The present invention provides for methods of manufacturing a pharmaceutical composition comprising selecting one or more than one starting material to make a liquid active pharmaceutical ingredient; and using the liquid active pharmaceutical ingredient to make a pharmaceutical composition. In another embodiment, the method comprises using a liquid active pharmaceutical ingredient where the liquid active pharmaceutical ingredient is never dried and subsequently reconstituted before making the pharmaceutical composition. In a further embodiment, the composition in a finished dosage form is selected from the group comprising an aerosol, caplet, capsule, cream, injection, ointment, oral suspension, patch, suppository, tablet, or vial. In still another embodiment, the manufacturing steps (production of the liquid API to a pharmaceutical composition in finished dosage form) are carried out on the same manufacturing train. In another embodiment, the present invention provides for compositions manufactured according to the methods disclosed.
PHARMACEUTICAL MANUFACTURING METHOD AND COMPOSITIONS

CROSS-REFERENCE TO RELATED APPLICATIONS


BACKGROUND

[0002] Pharmaceutical manufacturing is a highly regulated industry with numerous complexities including contamination concerns, waste, efficiency, supply reliability and cost. Multiple manufacturing quality control and quality assurance procedures are required by regulatory agencies. These procedures monitor manufacturing processes to ensure and maintain consistency of the processes and the process output. The procedures and regulatory requirements are driven largely by the need for the safety and efficacy of all medications delivered to animals and humans.

[0003] Regardless of the finished dosage forms, including but not limited to vials, prefilled syringes, tablets, capsules, caplets, ointments, or injections, the manufacturing processes for pharmaceuticals are fundamentally the same. They occur in two main stages, sometimes called Primary and Secondary Processing. During Primary Processing, an Active Pharmaceutical Ingredient (API) is produced from the necessary "raw" or "starting" materials. In Secondary Processing, the API is converted into a dosage form or delivery system that is suitable for administration to a human or animal. A finished pharmaceutical manufacturer or dosage form manufacturer (i.e., generally one who carries out Secondary Processing) will formulate the API into its recommended dosage and delivery form(s). The current manufacturing model for the supply of pharmaceuticals typically starts with large scale or bulk API manufacturing. Large batches are produced, approved, stored in various containers, and placed in a warehouse. When an order is placed, the API is then shipped (usually overseas) to the finished pharmaceutical manufacturer, sampled, tested, and stored again until the finished dosage form manufacturing is set to begin. Each step of these processes introduces risk and the supply chain is lengthy, complicated, and fraught with its own obstacles including, shipping delays, exposure to excessive temperatures, and theft.
Consequently, several strategies have been used to increase the efficiency of pharmaceutical manufacturing. One strategy has been to increase the stabilization of the API over time which will reduce deterioration and prolong the shelf-life. Other strategies have been to utilize different particle size operations to improve consistency and manufacturability during further processing. Thus far, however, these techniques have not been sufficiently successful at reducing the risk, cost and time in pharmaceutical manufacturing. Pharmaceutical manufacturing remains highly inefficient, costly and occasionally leads to supply interruptions and drug shortages.

Therefore, there is a need for a method of manufacturing pharmaceuticals that is not subjected to these disadvantages.

SUMMARY

The pharmaceutical method and system having features of the present invention will address these issues, fundamentally altering the approach by which pharmaceuticals are manufactured. The methods and systems comprise producing an API following the traditional technical manufacturing processes but on a much smaller scale, eliminating the final drying step in the API production process, and instead advantageously using the API in liquid form directly as the "feed" for the process that creates the finished dosage form.

Accordingly, in one embodiment of the present invention, there is provided a method of manufacturing a composition in finished dosage form for the treatment of a condition or disease, the method comprising selecting one or more than one starting material to make an active pharmaceutical ingredient in liquid form; and using the active pharmaceutical ingredient in liquid form to make the composition in finished dosage form. In another embodiment, the method comprises using an active pharmaceutical ingredient in liquid form where the active pharmaceutical ingredient in liquid form is never dried and subsequently reconstituted before making the composition in finished dosage form. In a further embodiment, the composition in finished dosage form is selected from the group comprising an aerosol, caplet, capsule, cream, injection, ointment, oral suspension, patch, suppository, syringe, tablet, or vial. In still another embodiment, the manufacturing steps (production of the API in liquid form to a composition in finished dosage form) are carried out on the same manufacturing train. In another embodiment, the present invention provides for compositions manufactured according to the method disclosed.

In another embodiment, the present invention provides for a method of manufacturing a pharmaceutical composition comprising selecting one or more than one
starting material to make an active pharmaceutical ingredient and producing a batch size of the
active pharmaceutical ingredient, where the batch size of the active pharmaceutical ingredient
produced equals the amount required to make the batch size of the pharmaceutical composition
being produced. In another embodiment, the active pharmaceutical ingredient is in liquid form.
In a further embodiment, the pharmaceutical composition is selected from the group
comprising an aerosol, caplet, capsule, cream, injection, ointment, oral suspension, patch,
suppository, syringe, tablet, or vial. In yet another embodiment, the active pharmaceutical
ingredient is never dried and subsequently reconstituted prior to making the pharmaceutical
composition. In still another embodiment, the manufacturing steps are carried out in sequential
steps on the same manufacturing train. In another embodiment, the present invention provides
for compositions manufactured according to the method disclosed. Essentially the active
pharmaceutical ingredient and the finished dosage form, deliverable to a patient, are produced
sequentially during the same manufacturing process. Therefore, the amount of the API being
manufactured is the amount required for the number of finished dosage forms being produced.
This significantly decreases the chances of contaminations and removes several unnecessary,
costly steps in the manufacturing process.

[0009] In yet another embodiment, the present invention provides for a pharmaceutical
composition in a form deliverable to a patient comprising making an active pharmaceutical
ingredient in liquid form and immediately using the active pharmaceutical ingredient in liquid
form to compound a pharmaceutical composition in a form deliverable to a patient. In a further
embodiment, the amount of the active pharmaceutical ingredient in liquid form made equals the
amount of the active pharmaceutical ingredient required to compound the pharmaceutical
composition in a form deliverable to a patient.

[0010] In another embodiment, the invention provides for methods of manufacturing
pharmaceuticals comprising synthesizing an active pharmaceutical ingredient in liquid form
and using the final solution of the active pharmaceutical ingredient as the first production step
in the finished dosage form manufacturing process. By immediately using the API in liquid
form the proposed manufacturing process advantageously excludes having to isolate the API as
a final, purified powder or crystal, or other partially or fully dried material that would otherwise
have to be later reconstituted for manufacture of dosage form(s.) In addition to avoiding the
drying and reconstitution steps when manufacturing an API, other steps also become
unnecessary such as, micronization, milling, or other special procedures for particle size control
prior to initiation of the manufacture of dosage forms.
Therefore, in yet another embodiment, the invention provides for a method of manufacturing a finished dosage form pharmaceutical, the method comprising synthesizing an active pharmaceutical ingredient in liquid form, adding one or more than one substance to the active pharmaceutical ingredient in liquid form to make a pharmaceutical composition, and formulating the pharmaceutical composition into the finished dose form. In another embodiment, the method further comprises selecting the finished dosage form from the group comprising an aerosol, caplet, capsule, cream, injection, ointment, oral suspension, patch, thin film, suppository, syringe, tablet, or vial. In another embodiment, the active pharmaceutical ingredient in liquid form is used immediately after synthesis to make the pharmaceutical composition. In still another embodiment, the synthesizing of the active pharmaceutical ingredient in liquid form and the adding one or more than one substance to formulate the pharmaceutical composition occur in sequential steps on the same manufacturing train. Further, compositions manufactured according to this method are another embodiment.

In another embodiment, the present invention provides for a method of manufacturing a pharmaceutical composition in a sterile deliverable comprising making an active pharmaceutical ingredient in liquid form under aseptic conditions and immediately filtering the active pharmaceutical ingredient in liquid solution form under aseptic conditions into a sterile deliverable. In a further embodiment, the making of the active pharmaceutical ingredient in liquid form under aseptic conditions and filtering the active pharmaceutical ingredient in liquid form into a sterile deliverable occur on the same manufacturing train.

In another embodiment, the present invention provides for a method of making a sterile pharmaceutical complex, the method comprises making an active pharmaceutical ingredient in liquid form and filtering the active pharmaceutical ingredient in liquid form aseptically into the sterile pharmaceutical complex. In a further embodiment, the sterile pharmaceutical complex is selected from the group comprising a vial, syringe, cartridge, or other container.

In still another embodiment, the present invention provides for a pharmaceutical composition for delivery to a patient comprising an active pharmaceutical ingredient where the active pharmaceutical ingredient was never dried from a wet cake or solid form.

In another embodiment, the present invention provides for a pharmaceutical product comprising an active pharmaceutical ingredient where the active pharmaceutical ingredient was never substantially dried and reconstituted.
According to another embodiment of the present invention, there is provided a method of manufacturing a pharmaceutical, where the method comprises synthesizing an active pharmaceutical ingredient in liquid form, and using the active pharmaceutical ingredient in liquid form as feed for a first production step in a finished dosage form manufacturing process. In another embodiment, the active pharmaceutical ingredient in liquid form is never dried as a wet cake or solid form. In another embodiment, the active pharmaceutical ingredient in liquid form is never dried and subsequently reconstituted. In another embodiment, the synthesizing of the active pharmaceutical ingredient in liquid form and the use of the active pharmaceutical ingredient in liquid form occurs on the same manufacturing train.

In yet another embodiment, the invention provides a continuous system for manufacturing pharmaceuticals the system comprising a first workstation and a second workstation, where the first workstation synthesizes an active pharmaceutical ingredient in liquid form and the second workstation manufactures a finished dosage form whereby the second work station receives the active pharmaceutical ingredient in liquid form from the first work station. In another embodiment, the continuous system is operable by a computer. In another embodiment, the active pharmaceutical ingredient in liquid form is never dried as a wet cake or solid. In another embodiment, the active pharmaceutical ingredient in liquid form is never dried and subsequently reconstituted. In another embodiment, the first workstation is in fluid communication with the second workstation.

In still another embodiment, the present invention provides for a system of manufacturing a finished dosage form of a pharmaceutical composition, the system comprising a means for synthesizing an active pharmaceutical ingredient in liquid form, a means for formulating a finished dose form and a means for converting the active pharmaceutical ingredient in liquid form into a finished dose form. In a further embodiment, the means for synthesizing is in fluid communication with the means for formulating. In still another embodiment, the synthesizing and converting occur on the same manufacturing train.

The system essentially comprises a continuous manufacturing train that synthesizes the API and immediately uses the final solution of the API as the first step in the Secondary Processing. Therefore, this invention addresses the interface or transition steps from API to finished dosage form manufacture and it will enable entities working on continuous processing to develop processes to manufacture the dosage forms in a continuous process starting with the raw materials for the API without isolation of the API.
This invention changes the dynamics of the supply chain for pharmaceuticals dramatically. The ability to manufacture in a continuous flow from API manufacturing to dosage form manufacturing with batch size of dosage form and batch size of API matched, provides for the creation of dedicated factories that can be located near the customers, thereby minimizing the risks associated with the supply chain. In addition to being locally situated, the factories can be dedicated to a single product thereby minimizing any risk of cross contamination. Furthermore, managing the inventory of the finished dosage form becomes much simpler as well because the manufacturing cycle time (the time from initiation of the manufacture of the API through to manufacture of the finished dosage form (FDF)) is dramatically shorter and requires far less total inventory (in both volume and value).

Pharmaceutical manufacturing systems designed to follow the principles of this invention are beneficial, flexible and economically attractive. The capital cost of dedicated mini-factories will be far less than the two traditional (API plus FDF) factories required in the historical model. The smaller size of the factories will also be less costly and more adaptable to sudden increases or decreases in demand by simply producing fewer batches of the total product.

When a new product is launched, a mini-factory as described above offers a huge reduction in risk. For example, before launching a new product, a company typically makes a forecast about the volume of product that will be required. For various reasons, often times this forecast can be far from target. With a mini factory, a newly launched product can be produced on a small scale, for example, by only producing on one shift per day. This will build some inventory for the launch. If the demand for the new product turns out to be larger than forecasted, the mini plant is able to produce more batches rapidly because of the shorter cycle time. If the demand turns out to be less than forecasted, the company will have saved both capital and operating cash because it will be able to operate the mini plant for fewer days.

In the traditional world of pharmaceutical manufacturing, major pharmaceutical companies have historically built very large, multi-product factories all over the world employing thousands of employees at a single site. Today these companies are left with factories that are no longer competitive, in cost or technology. Frequently the companies are unable to shut down the factories because this will create local economic havoc. This tragic result can be avoided with mini factories. In the event the plant needs to be shut down there will not be a massive financial write-off or local havoc. These mini factories can be easily
constructed, operated, and purposefully positioned near the markets where there is demand, which ultimately can be several locations around the world.

DRAWINGS

[0024] The following drawings form part of the present specification and are included to further demonstrate certain aspects of the present invention. The invention may be better understood by reference to one or more of these drawings in combination with the detailed description of specific embodiments presented herein.

[0025] FIGURE 1 is a flow diagram illustrating a pharmaceutical manufacturing process.

[0026] FIGURE 2 is a flow diagram illustrating an active pharmaceutical ingredient synthesis.

[0027] FIGURE 3 is an illustration of present API operations wherein the API is manufactured in bulk.

[0028] FIGURE 4 is an illustration of present finished pharmaceutical operations wherein the API is received in bulk.

[0029] FIGURES 5A, 5B and 5C are flow diagrams illustrating examples of finished pharmaceutical manufacturing processes.

[0030] FIGURE 6A is a flow diagram representing present pharmaceutical manufacturing process versus FIGURE 6B which is a flow diagram representing features of the present invention.

DESCRIPTION

[0031] Unless otherwise defined all terms of art, notations and other scientific terms or terminology used herein are intended to have the meanings commonly understood by those of skill in the art to which this invention pertains unless the context clearly indicates otherwise. In some cases, terms with commonly understood meanings are defined herein for clarity and/or for ready reference, and the inclusion of such definitions herein should necessarily be construed to represent a substantial difference over what is generally understood in the art. Many of the techniques and procedures described or referenced herein are well understood and commonly employed using conventional methodology by those skilled in the art, such as, for example, the widely utilized current Good Manufacturing Practice Guidelines.

Definitions

[0032] It is noted that, as used in this specification and the appended claims, the singular forms "a," "an," and "the," include plural referents unless expressly and unequivocally limited to one referent. Thus, for example, reference to "a compound" includes two or more different
compounds. As used herein, the term "include" and its grammatical variants are intended to be non-limiting, such that recitation of items in a list is not to the exclusion of other like items that can be substituted or other items that can be added to the listed items.

[0033] As used in this disclosure, except where the context requires otherwise, the term "comprise" and variations of the term, such as "comprising," "comprises" and "comprised" are not intended to exclude other additives, components, integers or steps. Thus, throughout this specification, unless the context requires otherwise, the words "comprise", "comprising" and the like, are to be construed in an inclusive sense as opposed to an exclusive sense, that is to say, in the sense of "including, but not limited to."

[0034] As used in this disclosure, except where the context requires otherwise, the method steps disclosed are not intended to be limiting nor are they intended to indicate that each step is essential to the method or that each step must occur in the order disclosed.

[0035] As used in this disclosure, "composition" or "preparation" means any chemical that is active for the diagnosis, mitigation, treatment, cure or prevention, of a condition or disease, combined with one or more than one chemical that is not active for the diagnosis, treatment or prevention of a condition or disease.

[0036] As used in this disclosure, "API" is an abbreviation for active pharmaceutical ingredient. API means, any substance or compound to be used in the manufacture of a drug product and that, when used in the production of a drug, becomes an active ingredient in the drug product. Such substances furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease or to affect the structure and function of the body.

[0037] As used in this disclosure, "active ingredient" means any component that furnishes pharmacological activity or has a direct effect in the diagnosis, cure, mitigation, treatment, or prevention a disease or condition, or affects the structure or any function of the body of man or other animals. The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect.

[0038] As used in this disclosure, "API Manufacture" means all operations from purchase of raw or starting materials and products, through production, quality control, release and storage, to distribution of API's, and the related controls.

[0039] As used in this disclosure, "aseptic" means processing conditions designed to achieve a sterile product.
As used in this disclosure "batch" means a specific quantity of a drug or other material that has uniform character and quality, within specified limits, and is produced according to a single manufacturing order during the same cycle of manufacture. A specific quantity of material produced in a process or series of processes so that it is expected to be homogeneous with in specified limits.

As used in this disclosure, "batch size" means the number of dosage units or the quantity of API (usually expressed in grams or kilograms). Batch (or lot) may be defined by a fixed quantity or the amount produced in a fixed time.

As used in this disclosure "compounding" means bringing together of excipient and solvent components into a homogeneous mix of active ingredients.

As used in this disclosure, "component" means any ingredient for use in the manufacture of a drug product, including those that may not appear in such drug product.

As used in this disclosure, "contamination" means the unintended, non-process related, introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or onto a material during production, sampling, packaging or repackaging, storage or transport.

As used in this disclosure, "cross contamination" means a particular form of contamination in which material from one product could or does contaminate another product.

As used in this disclosure, "dose" means the amount or form of a drug that is given to a patient.

As used in this disclosure "dosage form" means the physical structure and appearance in which the pharmaceutical product is to be administered for use.

As used in this disclosure, "drug product" is synonymous with "pharmaceutical product" or "finished dosage form" and means any preparation that contains an active pharmaceutical ingredient generally, but not necessarily, in association with inactive ingredients. The term also includes a finished dosage form that does not contain an active ingredient but is intended to be used as a placebo.

As used in this disclosure, "FDF" is an abbreviation for Finished Dosage Form and "FPP" is an abbreviation for Finished Pharmaceutical Product. FDF and FPP are synonyms.

As used in this disclosure, "final intermediate" means the last compound from which the API is produced. The final intermediate is thus a starting material for the process step which produces the finished API (which should not be salt formation or esterification).
As used in this disclosure, "Finished Pharmaceutical Manufacturer" or "Finished Dosage Formulation Manufacturer" means formulating the API into its recommended dosage and delivery form.

As used in this disclosure "excipient" means more or less inert substance added as a diluent or vehicle or to give form or consistency when the remedy is given in a tablet form; simple syrup, aromatic powder, honey, and various elixirs are examples of excipients.

As used in this disclosure, "GMP" is an abbreviation for good manufacturing practices and means the regulations enumerated in title 21 of the U.S. Code of Federal Regulations Part 211 containing the minimum current good manufacturing practice for preparation of drug products (excluding positron emission tomography drugs) for administration to humans or animals.

As used in this disclosure, "inactive ingredient" means any component other than an active ingredient.

As used in this disclosure, "in-process material" means any material fabricated, compounded, blended, or derived by chemical reaction that is produced for, and used in, the preparation of the API or drug product.

As used in this disclosure, "intermediate" is partly processed material which must undergo further processing before it becomes an API.

As used in this disclosure, "lot" means a batch, or a specific portion of a batch, having uniform character and quality within specified limits; or, in the case of a drug product or API produced by continuous process, it is a specific identified amount produced in a unit of time or quantity in a manner that assures it having uniform character and quality within specified limits.

As used in this disclosure, "raw material" is a general term used to denote starting materials, chemical compounds, reagents, intermediates, process aids, and solvents intended for use in the production of intermediates or APIs (Active Pharmaceutical Ingredients).

As used in this disclosure, "terminal sterilization" means a process applied to product sealed in its final container that transforms a non-sterile product into a sterile one.

As used in this disclosure, "train" means a series of parts or elements that together constitute a system or process for producing a result and especially for carrying on a process (as of manufacture).
Pharmaceutical Manufacturing

As mentioned above and illustrated in Figure 1, pharmaceutical manufacturing occurs in two general stages. First, during the Primary Processing an API manufacturer will convert raw materials into an active pharmaceutical ingredient. API production is highly sophisticated, requiring technically demanding chemical, biochemical and/or biological processes. In general, final formulation manufacturing or Secondary Processing requires different skills and equipment than does API manufacturing. During the secondary processing stage, a manufacturer is responsible for formulating the API into its recommended dosage and delivery form.

APIs can constitute a significant portion of the total cost of a drug. In general, APIs are manufactured in large amounts in certain countries where the cost tends to be lower. Commodity API manufacturing is a high-volume, low-margin business where economies of scale play an important role. By manufacturing in large quantities the cost per kilogram of API is much lower than if the API were produced in smaller quantities. When APIs are produced in smaller to mid-sized volumes, the cost can increase substantially.

Active pharmaceutical ingredients can be manufactured by chemical synthesis, extraction, cell culture/fermentation, other biological processes, recovery from natural sources, or any combination of these processes. Figure 2 illustrates steps in an API production process. For the sake of simplicity, many steps that may be involved in the process are not shown but are all known to one of skill in the art. Primary Processing begins by introducing the starting materials into the process. There are multiple reaction steps and separation steps whereby isolated and purified intermediates are produced. There are multiple reaction steps between the starting materials and the final intermediate. A final conversion step produces the final API which is isolated and purified. These manufacturing steps are performed on production lines by machines or equipment such as raw material dispensers, chemical reactors, filters, centrifuges, distillers, dryers, process tanks, and crystallizers.

Traditional Primary Processing is usually completed with a drying process where the API has been isolated, purified and dried. Typically an API when dried will contain 0.5 to about 7%, or sometimes as high as 10% water (moisture). A wet cake commonly can contain as much as 30, or even 50% moisture. During drying, the API is converted to a wet cake or a solid form, amorphous, co-crystal or crystalline, which confers various advantages during isolation, processing and storage of the active pharmaceutical ingredient. For example, materials in crystalline form generally result in better impurity profile, improved handling
characteristics (such as sticking and flow) and, in the majority of cases, better physical and chemical stability overall.

**TABLE 1**

<table>
<thead>
<tr>
<th>AMORPHOUS APIS V CRystalline APIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amorphous (non-crystalline solid)</td>
</tr>
<tr>
<td>Higher Solubility</td>
</tr>
<tr>
<td>Lower chemical and physical stability</td>
</tr>
<tr>
<td>Must control form for development</td>
</tr>
<tr>
<td>Lower yield of final API</td>
</tr>
</tbody>
</table>

APIs in crystalline form can be more desirable. However, the cost of production can be higher because of the research commitment due to the complexity, such as selecting the right polymorph and solvents. Crystallization involves both nucleation and growth. Controlling the balance of these two phenomena to influence formulation can be challenging. Additionally, batch crystallization, can produce particles that are often too large to meet the specification criteria desired by the formulator and requires further mechanical size reduction by milling, ultrasound hammering or some other technique known in the art as required to improve consistency and particle size. Reducing or controlling the API's particle size can be the last step in API manufacture or one of the first steps in making the finished dose form. Further processing of the API can also include a sterilization step. GMPs require all active pharmaceutical ingredients used in sterile medicinal products be sterilized (to anoint them as parenteral grade) unless the final dosage form is terminally sterilized, or produced by a process including a sterilizing filtration step.

Every step of all API manufacturing processes is governed by regulations and thus must be carefully monitored and controlled. Even when APIs are simply being stored, records must be maintained documenting the temperature and possible humidity conditions of their storage. During the expiry or retest period for the material, and often for a time following that period, the stability of the material must be monitored with samples being kept and tested to confirm stability. APIs with short shelf-lives like some biotechnology products and biologies sometimes have to be tested quite frequently. When ready for use these APIs must be transported in a manner so as not to interfere with or disrupt the quality or stability of the active material.
For example, biologies are generally produced in cell culture (mammalian, bacterial or even insect or plant cells). There is a separation/isolation stage and in the end, as with chemically produced APIs, the resulting API is in liquid form. In most cases for biologies, the solution is frozen instead of dried resulting in a block of ice containing the active biological. After transportation, the block is then defrosted before being used to produce the finished dosage form. One of the problems with this approach is biologies tend to have very limited stability in solution. As a result, there is a time limit for the period when the frozen "API" (in block form) is removed from the freezer until it becomes part of the dosage form and is re-frozen or lyophilized. Advantageously, the present invention uses the API immediately in the Secondary Processing or production of the finished formulation, and therefore there is no physical storage or transportation of the API and no need to monitor or comply with regulations overseeing these steps in the manufacturing processes.

The critical starting point for manufacturing safe and effective drugs is good, quality active pharmaceutical ingredients. In general, the finished dosage formulation (FDF) manufacturer has to buy all APIs in the open market from an FDA or other regulatory authority approved API supplier. The API is ordered and transported to the manufacturer, subjecting the shipment to contamination risk, potential material loss, import delays, theft, shipping segregation and transportation charges. Even if a FDF manufacturer produces its own APIs, it generally does so in a facility that is dedicated to the manufacture of APIs. The resultant effect is that while the supply chain is shorter, most of the same risks and higher than necessary costs remain an issue. Therefore, this invention is an improvement over prior methods where the API is manufactured in bulk in a specialized facility and must be stored and transported.

Figure 3 shows a schematic diagram 300 of the steps that occur through primary processing where the API is manufactured in bulk. The API manufacturer combines the raw materials 301 and synthesizes the materials through several possible reaction steps 303, separates the API 305, isolates 307, purifies 309, and dries (or freezes in some cases) 311 the active pharmaceutical ingredient. The ingredient now in a solid form is packaged in bulk 313 and transported 315 to a storage facility 317. When a customer places an order, an aliquot of the API is removed from the full batch packaged in bulk. The aliquot is then packaged and shipped 319 from the API manufacturer (often located in another country) to a finished formulation manufacturer. During transportation the API is subjected to possible shipping delays, regulatory holds, exposure to contaminants, the risks associated with exposures to
temperatures and humidities outside the approved range and loss of integrity due to accident and degradation.

[0070] Storage and transportation are major steps in most pharmaceutical manufacturing processes. These steps increase the overall complexity of manufacturing and therefore increase the manufacturing costs. In addition, the need to store and transport APIs complicates any complaint investigations and can contribute to the need for product withdrawals or recalls. Because of this major gap between production of the API and production of the finished formulation several unnecessary "individuals" can be introduced into the process such as agents, brokers, traders, distributors, repackers, or relabelers. Tracing back a problematic lot through this process can be avoided by removing all of these intermediaries from the production process as is possible with this invention. Under time sensitive circumstances, like a recall, one can see how valuable it would be to have a single responsible party who has used a focused manufacturing process with no significant break points and total control within one facility to the point of completion of all manufacturing activities.

[0071] Figure 4 illustrates events that occur when a finished formulation manufacturer receives 402 an API shipment for secondary processing 400. Upon receipt, the manufacturer must inspect the shipment and conduct identity and possibly other testing to verify the contents 404. The shipping container most likely will have to be opened exposing the API to the environment and possible contaminants. APIs that are received in a dried or partially-dried condition or solid form have to be reconstituted 406 or dissolved before entering the unique manufacturing process, feeding 408 wherein the API will be converted into a product suitable for administration, or the final formulation of the drug. In some instances, the API will need to be combined with another API or excipients that can be added to the formulation. In other instances, the API will need to be dissolved into a liquid form and combined with other ingredients recrystallized and introduced into the formulation process. In still other circumstances, the API will need to be weighed, reconstituted, and sterilized 410 or then aseptically introduced into the environment where filling into a vial or syringe or other delivery device can be appropriately accomplished. Once the API is in a liquid form, final formulations are made by mixing 412 APIs and excipients (other non-active ingredients), pressing or molding the mixture into tablets, or filling capsules or preparing solutions (including sterile) 414, and then labeling and packaging 416 the product for the ultimate market.

[0072] Figures 5A, 5B and 5C are flow diagrams illustrating examples of finished pharmaceutical manufacturing processes.
In contrast to Primary and Secondary Processing, the present invention closes the gap between the production of the API and the formulation of the finished pharmaceutical product suitable for administration. This continuous production process removes several steps of the existing manufacturing processes including: drying the API into a wet cake (partially dried) or solid form, shipping the API, and reconstituting the API for finished formulation processing.

This novel manufacturing process is detailed below by comparing an existing method of manufacturing piperacillin versus what would be a comparable novel method for manufacturing piperacillin. This example is not intended to limit the scope of the invention.

**EXAMPLE 1**

**THE MANUFACTURE OF PIPERACILLIN ENDING WITH PIPERACILLIN BEING ISOLATED**

One prior art manufacturing process ending with piperacillin being isolated which was described in U.S. Patent number 4,112,090. For example purposes the scale of manufacture has been increased 1,000 fold.

**Step 1:** Add 4.4 kg (50 moles) of N-ethyl ethylenediamine to a mixture containing 8 kg (54 moles) of diethylxalate in 8 L of ethanol at room temperature. After 3 hours, the mixture is heated to remove the ethanol. The residue is crystallized from 10 L of dioxane to yield 1-ethyl-2,3-dioxopiperazine.

**Step 2:** Suspend 710 g (5 moles) of 1-ethyl-2,3-dioxopiperazine in 15 L of dioxane. Stir in 700 g of trimethylsilylchloride and 830 mL of triethylamine. Continue stirring at room temperature for 20 hours to precipitate triethylamine hydrochloride. Filter and add the filtrate to a solution of 700 g (7 moles) of phosgene in 10 L of anhydrous tetrahydrofuran at 5°C to 10°C. After 30 minutes, the mixture is heated to room temperature for 2 hours. The solvent is then distilled off under reduced pressure to yield pale yellow crystals of 4-ethyl-2,3-dioxo-1-piperazinecarbonyl chloride.

**Step 3:** Suspend 1.75 kg (5 moles) of 6-[R(-)-a-aminophenylacetamidojpenicillanic acid in 50 L of tetrahydrofuran containing 20% water by volume. Adjust the pH to 8.0 to 8.5 by addition of triethylamine with stirring until dissolved. Cool to 0°C to 5°C.

**Step 4:** Dissolve 1 kg (5 moles) of 4-ethyl-2,3-dioxopiperazine-carbonyl chloride in tetrahydrofuran and add to the above solution. Maintain the pH between 7.5 and 8.0 by gradual addition of triethylamine. Hold the resulting solution at 0°C to 5°C for 30 minutes and then warm to 5°C to 10°C for 1 hour maintaining the pH at 7.5 to 8.0.
Step 5: The piperacillin is dried with anhydrous magnesium sulfate in step 5. Distill off the tetrahydrofuran under reduced pressure and dissolve the residue in 20L of water. Wash twice with 20 L of ethyl acetate.

Step 6: Add 50 L ethyl acetate and adjust the pH to 1.5 with dilute HCl, cool to 0° to 5°C. Separate the ethyl acetate layer, wash twice with 20 L of water and dry with anhydrous magnesium sulfate. The crystals are isolated and dried again until the composition has no more than one percent water wherein it will be released for quality control testing.

Step 7: Add 10 L of ethyl acetate containing 830 g of sodium 2-ethylhexanoate to precipitate white crystals of D-[(-)-a-(4-ethyl-2,3-dioxo-1-piperizinocarbonylamido)-phenylacetamidojpenicillanic acid sodium salt.

Step 8: Collect the crystals by filtration and wash with 20 L of ethyl acetate followed by 20 L of ethyl ether. Dry at 35+3°C. At the end of the production process piperacillin is isolated as crystals or a sodium salt.

As one in the art can appreciate steps 6, 7 and 8 in the production process are simplified in that there are multiple steps involved in each numeric step in order to convert the piperacillin in step 5 to a solid in step 8. Additional components have to be added, the mixture has to be diluted, washed, filtered and subjected to temperature changes. To state that the liquid solution of piperacillin has to be "dried" or converted into a solid drastically simplifies the many processes involved.

EXAMPLE 2

THE MANUFACTURE OF PIPERACILLIN ENDING WITH PIPERACILLIN IN LIQUID SOLUTION

As described below, by utilizing the piperacillin in the liquid form, steps 6, 7, and 8 of the prior art example above become unnecessary.

Step 1: Add 4.4 kg (50 moles) of N-ethyl ethylenediamine to a mixture containing 8 kg (54 moles) of diethylxalate in 8 L of ethanol at room temperature. After 3 hours, the mixture is heated to remove the ethanol. The residue is crystallized from 10 L of dioxane to yield 1-ethyl-2,3-dioxopiperazine.

Step 2: Suspend 710 g (5 moles) of 1-ethyl-2,3-dioxopiperazine in 15 L of dioxane. Stir in 700 g of trimethylsilylchloride and 830 mL of triethylamine. Continue stirring at room temperature for 20 hours to precipitate triethylamine hydrochloride. Filter and add the filtrate to a solution of 700 g (7 moles) of phosgene in 10 L of anhydrous tetrahydrofuran at 5°C to 10°C. After 30 minutes, the mixture is heated to room temperature for 2 hours. The
solvent is then distilled off under reduced pressure to yield pale yellow crystals of 4-ethyl-2,3-
dioxo-1-piperazinecarbonyl chloride.

[0087] Step 3: Suspend 1.75 kg (5 moles) of 6-[R(-)-a-
aminoophenylacetamidojpenicillanic acid in 50 L of tetrahydrofuran containing 20% water by
volume. Adjust the pH to 8.0 to 8.5 by addition of triethylamine with stirring until dissolved.

Cool to 0°C to 5°C.

[0088] Step 4: Dissolve 1 kg (5 moles) of 4 ethyl-2,3-dioxopiperazine -carbonyl chloride in
tetrahydrofuran and add to the above solution. Maintain the pH between 7.5 and 8.0 by
gradual addition of triethylamine. Hold the resulting solution at 0°C to 5°C for 30 minutes and
then warm to 5°C to 10°C for 1 hour maintaining the pH at 7.5 to 8.0.

[0089] Step 5: Distill off the tetrahydrofuran under reduced pressure and dissolve the
residue in 20L of water. Wash twice with 20 L of ethyl acetate.

[0090] Advantageously, in the present invention the piperacillin in liquid form in step 5
can be used immediately as "feed" for the finished formulation production. Additionally, the
volume of the piperacillin manufactured can be matched to the batch size of the finished
dosage form, be it an injectable as in the case of piperacillin, or a granulation for tablets or
capsules as it could be for other compounds.

[0091] Often times, both acid and basic active pharmaceutical ingredients are
manufactured with the final completion step having the drug in a "salt" form. A salt form of
the substance enables one to modify liquid solubility, dissolution rate, solution pH, crystal
form, hygroscopicity, chemical stability, melting point, and even mechanical properties. By
increasing the inorganic content, crystallinity and stability increase making the manufacturing
and processability easier. However, some salts have a greater propensity for forming hydrates,
and acid salts can readily dissociate and spray drying or lyophilization can dissociate strong acid salts. The need or requirement to put a drug
into a solid "salt" form becomes unnecessary when the liquid form of the API is used.

[0092] It is possible that the piperacillin produced in liquid form (which is used as feed for
the finished formulation) may need to be diluted or concentrated. For example, the final
solution may contain 1 gram per ml (milliliter) but the FDF manufacturing process may
require 0.5 gram per ml (milliliter). In this scenario, the batch size of the FDF is twice as
much as the batch size of the API which under the new invention can be controlled or
predetermined prior to beginning the manufacturing process.
EXAMPLE 3
ENCAPSULATION

During primary processing, the API manufacturer will combine raw materials to produce a partially dried or solid API in bulk. Then when needed depending on the location of the API inventory, an aliquot will be removed and measured for the amount necessary to produce the FDF. The partially dried or solid API will be dissolved along with a particle forming excipient in a solvent. The solvent will then be removed to produce a slab of a drug-loaded excipient. The slab will be ground to produce a powder of drug-loaded particles. The volatile organic solvents must be removed from the final product to acceptable safety levels. If the API is soluble in the excipient then homogenous particles result from grinding the slab.

If the API is not soluble in the excipient, then inhomogenous distribution can result. The API must then be micronized to a size much smaller than the desired microcapsule.

In the example above, an API in liquid form can be used as "feed" and combined with the excipient to formulate a drug loaded excipient. The API and excipient can be either co-melted, spray dried or solvent-free spray chilled resulting in homogenous particles. For this scenario, there is no need to dissolve the solid or semi-solid API in a solvent. Additionally, the micronization step is also avoided because there are no issues concerning particle size.

EXAMPLE 4
LIQUID FILLING OF CAPSULES

Low dose or highly potent APIs, low melting point APIs and those with a critical stability profile are ideal candidates for encapsulation as liquids into either soft or hard capsules.

An API in liquid form has better content uniformity than an API in powder form. Pumps on capsule filling machines used for dispensing liquids are capable of achieving weight variations of <1%. Consequently, for a low dose API in solution excellent content uniformity can be achieved. A formulation incorporates 20 µg of a model drug, triamterene, was shown to have a content uniformity of 1.8% for liquid-filled capsules compared to 3.1% for powder filled capsules.

Using an API in liquid form is safer, creates less waste and reduces the chances for cross contamination. A liquid formulation of phenacetin (3 mg dose) was used to demonstrate the potential for containment of API during filling of capsules. Swab tests on the surfaces of various parts of the filling machine after completion of a filling operation revealed that no API was present on any of the capsule-filling machine bushings, which would not be achievable.
when powders are filled. The lower detectable limit of the analytical method was 0.25 µg. This result indicates that the incorporation of potent drugs into liquid fill materials has the potential to drastically reduce the danger of exposure of operators to dust particles and minimize the cross contamination potential.

[0098] Figures 6A and 6B further illustrate the removal of the steps between the existing methods by which pharmaceuticals are manufactured as illustrated in Figure 6A versus the methods described in the present invention as shown in Figure 6B. These features are especially beneficial in aseptic manufacturing processes.

EXAMPLE 5

ASEPTIC MANUFACTURING

[0099] In another embodiment, the methods and systems of the present invention provide for an improved aseptic manufacturing process that significantly reduces the risk of increased contamination in the current approach for manufacturing pharmaceuticals, the initial isolation of the API and its introduction into the dosage form manufacturing process. For example, if the FDF is a sterile injectable (in a vial or syringe or other container,) it typically is sterile filtered from the non-sterile portion of the manufacturing "train" into the sterile or aseptic manufacturing space. When the last step in the API manufacturing process is in liquid form it can be directly filtered aseptically into the sterile area for filling thereby avoiding steps that include, isolation of the API as a dried or semi-dried powder, storage, sampling and weighing of the powder, reconstitution of the powder and all the errors and contamination risks possible during those steps.

[0100] In many ways, the most demanding pharmaceutical manufacturing process is aseptic manufacturing. Aseptic manufacturing is a process that requires the close coordination and complex interactions between managing personnel, unsterilized and sterilized products, the equipment and system, clean room, support facilities and sterilized filling components. The process generally requires the drug substance (API) and any excipients be sterilized prior to actual use and that all materials and equipment, to be used in the processing are also sterilized prior to use and that personnel in the aseptic manufacturing complex are properly trained to minimize the risk of them introducing microbial contamination into the area.

Aseptic processing receives the highest level of regulatory attention because of the detail involved and because the consequences of error can be drastic. Aseptic processes include sterile filling and capping of liquid in vial for injectable drugs, aseptic filling and stoppering of
liquid prefilled syringes and aseptic filling and capping of powders. Contamination in an aseptic process can have a serious impact on a company's financial viability, manufacturing license and industry reputation. GMP codes for aseptic manufacturing demand a full investigation for product sterility failure or media contamination. Additionally, environmental monitoring programs are in place to validate and verify environmental controls.

Sometimes drugs are terminally sterilized which means once the final drug form has been manufactured, terminal sterilization is added as an additional final step to assure sterility. However, some drugs are unstable if subjected to terminal sterilization procedures and therefore need to be manufactured under aseptic conditions in order to reduce the risk of microbial contamination throughout the process. Sterility under aseptic conditions is generally achieved by dissolving the non-sterile API in a solvent (including water), followed by filtration through a sterilizing filter. For example, if the finished drug formulation is a sterile injectable (in a vial or syringe or other container), it typically is sterile filtered from the non-sterile portion of the manufacturing "train" into the sterile or aseptic manufacturing space where further processing, generally the sterile filling process and sealing of the container, takes place. In a situation where the sterile filling is done using robotics technology, the API in usually a liquid solution can be directly filtered aseptically into the sterile area for filling thereby avoiding steps that include: isolation of the API as a dried or semi-dried powder, storage, sampling and weighing of the powder, reconstitution of the powder and all the errors possible during those steps.

The features of the present invention provide for mini-pharmaceutical manufacturing systems. An advantage of this present invention is that it allows for manufacturing facilities that are dedicated to one or a few products where the complete process, from creation of the API from starting materials through the production of the final dosage forms is handled as a single process with fewer delays and fewer total steps in the total process.

Interruptions and stoppages, even when intentional, in manufacturing processes generally lead to additional testing above and beyond what is already and otherwise required. In most current manufacturing systems, there is a designed lack of flexibility because of the need for consistency and there can be a higher risk of contamination if and when multiple drugs are manufactured in the same facilities using some or all of the same equipment. In a highly regulated, precise industry where attention to detail is critical it is of the utmost importance to ensure all equipment and processes are operated to specification as part of the
effort to prevent and avoid contamination and cross contamination. Equipment must be qualified and validated to provide full regulatory compliance. Any deliberately introduced modification to existing documents, processes, equipment, systems or testing methods will in many instances result in a required regulatory re-approval and or increased process documentation further complicating and potentially delaying the approval process.

[0104] The present invention advantageously removes the lengthy process and lead time(s) generally required by regulatory agencies for approval of the API manufacturing company and facility as a supplier to the FDF manufacturer and, separately, approval of the FDF manufacture. Under this system, only a single approval will be required for the entire process from raw chemical through dosage form manufacture. Further, because manufacturing facilities will likely be modular and largely dedicated, the risks of cross contamination will be lessened and manufacturing plants will be able to be shuttered then rededicated (after an appropriate cleaning process) to a different product. The net effect will be that in the event of drug shortages, recovery times will be reduced dramatically.

[0105] The availability of any finished pharmaceutical product for commercial sale is dependent upon the manufacturer’s ability to procure the raw ingredients, carry out the manufacturing of the dosage form(s), then packaging the product for distribution. Minor changes in the manufacturing processes for the raw ingredients and/or for the API or dosage form can require new approval or validation. If one supplier or product manufacturer fails or refuses to supply its product for any reason, it could take a significant amount of time and expense to qualify a new or alternate supplier or manufacturer. For example, changes in API manufacturer, change in batch size or change in manufacturing site.

[0106] Additionally, the loss of one supplier or product manufacturer can lead to a required regulatory approval in the form of a "prior approval supplement" or similar and to incur the efforts of re-validation and other costs associated with changes in the process or processes for the manufacture of the active pharmaceutical ingredient or the dosage form. Other than for officially described "minor changes," a company has to wait for FDA approval of a new active pharmaceutical ingredient supplier or product manufacturer. It easily can take as long as two years to qualify a new supplier or manufacturer. Additionally, the active pharmaceutical ingredients, packaging materials, or finished products from new suppliers or manufacturers may not be obtained on acceptable commercial terms and/or at reasonable prices, or at all. A loss of an active pharmaceutical ingredient supplier or a product manufacturer can result in not having a salable product to meet market demands or
investigational product for use in clinical trials. Having control over the complete process, from start to finish, removes dependency on single source suppliers or manufacturers. When the entire process is handled at a single facility and one mostly continuous operation there is less complication and cost.

The present invention allows for lower volume, dedicated manufacturing methods and systems which are more desirable for personalized medicines as opposed to the traditional high volume production of drugs. The pharmaceutical industry has shifted to a more targeted approach where therapies are specifically developed to treat patients that are more likely to respond. Often times, these therapies use diagnostic techniques to determine if the patient is a "good candidate" for the drug. It is foreseeable that drug manufacturers will be responsible for at least partnering with the manufacturers of the diagnostic kits. Because there is a smaller, focused patient population that will potentially receive the drug, the manufacturing has to be done on a smaller scale. Large volume manufacturers are not equipped to handle more frequent equipment changeovers, cleaning, and product-line clearances. With personalized medicines comes more operating complexity, therefore greater controls will be required of manufacturing operations.

The features of the present invention can reduce the total cost of producing a drug product. The cost per gram of the API, because of smaller volumes, might well be higher than "normal." However, by removing steps from the production process there will be an overall cost savings. Additionally, using the features of the present invention will reduce the capital cost of the factory to produce products, as well as supply chain costs, operating costs and environmental handling costs. When a continuous system is used, parameters are put in place to determine accuracy and consistency without major, unexpected disruptions to the process.

More or less immediate use of the API not only reduces the number of steps involved in the manufacturing process (isolation and drying) but also creates a continuous manufacturing process which is beneficial for several other reasons. Simply stated, when the number of variables in a complex process is increased, the chances for creating inconsistencies that might lead to reduced quality of the product(s) or their deterioration/degradation increase as well.

Further, the more parties and steps involved, the higher the likelihood for errors, potential for introduction of contaminants, supply chain issues including temperature control and monitoring during storage and shipment, and the greater opportunity for theft (especially
during transport) and generally a overall reduction of the kind of control one would desire from process start to completion of manufacturing of the final pharmaceutical dosage form.

Although the present invention has been discussed in considerable detail with reference to certain preferred embodiments, other embodiments are possible. Therefore, the scope of the appended claims should not be limited to the description of preferred embodiments contained in this disclosure. All references cited herein are incorporated by reference in their entirety.

Materials and Methods

Methods and materials are described herein. However, methods and materials similar or equivalent to those described herein can be also used to obtain variations of the present invention. The materials, methods, and examples are illustrative only and not intended to be limiting.

Incorporation by Reference

Throughout this application, various publications, patents, and/or patent applications are referenced in order to more fully describe the state of the art to which this invention pertains. The disclosures of these publications, patents, and/or patent applications are herein incorporated by reference in their entireties, and for the subject matter for which they are specifically referenced in the same or a prior sentence, to the same extent as if each independent publication, patent, and/or patent application was specifically and individually indicated to be incorporated by reference.

Other Embodiments

It will be apparent to those skilled in the art that various modifications and variations can be made in the present invention without departing from the scope or spirit of the invention. Other embodiments of the invention will be apparent to those skilled in the art from consideration of the specification and practice of the invention disclosed herein. It is intended that the specification and examples be considered as exemplary only, with a true scope and spirit of the invention being indicated by the following claims.
What is claimed is:

1. A method of manufacturing a composition in finished dosage form for the treatment of a condition or disease, the method comprising:
   (a) selecting one or more than one starting material to produce an active pharmaceutical ingredient in liquid form; and
   (b) using the active pharmaceutical ingredient in liquid form to make the composition in finished dosage form.

2. The method of claim 1, where the active pharmaceutical ingredient in liquid form is never dried and subsequently reconstituted before making the composition in finished dosage form.

3. The method of claim 1, where the composition in finished dosage form is selected from the group comprising an aerosol, caplet, capsule, cream, injection, ointment, oral suspension, patch, thin film, suppository, syringe, tablet, or vial.

4. The method of claim 1, where step (a) and step (b) are carried out on the same manufacturing train.

5. A composition manufactured according to the method of claim 1.

6. A method of manufacturing a pharmaceutical composition, the method comprising:
   (a) selecting one or more than one starting material to make an active pharmaceutical ingredient; and
   (b) producing a batch size of the active pharmaceutical ingredient, where the batch size of the active pharmaceutical ingredient equals the amount required to make the batch size of the pharmaceutical composition being produced.

7. The method of claim 6, where the active pharmaceutical ingredient is in liquid form.

8. The method of claim 6, where the pharmaceutical composition is selected from the group comprising an aerosol, caplet, capsule, cream, injection, ointment, oral suspension, patch, suppository, syringe, tablet, or vial.
9. The method of claim 7, where the active pharmaceutical ingredient in liquid form is never dried and subsequently reconstituted prior to making the pharmaceutical composition.

10. The method of claim 6, where step (a) and step (b) are carried out on the same manufacturing train.


12. A method of manufacturing a pharmaceutical composition in a form deliverable to a patient, the method comprising making an active pharmaceutical ingredient in liquid form and immediately using the active pharmaceutical ingredient in liquid form to compound the pharmaceutical composition in a form deliverable to a patient.

13. The method of claim 12, where the amount of active pharmaceutical ingredient made equals the amount of the active pharmaceutical ingredient required to compound the pharmaceutical composition.

14. A method of manufacturing a finished dose form pharmaceutical, the method comprising:
(a) synthesizing an active pharmaceutical ingredient in liquid form;
(b) adding one or more than one substance to the active pharmaceutical ingredient in liquid form to make a pharmaceutical composition; and
(c) formulating the pharmaceutical composition into the finished dose form.

15. The method of claim 14, where the finished dose form is selected from the group comprising an aerosol, caplet, capsule, cream, injection, ointment, oral suspension, syringe, patch, thin film, suppository, tablet, or vial.

16. The method of claim 14, where the active pharmaceutical ingredient in liquid form is used immediately after synthesis to make the pharmaceutical composition.
17. The method of claim 14, where synthesizing the active pharmaceutical ingredient in liquid form, adding the one or more than one substance and formulating the pharmaceutical composition occur in sequential steps on the same manufacturing train.

18. A composition manufactured according to the method of claim 14.

19. A method for manufacturing a pharmaceutical composition in a sterile deliverable, the method comprising:
   (a) making an active pharmaceutical ingredient in liquid form under aseptic conditions; and
   (b) immediately filtering the active pharmaceutical ingredient in liquid form under aseptic conditions into a sterile deliverable.

20. The method of claim 19, where step (a) and step (b) occur on the same manufacturing train.

21. A method of making a sterile pharmaceutical complex, the method comprising:
   (a) making an active pharmaceutical ingredient in liquid form; and
   (b) filtering the active pharmaceutical ingredient in liquid form aseptically into the sterile pharmaceutical complex.

22. The method of claim 21, where the sterile pharmaceutical complex is selected from the group comprising a vial, syringe, cartridge or other container.

23. A pharmaceutical composition for delivery to a patient comprising an active pharmaceutical ingredient where the active pharmaceutical ingredient was never dried in a wet cake or solid form.

24. A pharmaceutical product comprising an active pharmaceutical ingredient where the active pharmaceutical ingredient was never substantially dried and subsequently reconstituted.

25. A method of manufacturing a pharmaceutical, the method comprising:
   (a) synthesizing an active pharmaceutical ingredient in liquid form; and
(b) using the active pharmaceutical ingredient in liquid form as feed for a first production step in a finished dose form manufacturing process.

26. The method of claim 25, where the active pharmaceutical ingredient in liquid form is never substantially dried as a wet cake or solid form.

27. The method of claim 25, where the liquid active pharmaceutical ingredient in liquid form is never dried and subsequently reconstituted.

28. The method of claim 25, where step (a) and step (b) occur on the same manufacturing train.

29. A continuous system for manufacturing pharmaceuticals, the system comprising a first workstation and a second workstation, where the first workstation synthesizes an active pharmaceutical ingredient in liquid form and the second workstation manufactures a finished dose form and the second workstation receives the liquid form of the active pharmaceutical ingredient in liquid form from the first workstation.

30. The system of claim 29, wherein the continuous system is operable by a computer.

31. The system of claim 29, where the liquid active pharmaceutical ingredient is never dried as a partial solid or solid.

32. The system of claim 29, where the active pharmaceutical ingredient is never dried and reconstituted.

33. The system of claim 29, where the first workstation is in fluid communication with the second workstation.

34. A system for manufacturing a finished dose form of a pharmaceutical composition, the system comprising:
   (a) means for synthesizing an active pharmaceutical ingredient in liquid form;
   (b) means for formulating a finished dose form; and
(c) means for converting the active pharmaceutical ingredient in liquid form to a finished dose form.

35. The system of claim 34, where step (a) is in fluid communication with step (b).

36. The system of claim 34, where steps (a) and (c) are carried out in the same manufacturing train.
FIG. 1
RECEIVING

MEASURE AND IDENTIFICATION TESTING

RECONSTITUTION

FEEDING

STERILIZING/FILTERING

LIQUID MIXING/BLENDING

FILLING VIAL/AMPOULE/CREAM/OINTMENT BAG SYRINGE

LABELING/PACKAGING

FIG. 4
A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61 J 3/00, 1/00, 1/20 (2013.01)
USPC - 424/464, 489; 514/916, 960

According to International Patent Classification (IPC) or to both national classification and IPC.

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC(8): A61J 3/00, 1/00, 1/20
USPC: 424/464, 489; 514/916, 960

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)


C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate; of the relevant passages</th>
<th>Relevant to claim No.</th>
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<td>X</td>
<td>WO 2012/1 15640 A1 (ZIMMERMAN, RE et al.) August 30, 2012; paragraphs [0045], [0141], [0046], [0113], [0017], [0099], [0097], [0082], [0128], [0127]</td>
<td>1-3, 5, 12-16, 18, 23-27, 34</td>
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Further documents are listed in the continuation of Box C.

* Special categories of cited documents:
  "A" document defining the general state of the art which is not considered to be of particular relevance
  "E" earlier application or patent but published on or after the international filing date
  "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
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X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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\& document member of the same patent family

Date of the actual completion of the international search: 16 December 2013 (16.12.2013)

Date of mailing of the international search report: 20 DEC 2013

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