

# Discovering the cause of a drug's defect

*Drug manufacturers must follow good manufacturing practices when making their products. When a defective drug causes injury or death, documents showing how the drug was made are key to proving the defendant failed in its duty to consumers.*

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The Federal Food, Drug, and Cosmetic Act (FDCA) provides certain minimum standards that companies must meet when manufacturing drugs.<sup>1</sup> It identifies these standards as good manufacturing practices (GMPs).<sup>2</sup>

If a company fails to comply with the GMPs, the finished products are considered adulterated or misbranded.<sup>3</sup> The act prohibits the introduction of adulterated or misbranded products into interstate commerce.<sup>4</sup> Knowledge of the GMPs can aid in establishing whether a drug is adulterated or whether the defendant manufacturer was negligent in making it.<sup>5</sup>

The FDA is charged with monitoring drug companies' manufacturing practices and with administering and enforcing the FDCA.<sup>6</sup> The act does not allow private enforcement actions because of the possibility that such actions would duplicate state law remedies.<sup>7</sup> However, an FDCA violation may serve as an element of a state products liability action.<sup>8</sup> Violation of safety regulations and

statutes provides a basis for state law negligence claims.<sup>9</sup>

When a pharmaceutical company decides to market a new drug, in addition to ensuring that its proposed manufacturing procedures comply with GMPs, it must also submit its own proposed procedures for a specific drug's manufacture, including testing methods and validations of the proposed procedures and tests.

These procedures are submitted to the FDA for approval in New Drug Applications (NDAs); for generic drugs, the procedures are listed in Abbreviated New Drug Applications (ANDAs). Neither application supersedes the published GMPs, which ensures that drugs meet the act's safety requirements and have the ingredients, strength, quality, and purity that they purport to possess.<sup>10</sup>

The FDA uses the testing and validation data to determine whether a company's procedures are eligible for approval. Once procedures are approved, a company must strictly comply with

them, including the testing protocols no changes to the procedures or testing protocols without prior FDA approval are permitted.

The FDA's regulation of the manufacture of prescription drugs is generally viewed as a minimum standard.<sup>11</sup> The FDA's acceptance of submitted procedures is evidence, not conclusive proof, of the reasonableness of the company's manufacturing practices and procedures, and the trier of fact may assign FDA approval the weight it deserves.<sup>12</sup>

FDA approval to manufacture and market a drug is contingent on the drug company's production and testing of the product according to approved procedures. Failure to fully comply with these procedures constitutes a failure to meet minimum standards and violates the approval. If the patient takes a drug as directed and experiences an injury that the drug was promoted to prevent or has suffered an unlabeled adverse event, the manufacture of the product may be relevant.

In *U.S. v. Barr Laboratories, Inc.*, the initial drug testing that Barr performed in accordance with the approved GMPs found that some drugs were "out of specification" because they did not meet the specifications described in the U.S. Pharmacopeia (USP) or the ANDA.<sup>13</sup> The results occurred because of laboratory operator, and manufacturing errors.<sup>14</sup>

Barr's laboratory testing results reporting that the batches were "out of specification" should have triggered a well-documented failure investigation to determine why the drugs did not satisfy the USP and ANDA specifications.<sup>15</sup> The FDA-approved testing and investigation procedures, which are minimal standards, require that a documented failure investigation be performed. The failure of Barr to follow the testing protocols and the failure-investigation requirements created GMP violations.<sup>16</sup>

Examples of actionable GMP violations include

- failure to have adequate laboratory facilities
- failure to employ well-qualified personnel
- unsanitary storage of materials allowing contamination
- failure to adequately clean laboratory equipment
- failure to test raw materials
- failure to maintain written procedures of production
- failure to test batch uniformity
- inadequate labeling of materials
- inadequate laboratory procedures
- inadequate record-keeping
- failure to follow the approved or established GMPs for the specific product being tested.<sup>17</sup>

GMPs are subject to interpretation and may change over time.<sup>18</sup> If the GMPs are ambiguous, the drug company may refer to scientific literature, industry practice, and FDA letters.<sup>19</sup> But a drug company cannot rely on approved procedures if they become inadequate.<sup>20</sup>

The manufacturing process has three stages: raw materials, work in progress, and finished product. During the raw-materials stage, employees take samples

of the raw materials and test the materials to confirm that they are what they purport to be. Employees then measure and weigh the raw materials in accordance with the drug recipe.

The work-in-progress stage begins once all the raw materials have been added. During this stage, the ingredients are mixed together in strict adherence to the procedures the company submitted to the FDA. Numerous sample tests are conducted during this stage

chromatograph.

Microbiological tests provide information on the presence of any bacteria incapable of being detected by a chromatograph. Sterility testing is essential in the case of an injectable drug.

The product's chain of custody is equally important. The FDA requires traceability of every product. Drug companies assign lot numbers to the drugs they manufacture and ship for sale. The same is true for drugs imported into the

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to make sure the procedures are in compliance. Finally, the drug is a finished product and is stored, packaged, and labeled for shipment.

### **Prefiling Investigation**

When a client comes to you suspecting that he or she has taken an adulterated drug, you should tell the client to save the drug, the container, and all labeling and packaging information. A laboratory must analyze the drug and test for its active pharmaceutical ingredient (API) and for strength and purity. Gas chromatography, liquid chromatography, and microbiological tests are the three most common testing methods used for analysis.

A gas chromatograph separates the chemicals and generates a graph that can become part of the documentary evidence. The graph shows the quantity of each chemical constituent and the presence of any foreign contaminants. Gas chromatographic analysis has been largely replaced by high-performance liquid chromatography, which is faster and applicable to a wide variety of chemicals and mixtures. However, the gas chromatograph is still used for certain analyses where it can provide more accurate or specific data than the liquid

United States.

Lot numbers can be obtained either from the drug label or from the pharmacy that filled the prescription. These numbers are important because they provide the initial direction for your investigation and will lead you to the date, location, and, occasionally, time of the drug's manufacture.

Also, you can get information about a drug company through the Freedom of Information Act (FOIA). You can find out when the last FDA inspection occurred and whether the inspector noted any deficiencies by issuing a Form 483.

A Form 483 will list any violations of FDA regulations that the inspector noted and describe the company's manufacturing problems. Warning letters, more severe than the 483s, may also be

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