CHALLENGES & SOLUTIONS IN CYTOTOXINS AND HPAPIs

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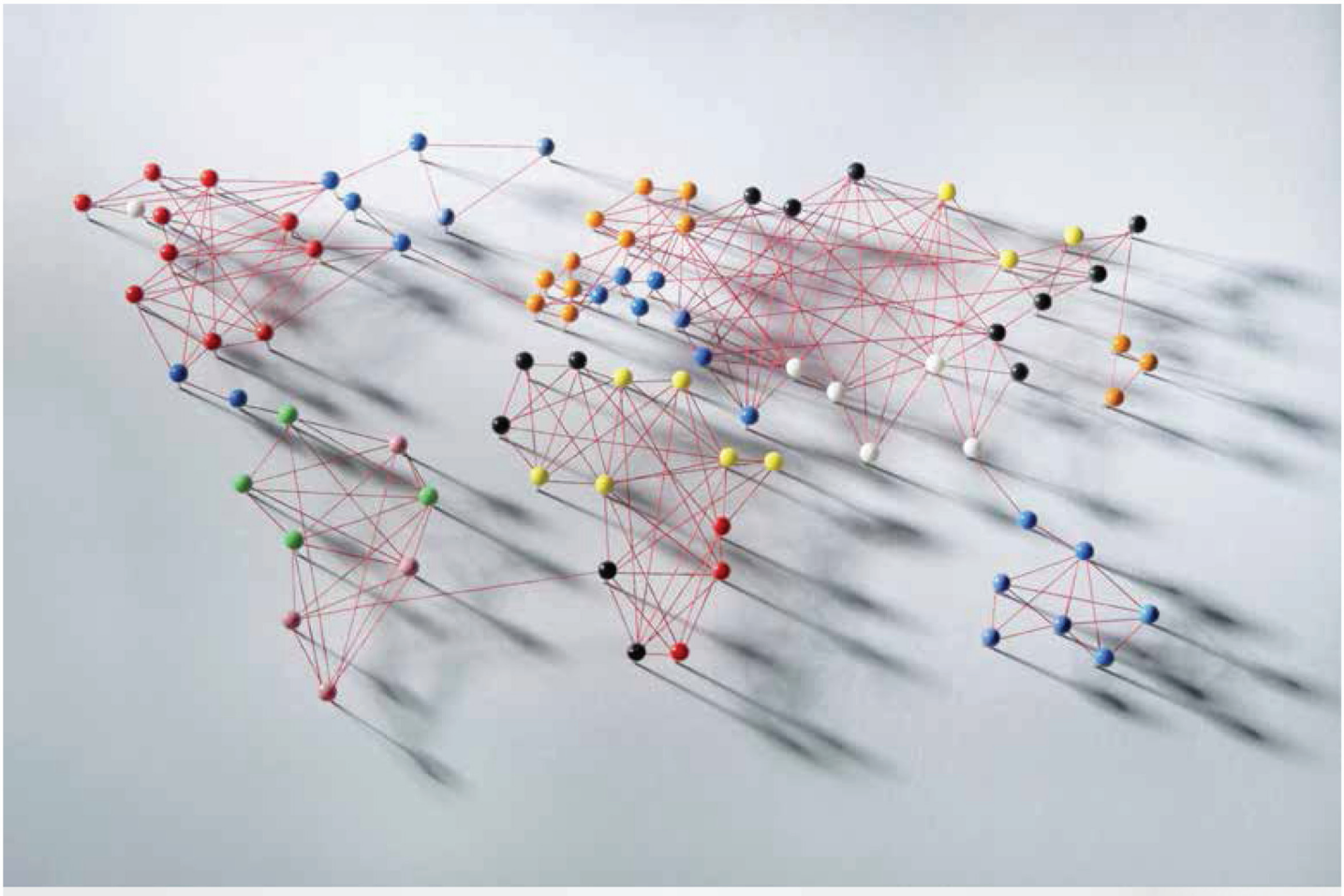

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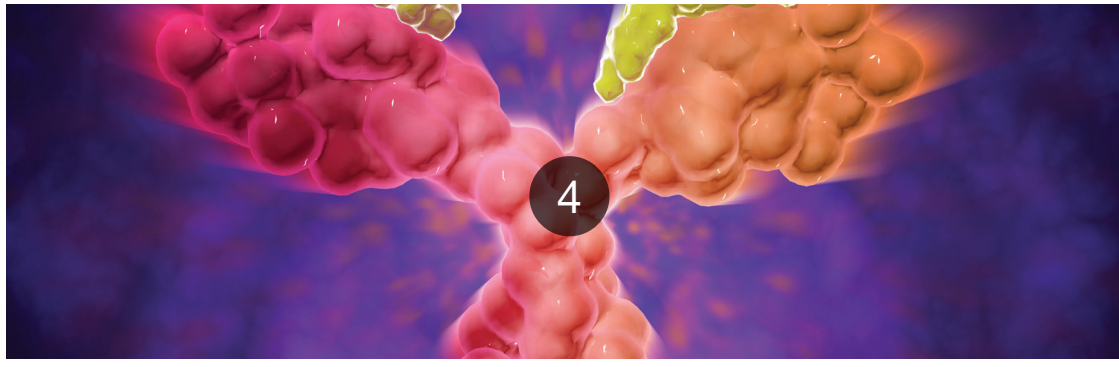

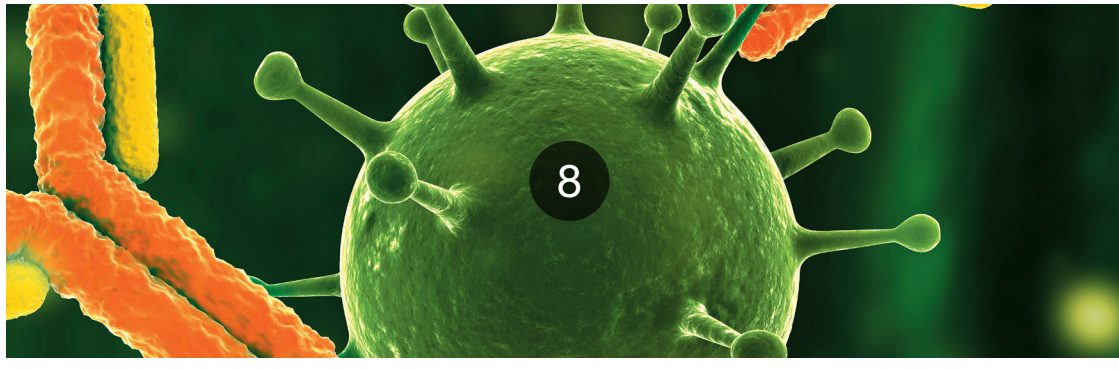

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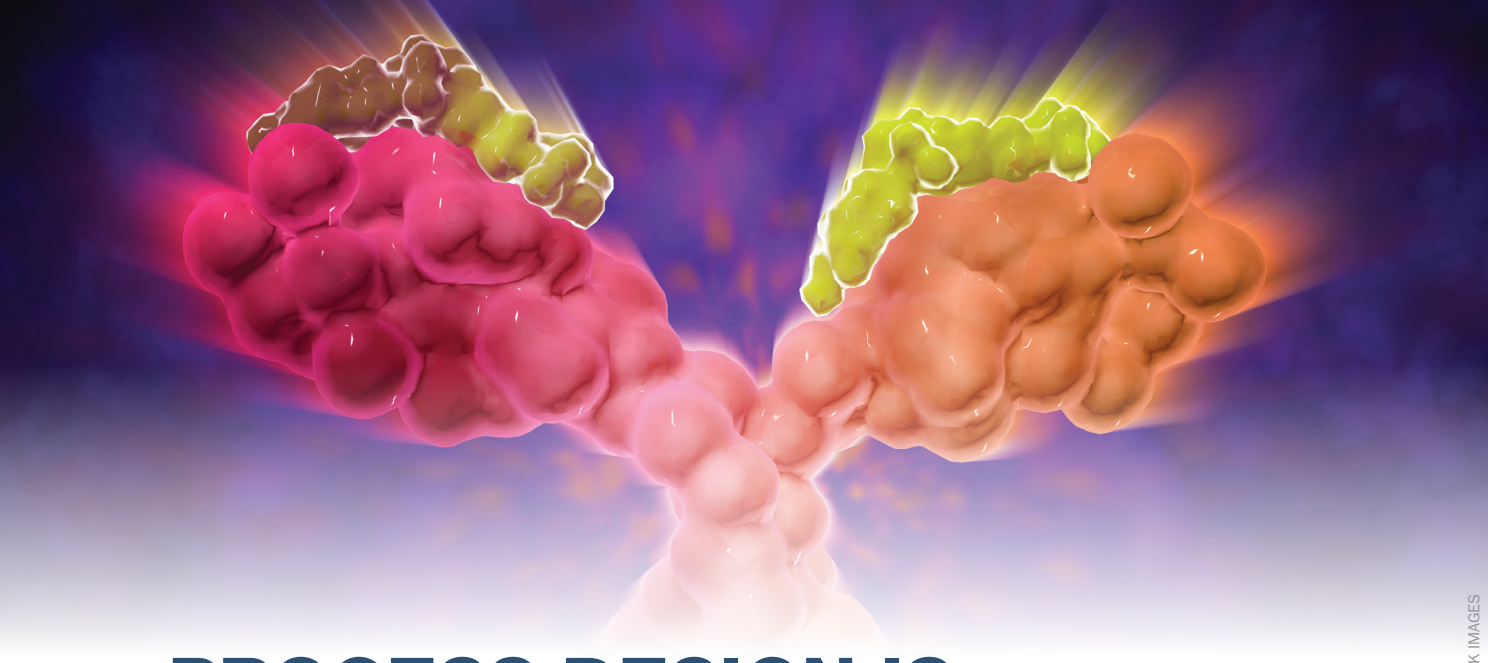

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PROCESS DESIGN IS CRITICAL FOR COMMERCIAL MANUFACTURE OF HPAPIs

Increasing potency and growing interest in antibody-drug conjugates are creating challenges for manufacturers of HPAPIs.

BY CYNTHIA A. CHALLENER

The majority of highly potent APIs (HPAPIs) to date have been developed for the treatment of cancer (cytotoxics and cytostatics), particularly tyrosine kinase inhibitors and derivatives. There are, however, other therapeutics, including hormones, narcotics, and retinoids, which are also highly potent. In addition, while HPAPIs are generally thought of as small-molecule drugs, many biopharmaceuticals have occupational exposure limits (OELs) of 10 µg/m^3·8 h or less, a general guideline for classifying APIs as highly potent, according to Srinivas Achanta, regulatory affairs manager with Hetero. Of particular interest are antibody drug conjugates (ADCs), drugs that include a small molecule, cytotoxic payload, and an antibody connected with a linker. These therapies are designed to deliver the highly potent payload to targeted cells, reducing the likelihood of harm to normal cells. The number of ADCs in development has grown in recent years, and this

growth is a key driver of the HPAPI market. The increasing number of ADCs and HPAPIs in general is creating challenges with respect to the prevention of cross-contamination in large manufacturing facilities with multi-use equipment and maintaining containment during larger-scale purifications.

IMPORTANCE OF ADCS

Because ADCs enable the targeted delivery of HPAPIs to the specific cancer cells (or other problematic cells), they have attracted significant attention, and the number of ADCs in development has increased dramatically. “The toxin that is conjugated to the antibody in ADCs has been the fastest growing segment of the HPAPI market, with demand quickly increasing in recent years,” says Dave Bormett, director of operations for SAFC. With three components to manufacture and combine together under containment conditions, the production of ADCs can be a complex process, adds Achanta. In addition, Bormett notes that certain new types of ADC compounds, which may be considered the next generation of ADCs, are considered to be even more potent than existing products and are pushing the limits on current capabilities with respect to the handling of low OEL materials.

OPPORTUNITY FOR SINGLE-USE SYSTEMS

Single-use manufacturing technologies are on the rise for small-scale highly potent products such as ADCs, according to Jeff Marcoux, technical business development manager at Novasep. “Another important trend is the widespread acceptance of portable dedicated equipment, including both single-use and permanent systems for small-scale production of very highly potent compounds such as ADC payloads, which often have OELs lower than 0.1 µg/m^3·8 h,” he notes. “Dedication of equipment and the adoption of single-use technologies can play an important role in controlling cross-contamination and maximum carry-over limits after cleaning (MACO) when implemented as part of a risk-based approach,” adds Marcoux.

At SAFC, on the other hand, single-use, disposable technologies have thus far been used in certain limited applications, but they are being considered for HPAPI manufacturing where they can improve containment, particularly for larger-scale manufacturing activities, according to Bormett.

“All high-potency APIs must be produced under conditions that not only protect the operators from exposure to the compounds, but also prevent contamination and the inadvertent carryover of a different product that was previously produced or is simultaneously being manufactured. While modern HPAPI facilities are meeting today’s requirements, there is a continual need to improve these technologies going forward. To accomplish this task, we need to focus on the development of production and handling methods including single-use systems and/or new technologies that can provide increased protection of the API from cross-contamination. Such protection systems must focus on the cleaning and removal steps,” observes Achanta. “The development of such new technologies is of increasing importance as the number of multiproduct facilities, which pose the greatest risk of contamination of HPAPIs, are growing around the world in order to meet the greater demand for these products,” he adds.

THE PURIFICATION CHALLENGE

ADC payloads are small molecules containing complex chemical structures. As such, the purification of these molecules is challenging from a safety, health, and environmental point of view, as well as with respect to the technological aspects, according to Marcoux. “The chemical structures of the impurities obtained from chemical processes used for the synthesis of ADC payloads are often closely related to the desired HPAPI. As a result, traditional purification processes, such as crystallization or low-pressure silica gel chromatography, are often inadequate or lead to unacceptable loss levels,” he explains. Novasep has found that HPLC purification technologies are particularly well suited for this class of compounds, ensuring robust, scalable, and reproducible purification under contained operational conditions.

Marcoux also notes that because tracking of impurities is a challenge at the ADC stage after conjugation of the payloads with the antibody, much of the purity control for ADCs occurs at the payload stage. Both conjugatable and non-conjugatable impurities are increasingly controlled at this stage of the manufacturing process.

Maintaining containment around large-scale purification steps, such as chromatography, can also be challenging, according to Bormett. “It is important, therefore, to implement appropriate facility and equipment controls to ensure that these operations are handled appropriately,” he comments.

NEED FOR APPROPRIATE PROCESS DESIGN

Appropriate process design is in fact crucial for the entire HPAPI production operation. “Most very highly potent APIs and ADC payloads require small clinical and commercial quantities, and the production of gram-scale GMP APIs and payloads can be challenging. The control of containment using flexible and small equipment, including glass equipment, is always a challenge and requires a tailored approach for each process and each unit operation,” Marcoux says. The appropriate process design at the development scale is also necessary to ensure that the process will fit the equipment and capabilities of the facility upon scale-up, according to Bormett. “The technical issues that must be addressed for scale-up of a manufacturing process are the same for an HPAPI or non-HPAPI. The challenge is ensuring that the proper engineering controls are in place for the process upon scale-up, and ensuring any limitations are considered when developing the process,” he notes.

One of the biggest challenges at large scale is the handling of powders and solids, according to Achanta. “Up to a scale of a few kilos, it is relatively straightforward to manage solids, because bottles with alpha-beta split butterfly valve connectors can be used for charging reactors to maintain containment. On a larger scale, however, this approach is impractical,” he explains.

Bormett also notes that appropriate cleaning methods must be implemented to achieve the required limits for residue levels in multi-use equipment. “The use of analytical methods that provide very low detection limits is necessary in order to confirm that the required residue levels have been achieved,” he says. Bormett further notes that there is certainly an interest in continually achieving lower detection limits when handling HPAPIs.

Finally, Achanta points to the ambiguity surrounding the classification of HAPAIs given that different pharmaceutical companies often use proprietary systems is an issue. In addition, he notes that because the classifications for new APIs are often unknown due to a lack of data, they must be carefully managed with appropriate process design and containment controls.

INCREASED INVESTMENT ACTIVITY

There has been an increase in investment in HPAPI capacity by both contract manufacturing organizations and large pharmaceutical companies, particularly to support ADC development and manufacturing, according to Bormett. SAFC, for example, has two major expansion projects under way to support HPAPI manufacturing. At the company's Verona, WI facility, three HPAPI-capable GMP manufacturing areas are being added, including a plant with 400 L and 800 L reactors. In addition, Bormett says that SAFC is building a commercial antibody drug conjugation facility in St. Louis, MO to meet growing market demand beyond the current clinical-scale facility.

Novasep, meanwhile, recently invested $4 million to expand its HPAPI manufacturing capabilities at its site in Le Mans, France. In the expanded cGMP facility, which has been commissioned, the company manufactures highly potent compounds with OELs lower than 0.03 µg/m^3·8 h at the kg-scale, according to Marcoux. The investment features cryogenic chemistry at -60°C in Hastelloy reactors, as well as large-scale HPLC chromatography and drying in contained areas to manufacture ADC payloads at commercial scale.

CYNTHIA A. CHALLENER, is a contributing editor to *Pharmaceutical Technology.*

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HPAPIs: FAST-GROWING SEGMENT PRESENTS CHALLENGES AND OPPORTUNITIES

Appropriate process design and engineering are critical for the production of small-molecule and biologic HPAPIs.

BY CYNTHIA A. CHALLENER

Highly potent active pharmaceutical ingredients (HPAPIs) make up the fastest growing segment of the worldwide API market, according to market research firm RNCOS, which predicts that the value of the global HPAPI market will reach $15.3 billion by 2017. Consultancy Transparency Market Research, meanwhile, estimates that the total HPAPI market will increase at a compound annual growth rate of 9.9% from $9.1 billion in 2011 to $17.5 billion in 2018.

MORE BIOLOGIC HPAPIs

While the majority of HPAPIs have thus far been developed for the treatment of cancer (cytotoxics and cytostatics), particularly tyrosine kinase inhibitors and derivatives, newer hormone, narcotic, and retinoid-based drugs are also highly potent. In addition, HPAPIs are generally thought of as small-molecule drugs, but many biopharmaceuticals have occupational exposure limits (OELs) of 10 µg/m^3 or less, a general guideline for classifying APIs as highly potent, according to Srinivas Achanta, regulatory affairs manager with Hetero. Of particular interest are antibody-drug conjugates (ADCs), which include a small-molecule, cytotoxic

payload and an antibody connected with a linker and are designed to deliver the highly potent payload to targeted cells, reducing the likelihood of harm to normal cells.

MARKET DRIVERS

Drivers of the HPAPI market, according to RNCOS, include a rising demand for cancer HPAPIs, increased private player participation, particularly in developed regions, and technological advances in process manufacturing of these challenging APIs. The number of ADCs in development has grown rapidly in recent years and is also a factor in the growth of the HPAPI market. The entrance of a growing number of competitors in the HPAPI market is, however, resulting in a highly fragmented market and may have a negative influence on growth, according to Transparency Market Research. The consulting firm also notes that a shortage of US FDA-approved manufacturing sites may act as a further restraint on growth for the HPAPI market.

North America currently accounts for the greatest share of the market, followed by Europe. The greatest growth, however, is expected in Asia Pacific, with major activity taking place in India and China due to rising health awareness, continuing expansion of these economies, improving healthcare systems, and a rapid increase in the production of generics, according to Transparency Market Research.

IMPORTANCE OF ADCS

Because ADCs enable the targeted delivery of HPAPIs to specific cancer cells (or other problematic cells), they have attracted significant attention, and the number of ADCs in development has increased dramatically. “The toxin that is conjugated to the antibody in ADCs has been the fastest growing segment of the HPAPI market, with demand quickly increasing in recent years,” says Cynthia Wooge, global strategic marketing manager at SAFC. With three components to manufacture and combine together under containment conditions, the production of ADCs can be a complex process, adds Achanta. In addition, Wooge notes that certain new types of ADC compounds, which may be considered the next generation of ADCs, are considered to be even more potent than existing products and are pushing the limits on current capabilities with respect to the handling of low OEL materials.

OPPORTUNITY FOR SINGLE-USE SYSTEMS

Single-use manufacturing technologies are on the rise for small-scale highly potent products such as ADCs, according to Jeff Marcoux, technical business development manager at Novasep. “Another important trend is the widespread acceptance of portable dedicated equipment, including both single-use and permanent systems for small-scale production of very highly potent compounds such as ADC payloads, which often have OELs lower than 0.1 µg/m^3·8 h,” he notes. “Dedication of equipment and the adoption of single-use technologies can play an important role in controlling cross-contamination and maximum carry-over limits after cleaning (MACO) when implemented as part of a risk-based approach,” he adds.

“All high potency APIs must be produced under conditions that not only protect the operators from exposure to the compounds, but also prevent contamination and the inadvertent carryover

of a different product that was previously produced or is simultaneously being manufactured. While today's modern HPAPI facilities are meeting today's requirements, there is a continual need to improve these technologies going forward. To accomplish this task, we need to focus on the development of production and handling methods including single-use systems and/or new technologies that can provide increased protection of the API from cross-contamination. Such protection systems must focus on the cleaning and removal steps," observes Achanta. "The development of such new technologies is of increasing importance as the number of multiproduct facilities, which post the greatest risk of contamination of HPAPIs, are growing around the world in order to meet the greater demand for these products," he adds.

NEED FOR APPROPRIATE PROCESS DESIGN

Appropriate process design is in fact critical for the entire HPAPI production operation. "Most very highly potent APIs and ADC payloads require small clinical and commercial quantities, and the production of gram-scale GMP APIs and payloads can be challenging. The control of containment using flexible and small equipment, including glass equipment, is always a challenge and requires a tailored approach for each process and each unit operation," Marcoux says. Appropriate process design at the development scale is also necessary to ensure that the process will fit the equipment and capabilities of the facility upon scale-up, according to Wooge.

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Finally, Achanta points to the ambiguity surrounding the classification of HPAPIs given that different pharmaceutical companies often have proprietary systems and the fact that often the classification of new APIs is unknown due to a lack of data as issues that must be managed with appropriate process design and containment controls.

CYNTHIA A. CHALLENER, is a contributing editor to *Pharmaceutical Technology.*

This article originally appeared in *Pharmaceutical Technology Sourcing and Management,* Volume 10, Issue 6 (2014).

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FUNCTIONAL DIFFERENTIATION OF CYTOTOXIC CANCER DRUGS AND TARGETED CANCER THERAPEUTICS

BY GIAN C. WINKLER, ESTER LOVSIN BARLE, WILLIAM M. KLUWE, NOVARTIS PHARMA; AND GIUSEPPE GALATI, PATHEON, INC.

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Defining Cytotoxic Cancer Drugs and Targeted Therapeutics

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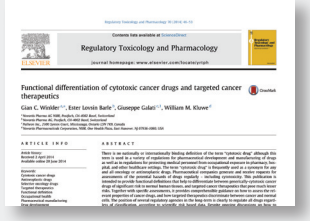
Regulatory Toxicology and Pharmacology

Functional differentiation of cytotoxic cancer drugs and targeted cancer therapeutics

INTRODUCTION

There is no nationally or internationally binding definition of the term “cytotoxic drug.” By common use, the term ‘‘cytotoxic drug’’ is frequently used as a synonym for any and all oncology or antineoplastic drugs. It is formally a part of many regulations for pharmaceutical development and manufacturing of oncology drugs (ICH, 2000; ANVISA, 2010; WHO, 2010; EMA, 2012a,b). On the other hand, the pharmaceutical manufacturers and regulatory agencies are moving to regulate all drugs based on scientific data and risk assessment and not based on terms lacking a specific definition.

Respective guidances have been published (ISPE, 2010; Bercu et al., 2013), and oncology

hospitals, pharmacies, and caregiver organizations often have their own regulations for administering oncology drugs, designed to protect personnel from occupational exposure and safely dispose of contaminated waste.

Lacking a well-recognized and standard definition of cytotoxic drug makes it difficult to provide consistent advice and ensure easily understood communications. The purpose of this report is to provide functional definitions that discriminate between cytotoxic cancer drugs and targeted cancer therapeutics for the purpose of guiding safe handling practice and product quality decisions.

FUNCTIONAL DIFFERENTIATION OF CYTOTOXIC CANCER DRUGS

For the sake of clarity, a cytotoxic cancer drug can be defined as "a therapeutic agent, whose primary activity is to indiscriminately and directly kill both healthy and cancerous cells in an effort to control the spread of cancer in the human body." This would include cancer drugs that kill cancerous cells via direct interaction with DNA or DNA-maintenance processes at doses, which also kill healthy cells. A therapeutic agent, whose primary activity is to indiscriminately and directly kill both healthy and cancerous cells in an effort to control the spread of cancer in the human body is considered to be cytotoxic if:

- the mechanism of action is to directly disrupt DNA structure or mitotic function causing cell death;
- the above mechanism of action does not selectively target tumor cells or differentiate in susceptibility between tumor and non-tumor cells;
- results of cell culture assays, genotoxicity, and experimental animal studies or human clinical studies demonstrate that the drug's toxicity is not specific to, nor displays, substantially different susceptibility to tumor cells in comparison to non-tumor cells in living tissue.

To meet the definition of cytotoxic drug, all three of these elements must be present.

From an active pharmaceutical ingredient (API) standpoint, dedicated production areas should be considered when material of high pharmacological activity or toxicity is involved unless validated inactivation and/or cleaning procedures are established and maintained (ICH, 2000; Eudralex Volume 4 Part II, 2014). From a Finished Product standpoint, certain cytotoxic cancer drugs should be manufactured in dedicated and self-contained facilities (Eudralex Volume 4 Part I Chapter 3, 2014; Eudralex Volume 4 Part I Chapter 5, 2014). The overall industry trend observed to date is a risk-based approach combining GMP and toxicological parameters.

In the spirit of the current GMP regulations in regards to certain cytotoxic cancer drugs, these drugs would not be acceptable for manufacturing in multi-product facilities.

It is important to distinguish that in the context of drug development, certain in vitro cytotoxicity assays are used to screen drug candidates. In some considerations, the results of these in vitro cytotoxicity assays may be the focus of questioning as to how a drug should be identified as cytotoxic.

EXAMPLES OF CYTOTOXIC CANCER DRUGS

Cytotoxic cancer drugs are usually of high acute toxicity. Examples include DNA alkylating agents, topoisomerase inhibitors, antimetabolites, and microtubule-active agents, all of which affect cell survival, division, or DNA synthesis in normal and tumor cells. Their relative selectivity is dependent upon the rate of cell division rather than a neoplastic state. In addition, cytotoxic cancer drugs may be very specific to certain cellular targets present in both cancerous and normal cells.

Maytansinoids

Maytansine possesses metaphase arrest antimitotic properties (Issell and Crooke, 1978). Flow microfluorimetry analysis of L1210 cells during exposure to maytansine indicated a shift in the distribution of DNA to a single peak, representing the DNA of cells in G2 and M phases (Wolpert-DeFilippes et al., 1975), making mitotic and G2 cells most sensitive to maytansine cytotoxicity, while G1 phase cells are the most resistant, with S-phase cells being intermediate (Rao et al., 1979). Experiments with sea urchin eggs and clam eggs have suggested that it causes the disappearance of a mitotic apparatus or prevents one from forming if added at early stages. Maytansine does not affect formation of the mitotic organizing center, but does inhibit in vitro polymerization of tubulin (Remillard et al., 1975).

In chronic studies, maytansine produced target organ toxicity in the pancreas, esophagus, stomach, small and large intestine, adrenal cortex, kidney, bladder, liver, and skin while the main dose-limiting toxicities in human studies relate to effects on the gastrointestinal tract and nervous system (Issell and Crooke, 1978).

Maytansine and its derivatives meet the functional definition of cytotoxic cancer drugs because they target rapidly dividing cells in a specific mitosis phase and do not discriminate between cancer and healthy cells.

Topoisomerase Inhibitors

Topoisomerases are highly conserved enzymes essential for survival of all eukaryotic organisms and present in normal and cancer cells. Topoisomerase enzymes are categorized as toposiomerase I and II; both are validated targets for treatment of a variety of cancers. The mode of action of topoisomerases directly affects DNA replication, chromosomal condensation, and chromosomal segregation (Hande, 2008).

The topoisomerase I enzyme acts to relax supercoiled DNA by inducing and then ligating single strand breaks (Binaschi et al., 1996). Inhibition of topoisomerase I by oncology agents stabilizes DNA strands following initial scission required for replication, thereby fixing lethal single-strand DNA breaks. Such breaks are detected as genotoxic and mutagenic events when prototypical topoisomerase I inhibitors are assessed in eukaryotic cell assays (Hashimoto et al., 1995).

Several cancer drugs (and antibiotics) act through topoisomerase II inhibition by inducing DNA breaks and apoptosis (Seiter, 2005). Topoisomerase II inhibitors are genotoxic in standard in vitro and in vivo studies. However, mutagenicity is usually restricted to eukaryotic

cells (Binaschi et al., 1996; Boos and Stopper, 2000; Albanese and Watkins, 1985). Toxicity of topoisomerase II inhibitors includes myelosuppression and gastrointestinal disorders in the short-term. Cardiac toxicity and secondary leukemia have been seen in the long-term. Toxicity of topoisomerase II inhibitors indicates that topoisomerase II inhibitors do not discriminate between normal and cancer cells (Seiter, 2005).

Both topoisomerase I and II inhibitors meet the functional differentiation of cytotoxic cancer drugs because the mechanism of action does not selectively target tumor cells or differentiate in susceptibility between tumor and normal cells.

EXAMPLES OF TARGETED CANCER THERAPEUTICS

In the following examples, these drugs do not meet the functional definition of cytotoxic cancer drugs, but do meet the functional definition of targeted cancer therapeutics because they discriminate between cancer and normal cells.

Selective tyrosine kinase inhibitors (TKIs)

Nilotinib was not genotoxic in a standard battery of in vitro and in vivo studies (EMA, 2007). With imatinib, a positive effect was seen at the highest cytotoxic concentration. Thorough in vitro and in vivo genotoxicity testing showed that imatinib is not genotoxic under the conditions of therapeutic use (EMA, 2004).

Imatinib and nilotinib potently inhibit the cytosolic ABL1 tyrosine kinase activity of Bcr-Abl (fusion oncogene), and to a lesser extent the tyrosine kinase activity associated with the platelet-derived growth factor receptor (PDGFR) and the stem cell factor receptor (KIT) (Broxterman and Georgopapadakou, 2004; Kantarjian et al., 2007). Bcr-Abl, PDGFR and KIT kinases are expressed in many normal human cell lines, but these enzymes are only active under certain stressed physiological conditions during which their receptors are stimulated by their respective ligands. Through such auto-regulatory mechanisms, as well as alternative signaling pathways, normal cells are not normally dependent upon the activity of a single kinase for survival. In contrast, a number of cancers require the continuous activity of a single oncogene for cell survival.

TKIs meet the functional definition of targeted cancer therapeutics because of their selective tyrosine kinase inhibition in cancers and their auto-regulatory mechanisms, as well as alternative, compensatory signaling pathways available in normal cells.

Heat shock protein 90 inhibitors (HSP90)

HSP90 inhibitors are non-genotoxic agents (Janz et al., 2007). HSP90 is an abundant protein, constituting approximately 1–2% of total protein in normal cells (Solit and Chiosis, 2008). When associated with its co-chaperones, HSP90 exerts its folding activity via its ATPase activity (Kamal et al., 2003). HSP90 is essential for eukaryotic cell survival. Small molecular weight HSP90 inhibitors competitively inhibit the ATPase activity of HSP90, resulting in degradation of client proteins. This translates into anti-tumor effects in non-clinical in vitro and in vivo studies. HSP90 inhibitors exhibit preferential cytotoxicity to cancer cells due to this enhanced susceptibility.

Although HSP90 is highly expressed in most cells, HSP90 inhibitors selectively kill cancer cells compared to normal cells. This has been attributed in part to selective accumulation of HSP90 inhibitors in cancer cells and to a 100-fold higher binding affinity of HSP90 inhibitors to cancer derived HSP90 as compared to HSP90 from non-transformed cells (Kamal et al., 2003; Solit and Chiosis, 2008).

Inhibitors of apoptosis protein antagonists (IAPs)

Apoptosis is a physiological program for cell death, which is essential for maintenance of homeostasis. Cancer cells, but not normal cells, highly depend on aberrations in the apoptosis-signaling pathway to remain viable. Drugs that can restore apoptosis in cancer cells might be effective in cancer treatment (Flygare et al., 2012).

Some IAP family members suppress apoptosis and provide a mechanism for rescuing abnormal cells that would otherwise be destroyed. Many types of human cancer cells exhibit defects in apoptotic pathways and are dependent upon XIAP function for survival. Tumors of this type overexpress IAPs that enable growth and survival. Inactivation of IAPs does not appear detrimental for normal cells. Small molecule IAPs antagonists are potent cancer drugs in vitro and in vivo (Gyrd-Hansen and Meier, 2010).

IAP antagonists discriminate between cancer and normal cells. By blocking IAPs, IAP antagonists selectively force cancer cells into apoptosis. As both cancer cells and normal cells produce TNF-a when exposed to IAP antagonists, it is expected that the drug triggers both efficacy and toxicity.

Proteasome and histone deacetylase inhibitors

Proteasome and histone deacetylase inhibitors inhibit ubiquitous cellular targets; however recent pre-clinical studies have demonstrated that malignant cells are more susceptible to the cytotoxic effects of proteasome inhibition or histone deacetylase inhibitors than normal cells (Crawford et al., 2011; Bolden et al., 2013).

The proteasome is a multicatalytic protein complex that causes turnover of cytosolic and nuclear proteins. Proteasome inhibitors do not directly disrupt DNA or mitotic function, and are reported to exhibit selective cytotoxicity to cancer cells over normal cells, by inducing apoptosis in proliferating or transformed cells or by overcoming deficiencies in growth-inhibitory or proapoptotic molecules (Almond and Cohen, 2002).

Histone deacteylases are enzymes that catalyze the removal of the acetyl modification on lysine residues of proteins (including core nucleosomal histones). The deacetylation of histones in nucleosomes is an important factor regulating gene expression. Deacetylation of histones by histone deacetylase causes DNA to be tightly wrapped around the histone core, resulting in the inhibition of gene expression. The inhibition promotes an increase in histone acetylation, causing the tightly wrapped DNA to relax. This leads to the expression of certain genes (tumor suppressor and/or cell cycle regulatory genes), which causes the inhibition of tumor growth (Richon and O'Brien, 2002).

Functional differentiation of targeted therapeutics

For drugs early in development (prior to preclinical/clinical studies), the cytotoxicity evaluation will be based primarily on the mechanism of action.

The mechanism for cancer selectivity may also be based on preferential exposure of cancer cells to the therapeutic agent, such as cell surface binding sites, transport mechanisms, tissue-specific activation or inactivation (metabolism), and subsequent degradation of cellular targets. A strategy to target cancer cells based solely on the rapid rate of cellular proliferation is not sufficient to obviate definition as cytotoxic. There are many normal tissues that contain cells that proliferate at a rate similar to, or exceeding, that of some tumor cells. Cytotoxic cancer drugs cause adverse effects on cancer cells and healthy cells at similar doses. Although some targeted cancer therapeutics may cause these effects, studies have shown that the doses required to cause adverse effects on tumor cells would be lower than those on healthy cells (Dubreuil et al., 2009; Shi et al., 2014). The dose required to cause these effects should be taken into account, and a clear safety margin in dose between cytotoxic or growth inhibitory effects on cancer cells and normal, rapidly dividing cells must be observed to ascertain a conclusion of targeted cancer therapeutic. In the event that the margin of safety is less than one, it will suggest that the toxicity occurs at therapeutic doses. The margin of safety would be greater for targeted cancer therapeutics. Although adverse effects on healthy cells may be observed in animal studies if dosed high enough, kinase inhibitors do not meet the first criteria of the functional definition of cytotoxic cancer drugs, namely, these do not directly disrupt DNA structure or mitotic function causing cell death.

CONCLUSION

The definitions and descriptors of cytotoxic cancer drugs and targeted cancer therapeutics provide guidance and facilitate a consistent classification of a variety of active agents used in cancer treatment.

Risk assessment for drugs with a thresholded mode of action or toxicity should be handled by calculating respective limits. Such scientific assessments would then be the basis for establishing safe limits for shared facilities. Despite ongoing discussions on replacing cytotoxic drugs by a risk-based scientific approach, the global use of the label cytotoxic is not expected to disappear.

There has been a long history of the regulatory use of the term “cytotoxic” without any clear definition, which has been a struggle for those impacted. With recently developed targeted monoclonal antibodies linked to a variety of microtubule-active antibody drug conjugates, such considerations have received renewed attention. GMP manufacturing of such combination drugs faces challenges regarding segregated, dedicated (ICH, 2000 Q7) or self-contained facilities (ANVISA, 2010) and related technical investments.

In the short-term, the cytotoxic drug designation will still be used in a variety of regulations for pharmaceutical development and drug manufacturing.

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