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Consecrate to Population Suffering From Life Threatening Diseases: A Regulatory Perspective to Biomarker and Surrogate Endpoint

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ABSTRACT

Biomarkers and surrogate endpoint largely replaced the clinical trials which are needed to be carried out before drug approval in regular approval process under FDA (Food and Drug Administration), a governing pharma regulatory body in USA and as a result approval process can be accelerated. It can be said that surrogate endpoint and biomarker are substituting the clinical trials and decrease the duration of product development phase as well as decrease the entry time period of novel products in the market. The article enlightens the extent to which the biomarkers and surrogate endpoint have benefited the pharma industry for expediting the entry of their products into the market at the earliest to get the maximum benefit of the product during the patent period. Simultaneously article also throws light on the history of risk factors of surrogate endpoint which are likely to jeopardize the interest of the human beings involved. It may conclude that Biomarkers and surrogate endpoints play pivotal role in accelerating approval process for drug approval in USA and the usage of these parameters to minimize the casualty of human lives who are suffering from serious life threatening diseases by providing recent research products which have caliber to cure or improving the quality of life.

Key words: Clinical trial, Biomarker, Surrogate end point, Accelerated approval, Caliber to cure, Casualty of human lives.

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INTRODUCTION

Biomarkers and surrogate endpoint largely replaced the clinical trials which are needed to be carried before drug approval in regular approval process under FDA, a governing pharma regulatory body in USA and as a result approval process can be accelerated. It is applicable to only those drug products which are used in the treatment of life threatening diseases which have no effective treatment therapy right now[1].

Clinical study is required in detail to establish efficacy and safety of drug products upon its consumption and it is important aspects in the interest of public health. Clinical study requires long period of time to satisfy its objective which is around 10 to 15 years and this is one of the reason why new product takes time to enter in the market and ultimately it delays product availability to the patients. Now if we talk about patients who are suffering from serious life threatening diseases, it is a primary concern to make such patients available with recent research product at earliest time. And this purpose can be served only when approval of product is fastened without compromising safety and efficacy parameters. Here, biomarkers and surrogate endpoints play pivotal role and the present article has focused on the usage of these parameters. The purpose of accelerating approval process is to minimize the casualty of human lives who are suffering from serious life threatening diseases by providing recent research products which have caliber to cure or improving the quality of life of such patients relying on the Biomarkers and surrogate endpoint results[1].

Doctors, scientists, and other health professionals use biomarkers as tools to obtain information about a person's health status or response to interventions. Defined as characteristics that indicate biological processes, biomarkers are essential for monitoring the health of both individuals and communities. Some biomarkers, called surrogate endpoints, are used as substitutes for actual clinical endpoints such as incidence of disease or death. Surrogate endpoints are intended to predict benefit or harm based on scientific evidence, and they are used in practice when it is difficult to collect data based on clinical endpoints.

- **Biological Marker (Biomarker):-** A characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention[2]. **Eg:** Lower Density Lipid decreasing capacity in Angina pectoris disease
- **Surrogate Endpoint:-** A biomarker intended to substitute for a clinical endpoint. A surrogate endpoint is expected to predict clinical benefit (or harm, or lack of benefit or

harm) based on epidemiologic, therapeutic, pathophysiologic or other scientific evidence[2].

- **Clinical Endpoint: -** A characteristic or variable that reflects how a patient feels, functions or survives[2].

Biomarker and Surrogate endpoint defined

In April 1999, the NIH (National Institutes of Health) and the FDA cosponsored a conference on "Biomarkers and Surrogate Endpoints: Advancing Clinical Research and Applications." (2) The concepts of biomarkers and surrogates have been summarized by the NIH Definitions Working Group as follows:

A biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.

- A clinical endpoint is a characteristic or variable that reflects how a patient feels, functions, or survives.
- A surrogate endpoint is a biomarker that is intended to substitute for a clinical endpoint.

In early clinical studies, suitable biomarkers should be applied to help to demonstrate proof of concept and identify appropriate dose regimens for efficacy studies as well as toxicity studies. Doing so and learning, for example, which subpopulations are most likely to be benefited by the new treatment, can help in planning later efficacy studies. Although the approach may seem straightforward, the use of biomarkers and surrogates carries with it a number of practical problems and pitfalls. Cardiovascular research will be used as an example here, because the concepts have often been applied in this clinical field. It should be noted that any clinical observation in a given subject might serve different purposes, and each purpose can have implications for the way these characteristics are used, documented, validated, and interpreted.

In clinical practice, for example, blood pressure (BP) is measured to assess the individual risk for a given patient and to decide upon that patient's further diagnostic and therapeutic management. The same characteristic may be determined in epidemiological research, for example. Finally, blood pressure may be used as an outcome measure for a company's decision making in a research project. It may help to answer such questions as

- "Does the antihypertensive drug work?" or
- "Does the new drug create any side effects related to blood pressure?"

The same measure may become a valid surrogate and an essential element in the regulatory review process to be used for the decision about marketing approval for the new drug.

Researchers in cardiovascular drug development have access to clearly defined and rigorously validated biomarkers, surrogate endpoints, and clinical endpoints. Biomarkers include biochemical and functional characteristics or signals; ideally they should be non-invasive. Examples for biochemical biomarkers for cardiovascular conditions are high density lipoprotein (HDL) cholesterol, lipoproteins, creatinekinase MB band (CK-MB isoenzyme), troponins (markers for myocardial cellular damage), high-sensitivity C-reactive protein (hs-CRP) (a marker for inflammatory processes), fibrinogen, or plasminogen activator inhibitor-1 (PAI-1) (an indicator of the activity of the blood coagulation system—and thus a risk for intravascular thrombus formation[3,4].

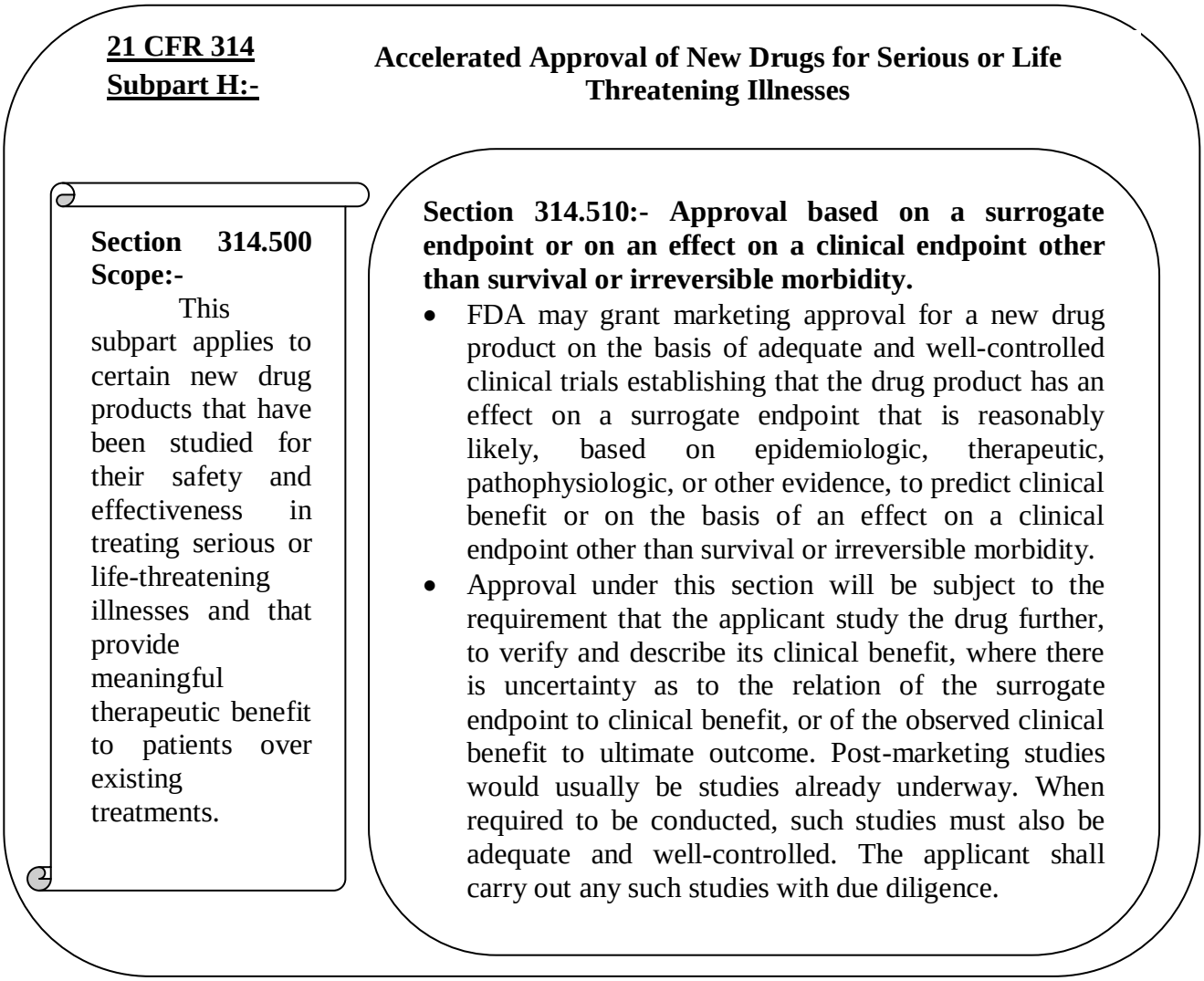

Figure 1: 21 CFR 314 Subpart H regulation includes usage of biomarkers and surrogate endpoint in accelerated approval of new drugs for serious or Life-Threatening Illnesses

FDA REGULATION: SUBPART H- SECTION 314.510[5]

CFR (Code of Federal Regulation) regulation has provided detailed explanation on accelerated approval process for drug products under section of 314 and subpart H. A tabular presentation of 21 CFR 314 subpart H is given below: (Figure 1)

CONCEPTUAL MODEL BIOMARKERS AND SURROGATE ENDPOINTS

Above conceptual model (Figure 2) explains how toxicity and efficacy of the drug product can be interpreted by using biomarkers and surrogate endpoints. In addition, it also correlates biomarkers and surrogate endpoints with clinical endpoints and its results.

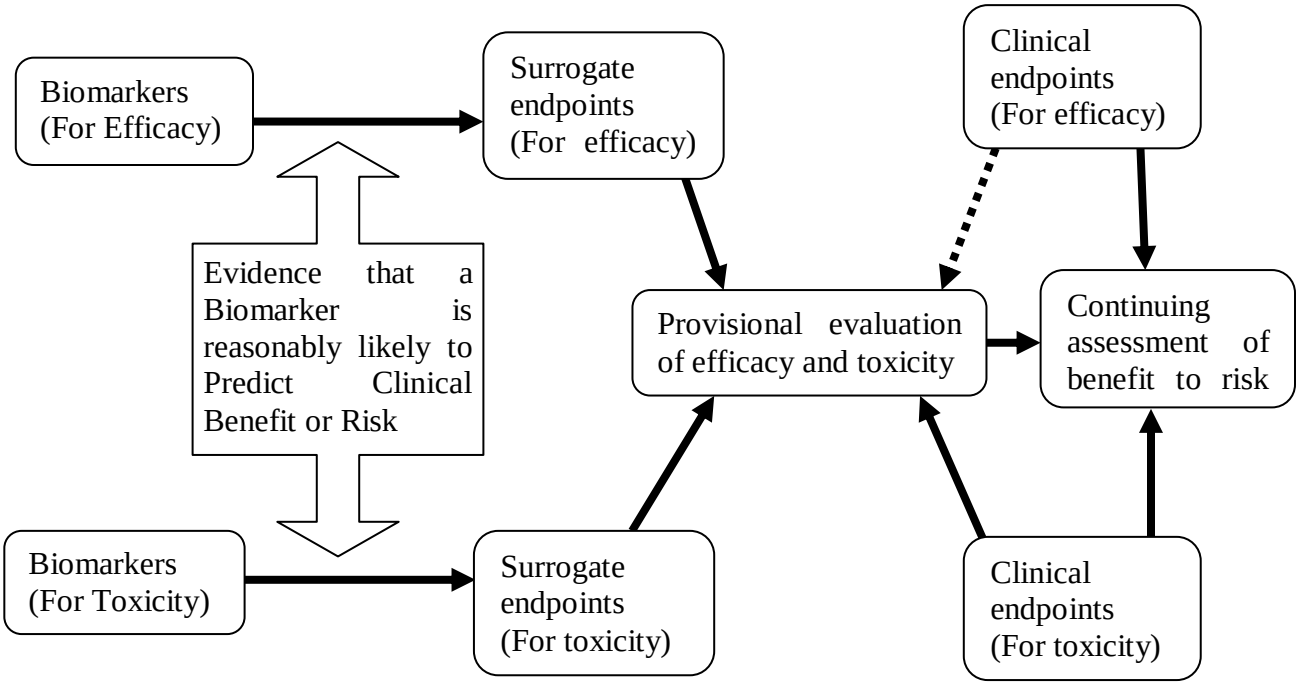

Figure 2: Conceptual model for biomarkers and surrogate endpoints and its correlation with clinical endpoint

SIGNIFICANCE AND RISK OF BIOMARKERS AND SURROGATE ENDPOINTS

Biomarkers are important in that they can enable faster clinical trials for interventions, improve understanding of healthy dietary choices, assist public health professionals in identifying and tracking health concerns, and help health care practitioners and patients make decisions. Cholesterol levels are among the most widely known examples of biomarkers. However, even though LDL (*Low-density lipoprotein)* cholesterol level is an excellent biomarker in many situations, it does not always fully predict cardiovascular disease outcomes; in other words, it cannot be assumed to be a surrogate endpoint. No surrogate endpoint is a perfect substitute for a clinical endpoint.

As the gatekeeper for entry of foods, drugs, and many other products into the U.S. marketplace, the FDA examines data and makes decisions about whether biomarkers or surrogate endpoints can be used for regulatory reviews. FDA sometimes uses surrogate endpoints such as LDL to make decisions about health claims and drugs. When manufacturers present evidence, for example, that a product reduces LDL levels, the FDA considers the evidence in relation to the surrogate endpoint and makes decisions about cardiovascular health claims or drugs based on that evidence.

ADOPTING A BIOMARKER EVALUATION FRAMEWORK

The biomarker evaluation process should consist of the following three steps:

- Analytical validation – Biomarker tests need be reliable, reproducible across multiple laboratories and clinical settings, and maintain adequate sensitivity and specificity before data based on them can be used in subsequent evaluation steps.
- Qualification – Qualification requires: 1) evaluation of the nature and strength of evidence regarding whether a biomarker is associated with the disease, and 2) assembly of available evidence demonstrating that interventions targeting the biomarker impact the clinical endpoints of interest.
- Utilization – Decisions to use biomarkers depend on the specific use proposed in addition to the strength of the available evidence. Strong evidence and a compelling context are needed for the use of a biomarker as a surrogate endpoint.

It is important to emphasize that the steps listed above are interrelated and may not necessarily be separated in time. Conclusions in one step may require revisions or additional work in other steps.

VALIDITY OF BIOMARKERS AND SURROGATES[6]

The most important criteria for valid surrogates are summarized in the ICH (International Conference on Harmonisation) Guideline E9, Statistical Principles for Clinical Trials. These mainly define the relationship between the surrogate endpoint (high blood pressure, for example) and the "hard" clinical endpoint (such as stroke) actually relevant when treating the condition.

To show this relationship, the following must be demonstrated:

• Biological plausibility

• Statistical relationship in epidemiological studies

• Evidence from clinical studies that treatment effects on the surrogate correspond to the clinical outcome.

For the same disease, the relationship between surrogate and clinical endpoints may depend on the mode of action. This means that for the same condition, regulatory authorities may accept that the surrogate is valid for one class of drugs, but not for other classes.

IMPROVING EVIDENCE-BASED REGULATION

The primary advantage of the use of surrogate end points is the ability to evaluate drugs more quickly and in smaller trials than would be required for the demonstration of a reduction in the risk of major cardiovascular events. At the time of approval, however, information remains incomplete about uncommon risks and about the actual health benefits of drugs evaluated on the basis of surrogate end points. Drug effects on LDL cholesterol levels, for instance, are unlikely to provide useful information about off-target adverse effects such as rhabdomyolysis or about health benefits that involve other mechanisms. Public health advantages of rapid approval for drugs that turn out to be safe and effective need to be balanced against harms that might occur when drugs approved on the basis of surrogate end points turn out later either to have significant safety problems or to lack efficacy. Recent experience with lipid altering drugs, ezetimibe and torcetrapib, provides new evidence about surrogate end point approaches to the drug approval process.

- **Ezetimibe**

In October 2002, ezetimibe, a drug that inhibits the absorption of cholesterol by the small intestine, was approved for the treatment of hypercholesterolemia on the basis of its ability to reduce levels of LDL cholesterol. FDA guidance on lipid-altering agents suggests that the 'demonstration of at least a 15% reduction from baseline in LDL cholesterol, in the absence of unfavorable alterations in other lipid parameters, is generally required for drug approval[7].'

The phase 3 trials of ezetimibe, summarized in the product label, were successful. In two 12-week trials that randomized 892 and 827 patients with hypercholesterolemia to placebo or active treatment[8,9] Ezetimibe was associated with 16.5% and 16.9% greater reduction in LDL cholesterol levels than placebo. Additional trials showed that ezetimibe was more effective than placebo in reducing LDL cholesterol levels in patients who were already taking statins and in patients who simultaneously initiated statin and ezetimibe therapies. Except for a slightly higher frequency of mild elevations of hepatic enzyme levels in several studies[8,10] the frequency of adverse events did not generally differ significantly between ezetimibe and placebo, and serious adverse events were uncommon.

- **Torcetrapib**

HDL cholesterol level, a marker of reverse cholesterol transport, is inversely associated with cardiovascular risk, even in older adults. Although LDL levels rather than HDL levels have been the traditional targets of lipid-alerting therapies, new drugs targeting HDL such as torcetrapib, an inhibitor of cholesteryl ester transfer protein, have been under development. In an early report involving 19 patients, torcetrapib taken at 120 mg per day was associated with large increases in plasma HDL cholesterol levels, 61% in individuals who were also treated with atorvastatin and 46% in those who were not. In two 8-week studies of 162 and 174 patients with below-average HDL cholesterol levels, torcetrapib dose was directly and strongly related to increases in HDL cholesterol levels. In the ILLUMINATE trial, 15,057 patients with high cardiovascular risk were randomized to receive torcetrapib plus atorvastatin or atorvastatin alone. Among patients who received torcetrapib for 3 months, mean levels of HDL cholesterol were 28.4 mg/dL higher and mean levels of LDL cholesterol were 19.7 mg/dL lower than individuals who received placebo. Systolic blood pressure was also higher by 4 mm Hg among patients who had received torcetrapib. After a median follow-up of 550 days, the trial was stopped early because of an increase in the risk of the primary end point, major cardiovascular events (hazard ratio, 1.25; 95% confidence interval, 1.09-1.44), and because of an increase in total mortality (hazard ratio, 1.58; 95% confidence interval, 1.14-2.19). In view of these results, the manufacturer halted the development of torcetrapib in December 2006[11].

- **Comment**

The differences in histories of ezetimibe and torcetrapib, both drugs designed to alter lipid levels and prevent cardiovascular events, are striking. Ezetimibe was approved and marketed aggressively. The randomized clinical trials evaluating its effects on atherosclerosis and clinical events have been slow to be reported or started. Torcetrapib was never approved. A large, long-term randomized trial evaluating its association with major cardiovascular events was well under way before approval.

NEED TO CORRELATE BIOMARKER AND ASSOCIATED CLINICAL OUTCOME

Below, examples of false positive and false negative biomarkers (used as surrogates for clinical endpoints) are discussed. The examples illustrate the need for a fact-based assessment of the relationship between a biomarker and the associated clinical outcome, even if such a relationship appears to be clearly evident.

False positive biomarker: Using anti-arrhythmic in patients with ventricular arrhythmias.

For a long time, cardiologists have generally accepted the empirical clinical hypothesis that prevention of sudden death can be achieved by pharmacological suppression of cardiac arrhythmias. This clinical dogma was based on the observation that about 75% of sudden deaths are due to ventricular tachycardia or fibrillation and that complex ventricular arrhythmias are a risk factor for sudden death in patients with MI (myocardial infarction), especially when associated with left ventricular dysfunction. The CAST (Cardiac Arrhythmia Suppression Trial) study published in 1991 proved the cardiologists wrong[12].

Even though arrhythmia as a risk factor was diminished by administering antiarrhythmic drugs such as encainide or flecainide (so-called class IC-antiarrhythmics) in 1498 post-MI subjects with ventricular extrasystoles and a low left ventricular function (ejection fraction <55%), mortality was significantly higher in subjects who received the antiarrhythmic drug than in the control group. Drug-induced alterations in intracardiac conduction properties most likely explain this result, but other effects of the antiarrhythmics, such as an effect on the adrenergic system, also may be responsible for the negative outcome associated with treatment in this population. This example highlights the need for extensive preclinical work in order to understand drug action and to increase the usefulness of a clinical biomarker such as arrhythmia, especially after unexpected results have been obtained in clinical studies[13].

In conclusion, a clinically reasonable association between biomarker and clinical outcome does not necessarily mean that a treatment-related effect on this biomarker will improve the clinical outcome. This has been noted by the regulatory authorities, which require a sound database on the association between drug-induced effects on the biomarker and on relevant clinical endpoints before they accept a biomarker as definitive surrogate endpoint.

False negative biomarker: Using beta-blockers in patients with congestive heart failure.

About 20 years ago, administering betablockers to patients with congestive heart failure was considered medical malpractice. This conclusion was based on pharmacological reasoning—mainly the negative inotropic effects of this drug class. Furthermore, cardiac output was considerably reduced by beta-blockers such as practolol (by as much as 12%), atenolol (by as much as 25%), and propranolol (by as much as 28%), when given intravenously to patients with ischemic heart disease—even those with no overt signs of heart failure.[14] That study concluded that “it will probably not be acceptable to give beta-blockers, even those with a considerable degree of intrinsic sympathomimetic activity, to subjects with congestive heart failure.” Today, beta-blockers belong to the standard-of-care of many subjects with congestive heart failure,

based on a number of well-controlled mortality studies and scientific evidence that excess activity of the adrenergic system contributes to the pathophysiology of this widespread disease.

This example shows that the assumed lack of a clinically beneficial effect of a drug on a biomarker does not necessarily mean that the drug will not improve the clinical outcome if used properly. It may be hard for scientists in a pharmaceutical company, though, to convince management to continue with development of a drug once the negative data are available. Sound scientific reasoning is necessary when choosing appropriate biomarkers during early drug development.

INTERPRETING OUTCOMES

Biomarkers play a critical role during Phase II of drug development (that is, during early proof-of-concept studies in a well-defined target population). This phase has been defined as "human trials providing sound evidence supporting the postulated effects of a new therapeutic drug product." The effects may be a relevant pharmacological action or a change in disease biomarkers, established surrogate endpoints, or clinical outcomes. Particularly, it should be noted that the relevant drug effects might be beneficial (that is, related to efficacy) and/or toxic (related to potential side effects). To properly interpret the outcome of clinical studies in which the primary outcome variable is a biomarker that substitutes for the relevant clinical outcome, researchers must consider the complex relationship between the medical condition, the biomarker, and the clinical outcome. Hypertension is a straightforward example; it is associated with the biomarker elevated blood pressure, one of the few generally accepted surrogate endpoints in cardiovascular drug development, is associated with a clinically relevant outcome such as stroke, myocardial infarction, or renal failure. But the apparently straightforward association between disease, biomarker, and outcome oversimplifies the underlying (patho-) physiology. Thus, a disease generally is associated with several clinical manifestations, which may or may not serve as biomarkers, and which may be associated with the relevant clinical outcome.

An example of a complex clinical condition is the metabolic syndrome, which is defined as insulin resistance (with or without manifest type 2 diabetes) and at least two of the following criteria—hypertension, dyslipidemia, obesity, and microalbuminuria. Clinically, this disease is associated with an increased cardiovascular risk. The possibility that the clinical outcome is time dependent must also be taken into account when interpreting the outcome of studies using biomarkers. An example is the pharmacological group of PDE (phosphodiesterase) 3 inhibitors (amrinone and milrinone, for example) for which a significant increase in cardiac contractility

could be demonstrated in subjects with congestive heart failure. Following chronic administration of these drugs, mortality increased in the subject population. It can be concluded that biomarkers and clinical endpoints are not completely dependent on one another, but that there is a more or less well-defined relationship between the two. The use of a clinical biomarker as the primary outcome of a pharmacological intervention must therefore be interpreted very cautiously, taking into account the underlying (patho-) physiology, the possibility of false positive or false negative results, and time dependency of the clinical outcome.

In cardiovascular medicine, blood pressure is a biomarker with a clearly demonstrated relationship to clinically relevant endpoints. BP has been accepted as surrogate endpoint for cardiovascular morbidity and mortality, by both the medical community (as reflected in current World Health Organization guidelines) and regulatory authorities. Major prospective, randomized clinical studies (including meta-analyses) and epidemiological evidence (the Framingham Heart Study conducted over more than 40 years)[15] have clearly demonstrated that high blood pressure is associated with increased morbidity and mortality, and that lowering blood pressure is beneficial.

To use a biomarker as a surrogate endpoint in a regulatory submission, researchers must validate the clinical study method for reproducibility, sensitivity, specificity, variability, and bias. When using blood pressure as biomarker, for example, a considerable diurnal fluctuation exists. Because the maximum BP values occur in the late morning and early evening, ABPM (ambulatory blood pressure monitoring) is more appropriate than occasional office blood pressure recording.

CONCLUSION

It may conclude that Biomarkers and surrogate endpoints play pivotal role in accelerating approval process for drug approval in USA and the usage of these parameters to minimize the casualty of human lives who are suffering from serious life threatening diseases by providing recent research products which have caliber to cure or improving the quality of life. Under Code of federal regulations 21CFR section 314.510 subpart H gives detail regarding accelerated approval process using biomarker and surrogate endpoint. The purpose of accelerating approval process is to minimize the casualty of human lives who are suffering from serious life threatening diseases by providing recent research products which have caliber to cure or improving the quality of life of such patients relying on the Biomarkers and surrogate endpoint results. ICH E9 guideline talks about validity of biomarkers and surrogates.

REFERENCES

1. Biomarkers and surrogate endpoints. J K Aronson, *Chairman of the Editorial Board* British Journal of Clinical Pharmacology Available at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1884846/ Accessed on 16th September 2011
2. Biomarkers and surrogate endpoints clinical research and applications G.J. Downing. Available at: http://books.google.co.in/books?id=QrN_TCCHJOQC&pg=PA27&source=gbs_selected_pages&cad=3#v=onepage&q&f=false Accessed on 12th September 2011
3. William W. Chu, Robert S. Dieter, Charles K. Stone. Evolving Clinical Applications of Cardiac Markers: A Review of the Literature. Wisconsin Medical Journal 2002; 101: 49–55.
4. William W. Chu, Robert S. Dieter, Charles K. Stone.A Review of Clinically Relevant Cardiac Biochemical Markers, Wisconsin Medical Journal 2002;101: 40–48 .
5. 21 Code of federal regulation (CFR) section 314, subpart H. [Online] Available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=314&showFR=1&subpartNode=21:5.0.1.1.4.8. Accessed on 18th September 2011.
6. International Conference on Harmonisation (ICH) Guideline E9, [Online] Available at: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/Step4/E9_Guideline.pdf Accessed on 17th October 2011.
7. Division of Metabolic and Endocrine Drug Products; US Food and Drug Administration. Guidelines for the clinical evaluation of lipid-altering agents in adults and children: Center for Drug Evaluation and Research, September 1990. [Online] Available at: www.fda.gov/.../DevelopmentApprovalProcess/.../ucm072244.pdf Accessed on 17th October 2011.
8. Knopp RH, Gitter H, Truitt T, et al; Ezetimibe Study Group. Effects of ezetimibe, a new cholesterol absorption inhibitor, on plasma lipids in patients with primary hypercholesterolemia. Eur Heart J. 2003; 24(8):729-741. [Online] Available at: http://eurheartj.oxfordjournals.org/content/24/8/729.full.pdf Accessed on 23rd October 2011.

9. Dujovne CA, Ettiger MP, McNeer JF, et al; Ezetimibe Study Group. Efficacy and safety of a potent new selective cholesterol absorption inhibitor, exetimibe, in patients with primary hypercholesterolemia. Am J Cardiol. 2002; 90(10):1092- 1097.
10. Gagne´ C, Bays HE, Weiss SR, et al; Ezetimibe Study Group. Efficacy and safety of ezetimibe added to ongoing statin therapy for treatment of patients with primary hypercholesterolemia. Am J Cardiol. 2002; 90(10):1084-1091.
11. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2006/ucm108792.htm Accessed on 12th November 2011.
12. Echt DS, Liebson PR, Mitchell LB, Peters RW, Obias- Manno D, Barker AH, Arensberg D, Baker A, Friedman L, Greene HL, et al. Mortality and Morbidity in Patients Receiving Encainide, Flecainide or Placebo: The Cardiac Arrhythmia Suppression Trial. New England J Medicine 1991; 324 :781–787.
13. Craig M. Pratt. Predicting Antiarrhythmic Performance. J Cardiovascular Electrophysiology1999;10: 302–306.
14. Svendsen TL, Hartling OJ, Trap-Jensen J, McNair A, Biddal J.Adrenergic Beta Receptor Blockade: Hemodynamic Importance of Intrinsic Sympathomimetic Activity at Rest. Clinical Pharmacology and Therapeutics1981; 29: 711–718.
15. Pamela A. Sytkowski, Ralph B. D'Agostino, Albert J. Belanger, William B. Kannel. Secular Trends in Long-Term Sustained Hypertension, Long-Term Treatment and Cardiovascular Mortality. Circulation 1996; 93: 697–703.