c&en BRANDLAB

SAFE AT EVERY STEP

New supply chain regulations will impact how pharmaceutical companies ensure the integrity of their chemicals

spectrum® CHEMICAL MFG CORP

TABLE OF CONTENTS

INTRODUCTION

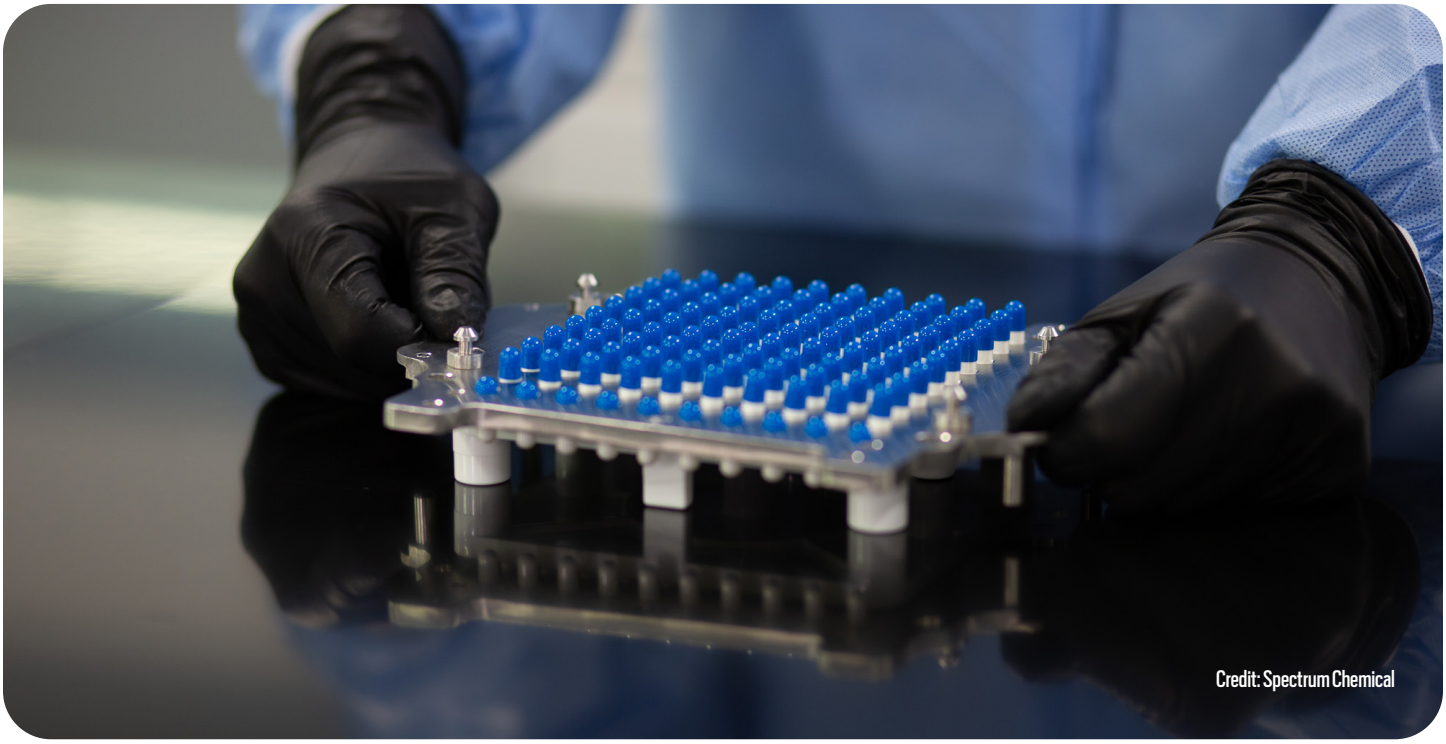
In 2012, a fungal infection stemming from a contaminated anti-inflammatory and immunosuppressant drug killed about 100 people and sickened more than 700 others in the US. The multistate outbreak of fungal meningitis was caused by preservative-free methylprednisolone acetate, a steroid administered intravenously, that had been improperly sterilized. The contaminated doses were distributed by the New England Compounding Center in Framingham, Massachusetts.[1] The compounding pharmacy had been working outside its state license and shipping drugs that were mislabeled and improperly sterilized.

During the subsequent investigative trials, the US Food and Drug Administration (FDA) and the Centers for Disease Control were asked why regulators didn't act sooner. Their response was simple—they had to defer to local Massachusetts authorities.[1] In 2013, Congress signed into law the Drug Quality and Security Act,[2] which has two parts: the Compounding Quality Act and the Drug Supply Chain Security Act (DSCSA). The first component of the act, which went into effect immediately, gave the FDA more control over drug compounding and established requirements for tracing drugs throughout the manufacturing system. The second part, the DSCSA, goes into full effect in 2023, but manufacturers, distributors, and wholesalers are gearing up.

The DSCSA and other regulations are intended to keep small-molecule and biologic drugs safe in an increasingly fragmented pharmaceutical ecosystem. The complexity of a globalized chemical industry, in which chemicals and reagents used to make a drug may originate in multiple countries, enhances efficiencies but can also increase risks, and regulations may differ from country to country. This e-book will highlight the coming changes in regulations that apply to drug manufacturers, the need for and application of these regulations in both the small-molecule and biologic drug arenas, and the challenges of maintaining a robust, safe drug supply chain.

REFERENCE

1. US Food and Drug Administration, "Former Supervisory Pharmacist of Defunct New England Compounding Center Resentenced in Connection with 2012 Fungal Meningitis Outbreak," press release, content current as of July 21, 2021, https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/press-releases/former-supervisory-pharmacist-defunct-new-england-compounding-center-resentenced-connection-2012.
2. The Drug Quality and Security Act, Pub. L. No. 113–54 (2013), https://www.govinfo.gov/content/pkg/PLAW-113publ54/pdf/PLAW-113publ54.pdf.



New regulations for the drug supply chain impact small-molecule drugs as well as biologics.

CHAPTER 1

KEEPING UP WITH REGULATIONS

AROUND THE WORLD

Over the past 50 years, the pharmaceutical industry has become a web of raw ingredient suppliers, manufacturers, packagers, distributors, and wholesalers located around the world. This globalization requires that regulatory agencies find ways to rely on one another's work to eliminate redundancy and expedite the sharing of information such as manufacturing site inspections, safety data, and clinical assessments.[1] While regulators such as the FDA and the European Medicines Association (EMA) have found ways to share information with each other while maintaining control of their own jurisdictions, more system-wide interagency cooperation is needed. The increased transparency by the DSCSA should help regulators around the world.

> **"At the end of the day, the market application holder—whoever's marketing the drug—is responsible for the product."**
>
> *- Christopher Borths, senior principal scientist at Amgen*

By 2023, under a provision of the DSCSA called enhanced drug distribution security (EDDS), a digital database will track chemicals as they move through the supply chain—from raw material to finished pharmaceutical. Being able to trace where materials originate not only assures that all components of a drug have been handled properly at all points throughout the supply chain but also allows companies to adjust during crises, including natural disasters and pandemics. While most chemical companies keep a healthy supply of starting materials on site, "it's important to understand where all your chemicals originate and to do a risk assessment of what a potential shutdown in a geographical region might mean," says James Luchsinger, vice president of business development and distribution at Spectrum Chemical. "You may think your supply chain will be unaffected because the impacted region doesn't directly supply a particular intermediate, but looking deeper you might find that another intermediate depends on a raw material from that region," he adds.

That includes all the other companies that furnished products to make the drug, he adds. In the US, the FDA carries out site inspections every two years to ensure that the manufacturing facility is following protocols and to inspect documentation of the raw materials and components that end up in the finished pharmaceutical. This globalized, interoperable database will give the pharmaceutical company marketing the drug another measure of security.

CHEMICAL TRACKING GOES DIGITAL

Currently, the buyer is provided with the seller's lot number and contact information but little else. If requested, more detailed information can be provided. The changes going into effect in 2023 will take this reporting process to the next level. The EDDS section will require that all chemicals used in final formulations are traceable electronically. Since 2019, the pharmaceutical industry has been piloting something similar, blockchain, to cut down on counterfeit drugs and address the FDA's new requirement to verify serial numbers on returned drugs before selling them.[2,3], Blockchain is a ledger technology that records asset transactions and makes them transparent and unchangeable.[4] This DSCSAs proposed database of drug-related chemicals will be available to all interested parties, from the manufacturer, suppliers, distributers, and packagers to the regulatory agencies and the pharmaceutical end users (doctors, pharmacies, and consumers).

The electronic tracking system for prescription drug manufacturing is detailed in the DSCSA and includes rigid labeling and information requirements. The FDA is developing guidance documents; draft documents are in the comment period at the time of writing and available on the FDA website.[5] Specifically, all manufacturers, wholesalers, dispensers, and repackagers must ensure that the origins and handling history of all chemicals used in the drugs be fully documented.

The US Pharmacopeia (USP), an independent nonprofit focused on ensuring a global supply of safe, quality medicines, has been advocating for an electronic tracking system for years.[6] The organization believes that greater transparency among chemical manufacturers, regulators, and end users is the best way to achieve its goal.[7]

The digital protocols established by the DSCSA are intended to increase the transparency and flexibility of pharmaceutical supply chains. The challenge will be in balancing commercial interests. The law calls for standardizing documentation, including the chemical analysis and handling protocols of all drug ingredients and their synthetic intermediates. To be useful globally, the databases must handle diverse international food and drug regulations. The newly developed database will be a digital logbook tracking origin, manufacture, and handling to help ensure a safe transfer of chemicals between parties.

BE PREPARED

The goals and challenges of managing the drug supply are not so different from those of the food supply: maintain safety and efficacy, eliminate waste, keep production consistent with market needs, and reduce costs. The USP suggests that requiring prescribers (doctors, pharmacies, and hospitals) to report and add to a globalized database what is being prescribed and to how many patients would help regulators and manufacturers better understand the supply of and demand for different pharmaceuticals on the market. In times of crisis or in cases of contamination, an entry like this allows regulators and manufacturers to respond appropriately. While USP is recommending that de-identified patient information be tracked, it is unclear if this will be part of the DSCSA's EDDS electronic database.

To prepare for when that database comes on-line, companies are instituting testing and tracking procedures, as well as compliance documentation. To help drug companies meet compliance requirements, Spectrum Chemical has launched a line of bioCERTIFIED™ chemicals. The bioCERTIFIED chemicals either meet or exceed the testing and handling guidelines for biopharmaceutical or biological applications.

"Our customers want to know the origin of the material they are purchasing," says Jigisha Patel, vice president for regulatory compliance and technical services at Spectrum Chemical. "We can trace our chemicals lot by lot, step by step; any areas where a material was handled by another producer or manufacturer or packager is recorded. We provide all that data to our customers to assure them of our products' quality," she says. Spectrum Chemical follows all current good manufacturing practices (cGMP) and FDA guidance, Patel adds. The company's bioCERTIFIED line is handled in totally controlled environments, and Spectrum Chemical performs quality control testing, offering additional testing if a customer's internal protocols require it.

In anticipation of the DSCSA's database, the USP has proposed and instituted substantial changes to its own quality standards. These call for more rigorous and a wider testing of all chemicals and supplies that come into contact with drugs along the pipeline.

The DSCSA was passed to address two important aspects of drug safety—compounding and supply chain tracking—that are intended to increase confidence in the pharmaceutical industry and to protect consumers. More rigorous testing and tracking is being promoted as a way to avoid impurities in small-molecule drugs and to maintain quality in biologics. A recent case that involved an unexpected contaminant in a class of small-molecule drugs highlighted the need for a well-documented chemical supply chain.

REFERENCE

1. Standards Make the Supply Chain Stronger, US Pharmacopeia website, accessed Sept. 10, 2021, https://www.usp.org/.
2. Mackenzie Garrity, "Pharma Companies Consider Blockchain to Track Counterfeit Drugs," *Hosp. Rev,*, April 1, 2019, https://www.beckershospitalreview.com/pharmacy/pharma-companies-consider-block-chain-to-track-counterfeit-drugs.html, last accessed 11/10/21
3. Spectrum Chemical, *Five Lessons from the COVID-19 Pandemic for Industries Leaning on Chemical Supply Chains,* C&EN BrandLab white paper, accessed Nov. 10, 2021, https://www.spectrumchemical.com/supplychainlessons.
4. Nitish Srivastava, "What Is Blockchain Technology and How Does It Work?," Blockchain Council, accessed Nov. 10, 2021, https://www.blockchain-council.org/blockchain/what-is-blockchain-technology-and-how-does-it-work/.
5. US Food and Drug Administration, Drug Supply Chair Security Act Law and Policies, content current as of Aug. 4, 2021, https://www.fda.gov/drugs/drug-supply-chain-security-act-dscsa/drug-supply-chain-security-act-law-and-policies.
6. Standards Make the Supply Chain Stronger, US Pharmacopeia website, accessed Sept. 10, 2021, https://www.usp.org/.
7. US Pharmacopeia, *Increasing Transparency in the Medicines Supply Chain,* accessed Oct. 6, 2021, https://www.usp.org/sites/default/files/usp/document/about/public-policy/increasing-transparency-medi-

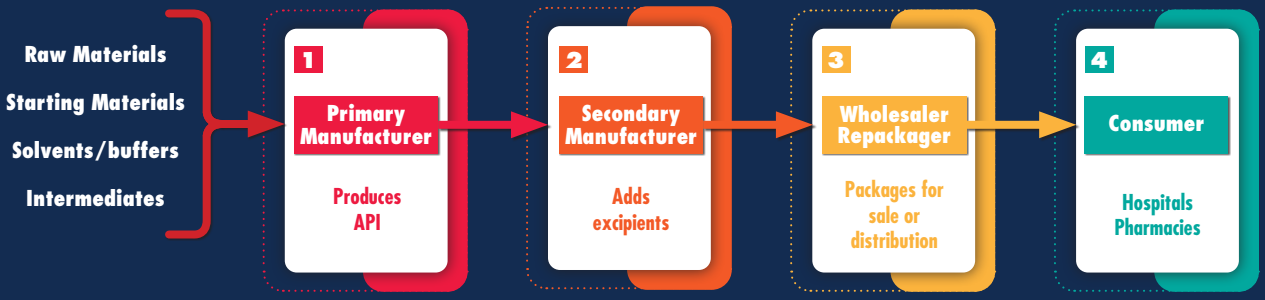
By 2023, a digital database will track chemicals as they move through the supply chain—from raw material to finished pharmaceutical.

WHAT DO YOU NEED TO KNOW ABOUT DRUG SAFETY?

DRUG SUPPLY CHAIN SECURITY ACT (DSCSA)

Slated to go into full effect in 2023, the purpose of the DSCSA is to improve security, responsiveness, and transparency for prescription drugs in the U.S. It calls for an electronic system to identify and trace prescription drugs and their ingredients. This system is intended to improve detection of contaminants and speed up recalls of potentially problematic drugs.

THE DRUG SUPPLY CHAIN



There are multiple factors to consider for tracing and tracking pharmaceuticals. For example, if an active pharmaceutical Ingredient (API) requires multiple synthetic steps, it's important to know the step at which documentation is required. Some DSCSA requirements have already gone into effect, and by 2023 all manufacturers will be required to provide documentation for each step along the drug supply chain.

GOOD MANUFACTURING PRACTICES (GMP)

For all raw materials, intermediates, and packaging materials, the following will need to be provided:

- **Name of manufacturer, identity, and quantity**
- **Results of quality tests and analysis**
- **Records tracing the origin and fate of materials**

HOW CAN COMPANIES GET READY?

- **Become familiar with requirements for documentation and labeling**
- **Work with suppliers to ensure their familiarity with documentation**
- **Find suppliers that already engage in GMP documentation and tracing**
- **Build infrastructure for documentation, labeling, and security**
- **Know where raw materials for intermediates originate**

spectrum® CHEMICAL MFG CORP

c&en BRANDLAB

CHAPTER 2

SMALL-MOLECULE DRUGS

When it comes to manufacturing, there are different levels of concern—and therefore regulation—based on the type of drug, how it is made and delivered, and whether it's the innovator (original) drug or a generic. Orally active drugs are generally less regulated, as the digestive track often eliminates minor impurities. Most biologic drugs are orally inactive—unable to be absorbed or unstable in the digestive tract—and must be delivered via intravenous injection at a health-care facility or self-injection at home.[1] Intravenous drugs are more closely scrutinized, as they are injected directly into the bloodstream without any of the protections provided by the digestive tract.

About 90% of drugs used today fall into the small-molecule, orally active drug category. Some examples are acetaminophen (Tylenol, pain relief), brexpiprazole (REXULTI, antidepressant), and atorvastatin (Lipitor, hypertension). The small-molecule title refers to the active pharmaceutical ingredient (API)—the ingredient in any drug that is responsible for the effect of the drug. The API in a small-molecule drug is usually synthesized, each product subjected to multiple spectroscopic evaluations, which gives the manufacturer multiple opportunities to asses the substance to ensure compound identity and purity. The results of the spectroscopic analysis all add up to the unique molecular fingerprint for the final drug compound.

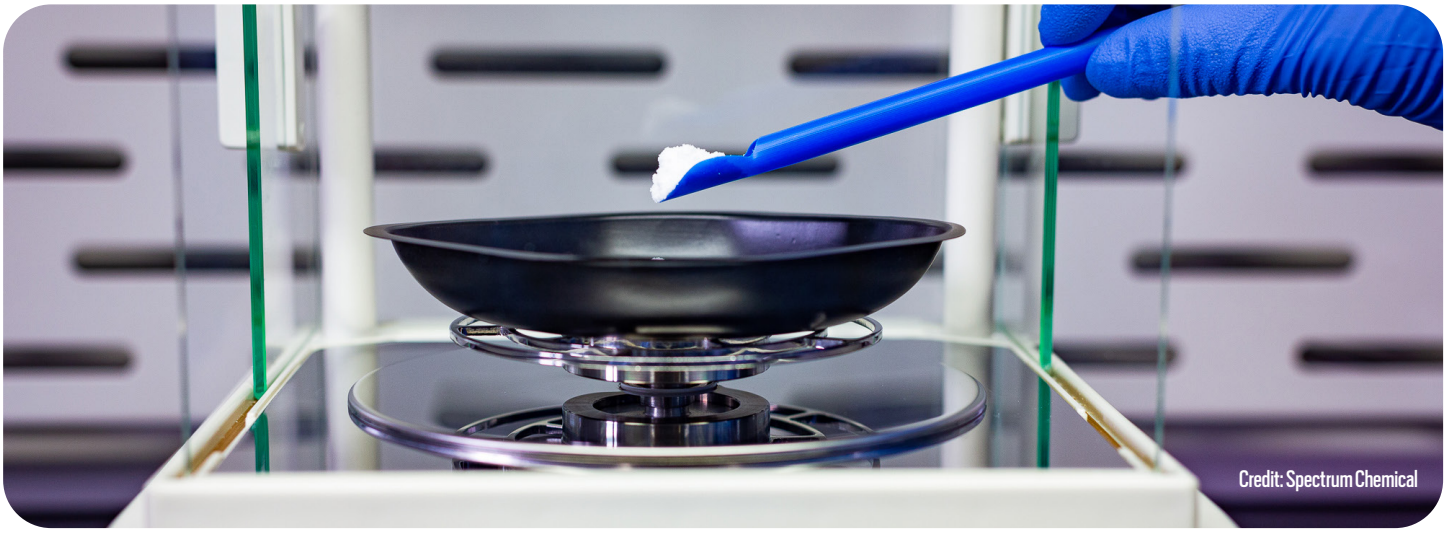
As innovator patents expire, a drug becomes eligible for production as generic versions. A generic drug is defined as one that has the exact same API as the innovator's brand-name drug. While generics do go through FDA approval, they have a much less rigorous application process than their progenitors. In this abbreviated process, the manufacturer must prove to the agency that the generic drug is the same API and has the same absorption rate and effectiveness in laboratory studies as the innovator drug at the same dosage. Since the API has already proved safe, generic drugs do not have to go through clinical trials or be manufactured using the same approach as innovator drugs. This is where trouble can start.

While the manufactured API—whether original or generic—can be easily characterized with standard analytical techniques to ensure the final product's identity and purity, generic-drug makers may take different synthetic paths to arrive at the final API. They may seek syntheses other than those patented to lower the cost of the source materials or may outsource intermediates to different contract companies.[2] Such seemingly small changes can have big consequences: the source materials matter. The accidental discovery of trace amounts of a contaminant in a common blood pressure medicine, valsartan, is a case in point.

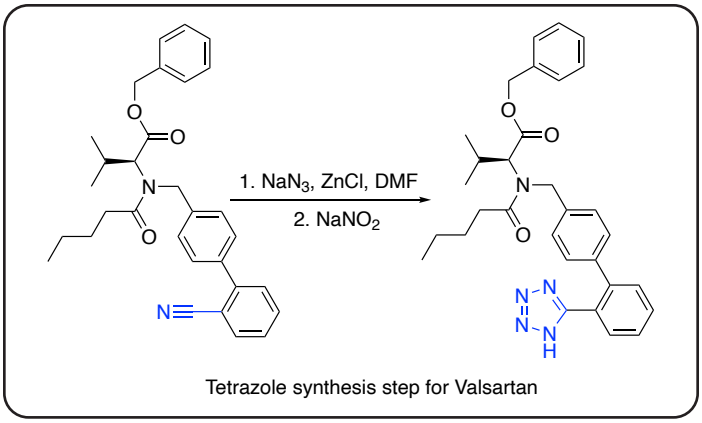
VALSARTAN: *N*-NITROSODIMETHYLAMINE IMPURITY

Valsartan is a member of the sartan class of chemicals, which are angiotensin II receptor blockers used to treat high blood pressure. It is estimated that over 1.8 million people bought valsartan in 2017,[3] but the following year valsartan was voluntarily recalled by over a dozen pharmaceutical distributors.[4]

During a newly implemented screen for mutagens, an analytical chemist found N-nitrosodimethylamine (NDMA)—a suspected human carcinogen—in samples of valsartan.[5,6] After investigating the issue, the FDA and the EMA recalled all drugs containing the sartan-based APIs.[7]



Makers of generic drugs may attempt novel synthetic pathways, with unexpected safety consequences.



Tetrazole synthesis step for Valsartan

The source of the contamination was attributed to a change in the synthesis of valsartan: specifically, the conditions used to form the tetrazole ring (see image above)—the five-membered ring that contains four adjacent nitrogen atoms and one carbon atom. The original conditions in the innovator patent for this transformation used tetrabutyltin azide to add three nitrogens to the cyanide group of the precursor molecule.[8]

To increase yield, the original synthesis was modified to use sodium azide, zinc chloride, and dimethylformamide (DMF) as the solvent for the formation of the tetrazole ring. Once the reaction finished, sodium nitrite was used to quench any excess sodium azide. The problem arose in that DMF has a known impurity, dimethylamine, which under acidic conditions in the presence of nitrites will form NDMA. The NDMA contamination has led to a review of small-molecule drugs by the European Medicines Agency (EMA) and FDA. The main questions being asked include what testing needs to be mandated and how changes in synthetic protocols should be communicated throughout the chemical supply chain.

COMPUTER-ASSISTED RISK ASSESSMENT

Drug companies have prediction tools available to help them predict side reactions and decomposition pathways. A computer program called Zeneth, from Lhasa Limited,[9] can predict degradation products and potential degradation products. "It's pretty good," says Steven Baertschi, president of Baertschi Consulting. "It has the capability of predicting impurities from synthetic steps and API interactions with excipients. According to Baertschi, "Zeneth predicts degradation products from synthetic steps such as acid/base hydrolysis and oxidations, as well as degradations caused from drug-excipient interactions." But in the case of NDMA impurities in valsartan, the change in synthetic method was not communicated to the distributor, which would then not have known to look for this impurity. The EDDS database may include requirements to report changes in synthetic pathways, the reporting of which would increase security and transparency.

MULTIPLE APPROACHES

A multi-pronged approach to risk assessment, if well done, is robust, Baertschi says. Complementary risk assessment strategies include examining synthetic routes for hazardous side products using computer programs like Zeneth and using raw materials that include physical and digital documentation. Together, these approaches help reduce the risk of impurities in the final drug.

Regulators work to ensure the integrity of raw materials as well. Suppliers to final API producers undergo reviews of their standard operating procedures and on-site inspections from regulatory bodies like the FDA and EMA.

> **"Among other things, ensuring drug safety is about working with reputable companies that you have audited and that have a good history of appropriate cGMP and maintaining high quality."**
>
> *- Christopher Borths, senior principal scientist at Amgen*

Amgen's supplier audits include reviews of documentation and operating procedures, as well as inspections, he says. "Basically," he adds, "what the regulatory agencies expect of us, we expect of them."

REFERENCE

1. An Overview of Biologic Delivery Technology, Proven Process Medical Devices website, accessed Oct. 26, 2021, https://provenprocess.com/overview-biologic-delivery-technology#:~:text=1%20Traditional%20Biologic%20Delivery%20and%20Challenges%20for%20New,Device%20Design%20and%20Development%20at%20Proven%20Process.%20.
2. US Food and Drug Administration, Generic Drugs: Questions & Answers, content current as of March 16, 2021, https://www.fda.gov/drugs/questions-answers/generic-drugs-questions-answers#q2.
3. US Department of Health & Human Services Agency for Healthcare Research and Quality MEPS summary tables, https://meps.ahrq.gov/mepstrends/hc_pmed/ accessed Dec. 14, 2021 (page now unavailable, redirected to https://datatools.ahrq.gov).
4. Tien Nguyen, "A Side Reaction May Have Led to Impurities Found in Valsartan Heart Drugs," *Chem. Eng. News online,* Feb. 19, 2019, https://cen.acs.org/pharmaceuticals/process-chemistry/side-reaction-led-impurities-found/97/web/2019/02.
5. Leigh Krietsch Boerner, "NDMA, a Contaminant Found in Multiple-Drugs, Has Industry Seeking Sources and Solutions," *Chem. Eng. News, 98,* no. 15 (April 20, 2020): 26, https://cen.acs.org/pharmaceuticals/pharmaceutical-chemicals/NDMA-contaminant-found-multiple-drugs/98/i15.
6. Derek Lowe, "The Sartan Contamination Story," *Science,* Jan. 4, 2019, https://blogs.sciencemag.org/pipeline/archives/2019/01/04/the-sartan-contamination-story, accessed 9/20/21.
7. US Food and Drug Administration, Warning Letter to Zhejiang Huahai Pharmaceutical, content current as of Dec. 11, 2018, https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/zhejiang-huahai-pharmaceutical-566685-11292018.
8. Andrew Teasdale and Michael W. Urquhart, "Regulatory Highlights," *Org. Process Res. Dev.* 25, no. 8 (Aug. 20, 2021): 1714-18, DOI: 10.1021/acs.oprd.1c00270.
9. Lhasa Limited, accessed Sept. 17, 2021, https://www.lhasalimited.org/products/zeneth.htm.

CHAPTER

3

BIOLOGICS AND BIOSIMILARS

Pharmaceuticals derived from living organisms have grown exponentially with advances in biotechnology. Biologics include protein therapies, messenger RNA vaccines, gene therapies, and other biologically derived products. Roughly 200 biologics have been granted drug approvals from the FDA since human insulin was approved in 1982.

Unlike small-molecule drugs, which are generally taken orally, biologics typically require intravenous or subcutaneous administration in the form of infusions and other injectables. This delivery system demands exceptionally high standards for all drug components. From the API to the buffer that stabilizes it, documentation concerning purity and handling must be scrutinized to help avoid adverse events like the methylprednisolone acetate crisis in 2012.

HIGH COSTS

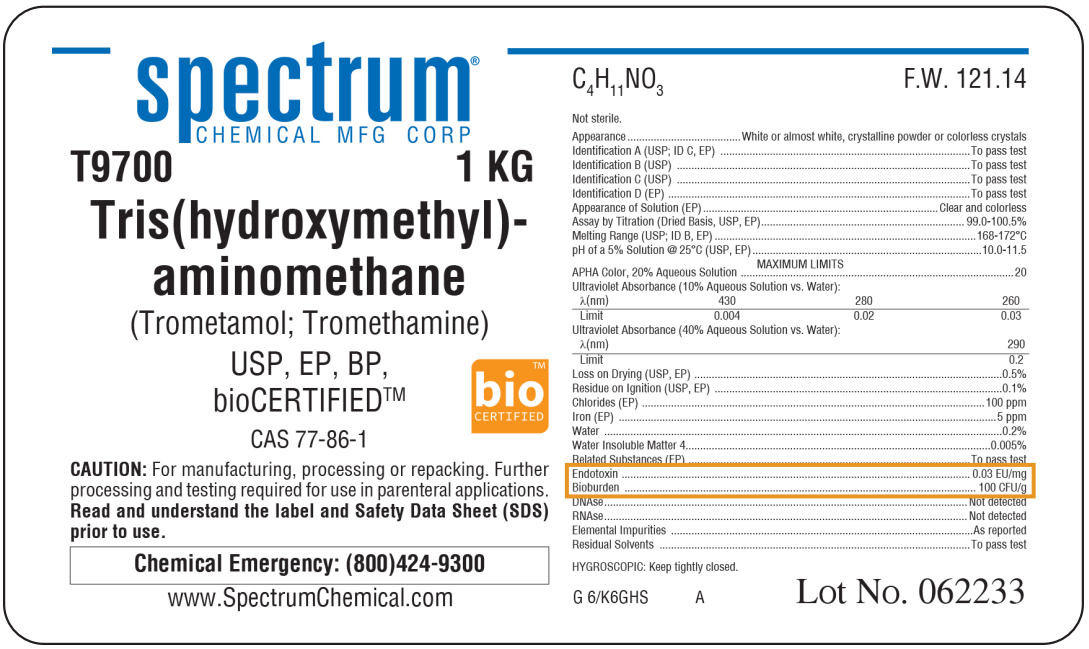
Biologic drugs are improving quality of life for people with conditions like multiple sclerosis (MS), rheumatoid arthritis, and diabetes. Biologics include protein therapies, mRNA vaccines, gene therapies, and other biologically-derived products. But biologics are expensive, for example, a single dose of Rituxan, a monoclonal antibody used to treat autoimmune diseases including MS and neuromyelitis optica, can cost as much as $10,000, and the treatment must be administered every few months.

One factor influencing cost is the complex biomanufacturing process. For example, in protein therapies the gene that codes for the desired protein must be identified and synthesized. Then a host cell must be identified which will produce the biologic. This is the most time-consuming part, as companies typically screen hundreds or even thousands of cell lines. Once identified, this master cell bank is frozen for longevity. These banks ensure that the proteins and antibodies produced are identical.

Often overlooked, buffers are crucial to biologics, serving as growth and storage media. Impurities in a buffer can change fermentation outcomes. “Different trace impurities in raw materials can impact cell growth,” Spectrum Chemical’s Luchsinger says. “And a sizable difference in growth could impact your bottom line, making a viable drug nonviable from a capacity and profit point of view.” Using chemicals that undergo additional rigorous testing, such as those in Spectrum Chemical’s bioCERTIFIED products (see sidebar), is a regulatory requirement for many biologics.

COMPETITION TO DRIVE DOWN COSTS

Market competition in the form of generic equivalent for biologics is being considered to reduce the cost. This isn’t as straightforward as it is for small-molecule drugs, however. Biologics are complex; many factors contribute to the final API



spectrum® CHEMICAL MFG CORP

T9700 1 KG

Tris(hydroxymethyl)-aminomethane

(Trometamol; Tromethamine)

USP, EP, BP, bioCERTIFIED™

CAS 77-86-1

bio CERTIFIED

CAUTION: For manufacturing, processing or repacking. Further processing and testing required for use in parenteral applications. **Read and understand the label and Safety Data Sheet (SDS) prior to use.**

Chemical Emergency: (800)424-9300

www.SpectrumChemical.com

$C_4H_{11}NO_3$ F.W. 121.14

Not sterile.

Appearance	White or almost white, crystalline powder or colorless crystals
Identification A (USP; ID C, EP)	To pass test
Identification B (USP)	To pass test
Identification C (USP)	To pass test
Identification D (EP)	To pass test
Appearance of Solution (EP)	Clear and colorless
Assay by Titration (Dried Basis, USP, EP)	99.0-100.5%
Melting Range (USP; ID B, EP)	168-172°C
pH of a 5% Solution @ 25°C (USP, EP)	10.0-11.5

MAXIMUM LIMITS

APHA Color, 20% Aqueous Solution	20

Ultraviolet Absorbance (10% Aqueous Solution vs. Water):

λ(nm)	430	280	260
Limit	0.004	0.02	0.03

Ultraviolet Absorbance (40% Aqueous Solution vs. Water):

λ(nm)	290
Limit	0.2

Loss on Drying (USP, EP)	0.5%
Residue on Ignition (USP, EP)	0.1%
Chlorides (EP)	100 ppm
Iron (EP)	5 ppm
Water	0.2%
Water Insoluble Matter 4	0.005%
Related Substances (EP)	To pass test
Endotoxin	0.03 EU/mg
Bioburden	100 CFU/g
DNAse	Not detected
RNAse	Not detected
Elemental Impurities	As reported
Residual Solvents	To pass test

HYGROSCOPIC: Keep tightly closed.

G 6/K6GHS A

Lot No. 062233

BioCERTIFIED™ label for tris(hydroxymethyl)aminomethane, more commonly known as Tris buffer. The endotoxin and bioburden testing are critical for chemicals in the biologic supply chain.

Credit: Spectrum Chemical

and currently biologics cannot be synthesized directly unlike in generic formulations.[1] Despite legislation in 2009 allowing the production and marketing of biosimilars, growth has not been as dramatic as it was for the original generic drug industry. This can be attributed to different standards of purity, efficacy, and testing required of biosimilars as well as legal disputes. "There are four approved biosimilars for Humira for example, but none are currently on the market due patent disputes and agreements not to market until 2023," says Susan Sharfstein, professor of nanobioscience at SUNY Polytechnic Institute.

In addition, there is a risk that a patient having success with a therapy may have an immune response to a biosimilar. "Once a patient has had an immune response, the antibodies they develop will recognize a variety of other epitopes on the molecule, and then the patient may also have an immune response to the brand name biologic," says Sharfstein. "This means you may now have eliminated a therapy that was working really well for that patient."

DATABASE REQUIREMENTS

Knowing where all components of a drug come from and how they are handled throughout the supply chain has become increasingly important, especially with injectable medications. A case in point: the compounder's improper sterilization of preservative-free methylprednisolone acetate intravenous solutions, which that led to widespread fungal infections in 2012.

> **"Microbiological contamination is the biggest concern for an injectable or near-injectable product."**
>
> *- Jigisha Patel, vice president for regulatory compliance and technical services at Spectrum Chemical*

DSCSA's database requirements are expected to produce more detailed background on all components of a particular biologic or biosimilar. Data points such as where the starting materials originated, who processed them, how they were tested and by whom will be recorded.

It is still too early to tell if the biosimilars market will grow like the generics industry or if biosimilar production will be vulnerable to quality issues. While many drugs came off patent in 2020, patents that cover the bioprocessing aspects of the innovator biologics have kept many biosimilars from being produced and marketed widely. The need for the requirements associated with DSCSA is clear, however, and will be essential to ensure that buffers, excipients, and growth media are fully tested and traceable.

There are many considerations when buying chemicals for biopharmaceutical manufacturing. "Total price, including shipping, is often the main factor for selecting reagents and solvents, whether for synthesis of small molecules or oligonucleotides," according to Patrick Hrdlicka, a professor of chemistry at the University of Idaho. But when purity matters, such as at end of a multi-step synthetic route, Hrdlicka relies on specific companies he can count on to reliably provide high-quality, high-purity solvents and chemicals.

The balance between the need for affordable pharmaceuticals and pure, stable end products is key to a globally sustainable health-care system. The benefits of a digital tracking system—greater safety and reliable sourcing of raw materials and intermediates—are expected to outweigh the costs. The database being created in response to the DSCSA's EDDS section is just one more step toward a more robust pharmaceutical industry.

REFERENCE

1. Hussain Dahodwala and Susan T. Sharfstein, *ACS Med. Chem. Lett.* 8, no. 7 (July 13, 2017): 690–93, http://doi.org/10.1021/acsmedchemlett.7b00199.

Biologics require additional scrutiny with respect to microbiological contamination.

SIDEBAR

EXTRA TESTING FOR INJECTABLE MEDICATIONS

Because they pose unique risks, drugs destined to be used intravenously require additional testing, according to FDA regulations. Microorganisms can be introduced to the final drug through water, raw materials, the API manufacturing process, added excipients, or packaging materials. Therefore, to ensure a safe product, bioburden and endotoxin testing must occur frequently and at all levels of the drug manufacturing process.

BIOBURDEN

Bioburden testing is a microbial assessment that checks for bacteria and fungi in a drug substance, medical device, or solution. The type of product will determine the acceptable bioburden limit; for biologics, the limit is zero, which makes it critical that anything used in the production of biologics have minimal bioburden. There are three main bioburden tests: membrane filtration, direct plating, and most probable number.[1,2]

In membrane filtration, the sample is passed through a fine membrane, which is then cultured to see if anything grows. Direct plating transfers the sample onto a petri dish for incubation and microbial growth assessment. The most probable number test involves counting microbes in diluted samples using a microscope and statistical methods to estimate bioburden in the bulk sample.

ENDOTOXINS

Endotoxin tests look for specific chemicals—toxins—produced by certain microorganisms. These toxins may cause fevers, infections, sepsis, or death. The bacterial endotoxin test relies on amoebocyte lysate from the horseshoe crab, which reacts with endotoxins in a way that researchers can quantify using three methods: gel-clot, turbidity, and color.[3]

The gel-clot test is considered positive when the sample solution clots in the presence of the lysate. Endotoxins can impact a sample's turbidity and color, changes that can be detected with photometric measurements.

Endotoxin limits differ depending on the product. Unlike for bioburden, these limits are set on the amount of drug, water, or other product being used.[4]

REFERENCE

1. **Millipore Sigma.** Bioburden Testing. *Millipore Sigma.* [Online] [Cited: 12 19, 2021.] https://www.sigmaaldrich.com/US/en/applications/microbiological-testing/bioburden-testing
2. **US Pharmacopeia.** <61> Microbiological Examination of Nonsterile Products Microbial Enumeration Tests. *USP.* [Online] [Cited: 12 19, 2021.] http://www.triphasepharmasolutions.com/Private/USP%2061%20MICROBIOLOGICAL%20EXAMINATION%20OF%20NONSTERILE%20PRODUCTS%20MICROBIAL%20ENUMERATION%20TESTS.pdf
3. **US Pharmacopeia.** q06_current_webpage_stage_6_monograph_23_nov_2011.pdf. *USP.* [Online] [Cited: 12 19, 2021.] https://www.usp.org/sites/default/files/usp/document/harmonization/gen-method/q06_current_webpage_stage_6_monograph_23_nov_2011.pdf
4. **US Food and Drug Administration.** US FDA. *Bacterial Endotoxins/Pyrogens.* [Online] [Cited: 12 19, 2021.] https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-technical-guides/bacterial-endotoxinspyrogens

bio CERTIFIED™

Spectrum Chemical's bioCERTIFIED line of products undergo stringent quality control processes. In-house testing is conducted on all raw materials to ensure they meet or exceed standards set by US Pharmacopeia, as well as specific standards required for biopharmaceutical production. Further, bioCERTIFIED chemicals undergo additional testing for bioburden, endotoxins and elemental impurities such as metals from the catalytic processes.

Additional testing and documentation tailored to meet the needs of customers is a hallmark of the bioCERTIFIED line. Spectrum Chemical provides complete traceability including change control and batch tracing, a dossier of regulatory and scientific information and auditing and quality management. All products are packaged in clean rooms with very specific protocols.

spectrum®
CHEMICAL MFG CORP

spectrumchemical.com

c&en BRANDLAB