community code relating to medicinal products for human use (Directive 2001/83/EC), introduced in 2001, by Directive 2011/62/EU (known as the Falsified Medicines Directive), it has been the responsibility of the drug manufacturer to verify whether the distributor of the active ingredients complies with Good Distribution Practice (GDP). The manufacturer must do this by carrying out audits at its distribution sites (Article 46 f). The distributor is thus placed on the same level as the manufacturer for its activities.

Subsequently, in 2015, the legally binding Good Distribution Practice for active ingredients was established (Guidelines of 19 March 2015 on principles of Good Distribution Practice of active ingredients for medicinal products for human use (2015/C 95/01)).

As a result of Regulation (EU) 2019/6, Good Distribution Practice is now also legally binding in relation to veterinary medicinal product active ingredients and has been concretely defined in the Implementing Regulation (EU) 2021/1280.

To prevent pharmaceutical scandals such as mentioned previously, not only active ingredients but also other drug components, so-called excipients, must be appropriately handled. Although there are no legal obligations to handle excipients in compliance with GDP, it seems obvious that excipients should also, or especially, be subject to an equivalent standard of quality. On this topic, the International Pharmaceutical Excipient Council (IPEC) has produced a GDP Guide.

What does GDP mean?

The various Good Distribution Practice guidelines require the establishment of clear principles as a basis for the activities of distributors of active ingredients and excipients. These principles include responsibility, diligence, reliability, transparency and traceability. Based on these principles, distributors must establish procedures for quality assurance of active ingredients and excipients. This applies to both the processes involved in physical product handling and administrative procedures. GDP does not provide specific instructions for implementation or even prohibitions, but rather requires distributors to evaluate the rationale behind their own actions and the documentation of these actions.

We will now examine what exactly the GDP guidelines require in administrative and logistical processes and what successful implementation for both pharmaceutical active ingredients and excipients might look like, taking the example of the healthcare segment at Biesterfeld.

Administrative requirements of GDP

The aim is to implement basic structures and principles for the distribution of pharmaceutical raw materials and to ensure a seamless flow of information and the documentation of all activities.

1. Commitment of senior management

GDP requirement:

- Commitment on the part of the company management to integrate GDP requirements into the basic principles of the company's operations.

Biesterfeld:

- The clear commitment of senior management to compliance with GDP requirements is set out in the Corporate Quality Policy. Their active willingness to make all the necessary resources available to map the additional complexity may be regarded as a clear strategic decision. During regular audits, the auditors regard this as a strong sign that activities in the pharmaceutical domain are given the necessary attention.
- In addition, Biesterfeld has decided to officially certify its internal operations and, following a thorough review, received an officially issued GDP certificate for active ingredient trading.

2. Quality management system

GDP requirement:

- Reliable quality management system (QMS) with a clear description of all relevant processes, including the definition of responsibilities.

Biesterfeld:

- Quality management activities are based on a QMS in accordance with ISO 9001, established and controlled centrally by the group of companies. Processes are selectively and specifically supplemented to fulfil the additional requirements of GDP.

3. Transparency & traceability

GDP requirement:

- Fully accessible, complete and transparent representation of all the distributor's activities, including all actors throughout the supply chain.

Biesterfeld:

- At Biesterfeld, traceability is achieved by means of a complex interaction between the quality management system and the implemented software solutions. The validated Enterprise Resource Planning (ERP) system and a corresponding warehouse management system, together with additional software solutions, guarantee 100% traceability for goods movements, complaints processing and batch approval, to just name a few examples. This includes detailed information about responsible individuals, handling processes and the basis for decision-making.
- To create transparency, disclosures can also be issued for all participants in the supply chain and extensive voluntary disclosure documents can be made available on distribution and quality assurance activities. Greater depth of detail can be achieved by concluding a quality assurance agreement. Finally, the customer receives the highest level of transparency and insight through an audit report or a personal audit on site at Biesterfeld.

4. Qualification of suppliers and service providers

GDP requirements:

- Verification of the basic suitability of the supplier or manufacturer of pharmaceutical raw materials.
- Qualification and monitoring of external service providers, such as warehouse operators or forwarders.

Biesterfeld:

- Biesterfeld requests the necessary qualification information from manufacturers of pharmaceutical raw materials. Only after these documents have been carefully scrutinized and evaluated is the qualification process successfully completed. Customers can see the advantage of this process, that they are only offered products from manufacturers with confirmed reliability and Good Manufacturing Practice (GMP) compliance.
- A distributor's most important service providers are the transport companies and warehouse operators it uses. Here too, the qualification process ensures that the company only works with reliable and competent partners. The company also has a quality assurance agreement (QAA) with warehouse operators to precisely define each party's responsibilities. Together with the other qualification documents, these agreements form the basis for the monitoring of the warehouse operator with regular audits carried out by Biesterfeld.

5. Product approval

GDP requirements:

- Clearly defined process for the approval of a pharmaceutical raw material for sale, including scrutiny of the associated documents and containers used for the pharmaceutical raw material.

Biesterfeld:

- The company carries out the approval process with the aid of the validated SAP system by checking all analysis certificates received against the specification. The documents relating to supplier and manufacturer qualifications are also examined. In combination with a successful incoming goods check in the warehouse (see Logistical requirements), the products are approved and then posted from quality inspection stock to unrestricted-use stock.

6. Computer system validation

GDP requirements:

- Validation of software that supports critical processes in the pharmaceutical environment (e.g. product approval).

Biesterfeld:

- The company operates multiple validated systems, including SAP. As part of the initial validation which was performed before a system is put into operation and often in collaboration with external consultants, acceptance criteria are defined and documented for the corresponding critical system functions. Next, suitable test procedures were defined to verify that the system was functioning correctly. Only when a test has been successfully carried out can the system be approved for productive operation.
- For the ongoing life cycle of the computer system, whenever the system is modified, Biesterfeld prospectively performs a validation of the modified or new functions.

7. Change management

GDP requirements:

- Continuous evaluation of external and internal changes and identification of necessary measures to manage and communicate the impacts to all internal and external stakeholders.

Biesterfeld:

- The company applies comprehensive change management, which continually and reliably monitors both external change notifications and internal changes (e.g. new storage locations or altered distribution channels) and sends them to all relevant participants within a defined past time frame with the help of the validated SAP system.

8. Complaints management

GDP requirement:

- Complaints should be recorded and assessed in a structured process.
- Rapid flow of information between all stakeholders.

Biesterfeld:

- The company first enters every complaint in its own complaints database. In subsequent processing, the details of the complaint are thoroughly investigated, the risk is assessed and the company defines whether the cause of the complaint lies within Biesterfeld's sphere of responsibility (primarily transport damage) or that of the manufacturer of the pharmaceutical raw material (primarily quality complaints). Immediate measures can then be introduced, for example notifying other customers of the affected batch and quarantining any remaining stock. If the cause of the complaint falls within the manufacturer's sphere of responsibility, the complaint is promptly forwarded to the manufacturer to enable them to investigate the complaint and draw up a final complaint report.

Logistical requirements of GDP

The aim is to maintain the quality of the pharmaceutical raw materials during storage and transport.

1. Storage

GDP requirements:

- GDP-compliant warehouse with an effective quality management system, the processes of which ensure the maintenance of product quality and packaging integrity.
- Prevention of mix-ups with materials in quarantine (quarantined/damaged).
- Training management to establish quality awareness among employees.

Biesterfeld:

- Biesterfeld works with partners who have introduced and implemented GDP processes. All quality-related processes are strictly governed by a quality assurance agreement between the distributor and each of its partners.
- When incoming goods are checked, product details such as integrity, shelf life and batch number are recorded using a reliable four-eyes principle. It is also at this point that products are directly classified into ‘standard‘ products and pharmaceutical raw materials.
- In the high-bay warehouse, pharmaceutical raw materials are physically separated from ‘standard‘ products in a special access-controlled and temperature-monitored area. The distributor stores hazardous materials in a separate warehouse, where both the relevant strict legal requirements and GDP processes are implemented.
- Damaged or quarantined goods are placed in a separate, access-controlled quarantine area. This ensures that they cannot contaminate other products and/or be shipped accidentally.
- When goods are shipped, the four-eyes principle is applied to ensure that no mix-ups occur and that the goods are packaged securely for safe transport. As a basic principle, pharmaceutical raw materials are distributed in the manufacturer‘s original, unaltered containers.
- The whole process, from goods receipt to storage and goods issue, is supported by an electronic communication system. An EDI interface between the warehouse operator‘s warehouse management system and Biesterfeld‘s validated SAP system ensures an efficient and error-free information flow.
- Thanks to regular training sessions, employees always have up-to-date knowledge of the correct and GDP-compliant handling of pharmaceutical raw materials with their challenging requirements.

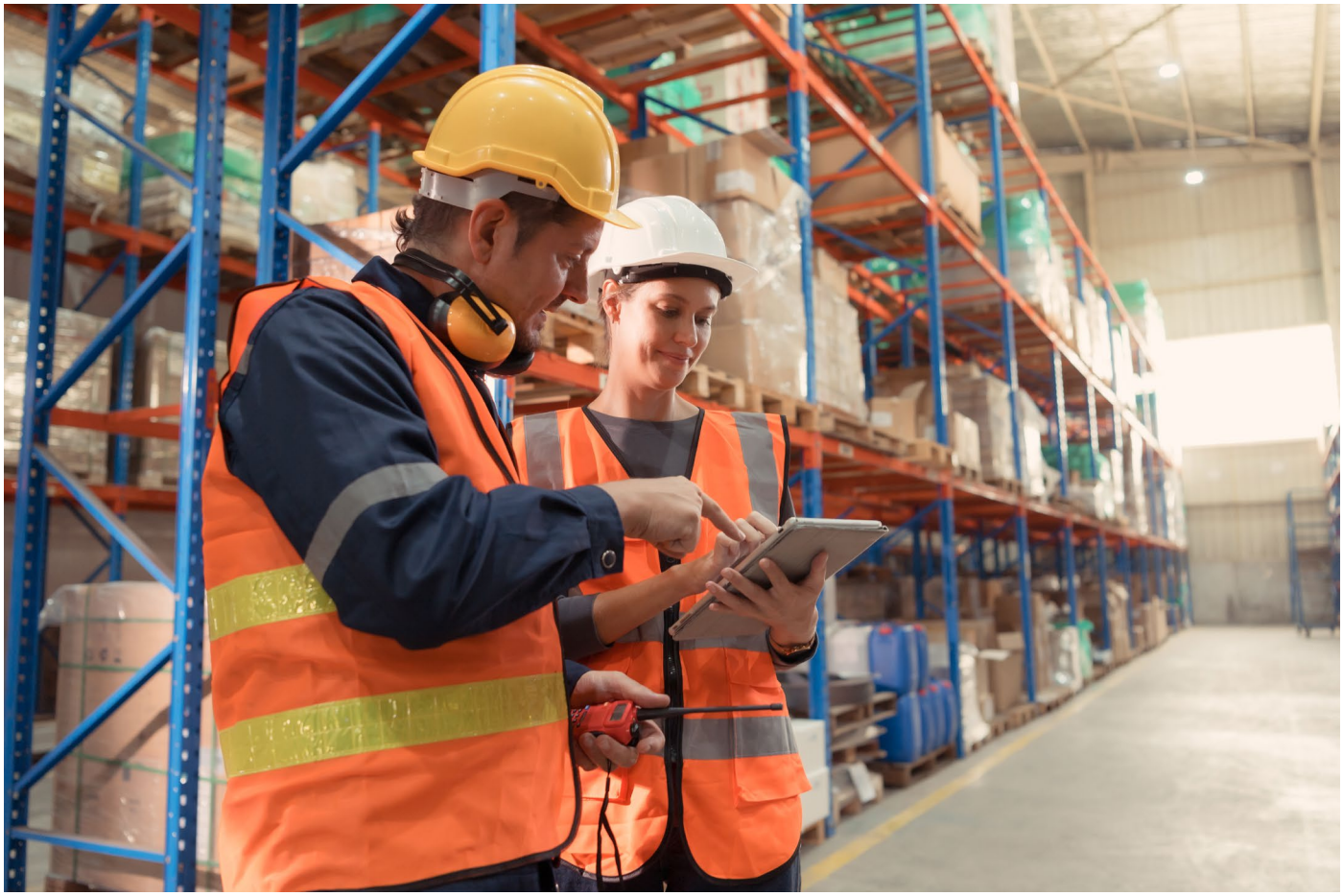
2. Transport

GDP requirement:

- Transport of pharmaceutical raw materials under the quality assurance conditions stated on the label by the manufacturer.
- Knowledge of the identity of the freight carrier and traceability along the supply chain.

Biesterfeld:

- Biesterfeld works with multiple qualified transport service providers who are capable of transporting batches of different sizes safely and cost-efficiently. In particular, this involves the use of LTL charter (Less Truck Load) and general cargo shipments. With LTL charter transport, various shipments from multiple senders are combined and transported together to different recipients. In the case of general cargo deliveries, transport is organized via a carrier network with which the goods are transported from the sender to the customer by way of multiple transshipment centers and transporters. The coordination of quality requirements and consistent compliance with GDP guidelines require planning and detailed coordination between all parties involved. For this purpose, Biesterfeld is in continual contact with its key account logistics partner (partner in the umbrella organization of the general cargo network), which is responsible for the GDP-compliant handling of deliveries, and thus ensures that the defined requirements are passed on to each participant and fulfilled.



Consulting as decisive added value

"Our partners and customers value our complete focus on quality-assuring processes and our willingness to always go the extra mile," says Hartmut Zeller, Global Business Director at Biesterfeld.

With 20 years of professional experience under his belt, Zeller is familiar with the challenges of pharmaceutical and chemical distribution and instills in his team a service mindset of a very high standard.

"Our aim is to provide more than just distribution support. Instead, we support the complete process from purchasing to delivery, providing assistance with technical tasks and even regulatory submissions of approval and modification applications worldwide."

Additional added value through extensive quality assurance

Voluntary disclosure questionnaires

To respond to the drug manufacturer's information requirements for the purposes of supplier qualification, Biesterfeld provides extensive voluntary disclosure. For manufacturers, Biesterfeld can provide similar voluntary disclosure or completed questionnaires. These information packages represent an extensive and high-quality information source and save time during the supplier qualification process.

Quality assurance agreements

A next step in supplier and manufacturer qualification is the conclusion of a quality agreement (QA) or quality assurance agreement (QAA). An agreement such as this defines the responsibilities of the contractual partners with respect to the quality assurance processes and the exchange of information.

Biesterfeld concludes QAAs with its customers and manufacturers to ensure that the responsibilities of all partners in the chain from manufacturer to customer are clearly defined.

Jan-Christian Boy, Head of Quality & Regulatory at Biesterfeld, explains the added value that this creates:

"For the manufacturer it has the advantage of only having to sign one QAA, yet being able to supply numerous customers through one distributor. The customer can rely upon the fact that the QAA clearly defines and guarantees the quality-related responsibilities of all participants. For us this is a natural part of our service offering, and for our partners a decisive additional benefit."

Audits

For the procurement of pharmaceutical active ingredients, the supplier qualification described above is insufficient by itself. Here, the drug manufacturer has an obligation to audit the suppliers and manufacturers of active ingredients.

Biesterfeld assists its customers in carrying out manufacturer audits themselves or having them carried out by independent audit firms. The reports provided by

these specialist firms are of high quality and information density, and Biesterfeld can also assist with the distribution of such reports.

Biesterfeld itself was audited by a specialist audit firm in 2017 and has been regularly ever since. A JAVfX audit report for Biesterfeld is also available.

Change notifications

Before Biesterfeld passes on a manufacturer's original change notifications, the contents are first assessed and any necessary clarification is sought from the manufacturer. In this way Biesterfeld makes sure that all further changes thus triggered are communicated fully and transparently throughout the supply chain.

Any queries regarding notified changes are bundled by Biesterfeld, the necessary clarifications are sought from the manufacturer and the queries are then communicated as a single package to customers. In all cases, rapid and efficient communication for all parties is ensured.

Complaints management

The structured complaints process allows complaints about transport damage to be processed quickly and efficiently in the interests of the customer. In the event of quality-related complaints, Biesterfeld can often provide substantial feedback and deal fully with the complaint without having to consult with other parties.

However, should any clarification be needed from the manufacturer, this is based on extensive information, allowing the manufacturer to respond to the customer quickly and efficiently. Biesterfeld actively monitors the complaints process and, if necessary, provides the customer with interim reports until a final complaint report is available.

Regulatory Affairs

For approval purposes, drug manufacturers must provide detailed information about the active ingredient a drug contains, for example with regard to the production process, control and stability. To this end, manufacturers must provide active ingredient dossiers, for which they can use different formats (ASMF, CEP, US-DMF, etc.).

As an expert partner in the pharmaceutical supply chain and an experienced holder of a CEP for guaifenesin and an ASMF for tripelennamine, Biesterfeld has extensive knowledge of regulatory affairs. With this experience, Biesterfeld is in a position to advise and assist customers and active ingredient manufacturers worldwide in the successful submission of approval or modification applications. If specifically required, close expert support can also be provided for the preparation of regulatory active ingredient dossiers or individual sections thereof.

In this way, the company makes a significant contribution to the maintenance of existing markets and the establishment of new ones.

Conclusion

An experienced distributor with extensive expertise in the international pharmaceutical industry, a strong quality awareness, established processes and industry-leading certifications can offer decisive added value to manufacturers and customers. A partnership of this kind not only significantly reduces potential risks but also results in greater efficiency and reliability, which ultimately ensures the safety of the final product and compliance with regulatory requirements.

Imprint

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